TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomised, double blind (sponsor unblinded), placebo controlled, single ascending dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of a IV dose of GSK2831781 in healthy volunteers and patients with plaque psoriasis.

Compound Number: GSK2831781

Development Phase: I

Effective Date: 24-JUL-2017

Protocol Amendment Number: 10

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Revision Chronology

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2014N192690_01	2014-FEB-28	Original
2014N192690_02	2014-MAR-27	Amendment No. 1
To respond to comments from MHRA		
2014N192690_03	2014-JUN-06	Amendment No. 2
To include a test at screening to only allow ADA- subjects to be included in Parts A and B of the study. Changes to correct inconsistencies and clarifications for exploratory assays.		
2014N192690_04	2014-NOV-07	Amendment No. 3
To remove eligibility criteria regarding vaccinations and amend criteria regarding tuberculosis history. Changes to correct text that was not logistically possible, or required clarification.		
2014N192690_05	2014-NOV-27	Amendment No. 4
To reinstate eligibility criteria regarding vaccinations at MHRA request, and to enable this, to add potential to vaccinate during screening and potential to use serology.		
2014N192690_06	2015-MAR-25	Amendment No. 5
To replace 2 Healthy volunteer DTH challenge cohorts with Healthy Volunteer No DTH challenge cohorts and improve flexibility for vaccinations. Changes to correct text no longer accurate due to improved assays. Eligibility criteria text updated to meet country specific ethics requirements.		
2014N192690_07	2015-JUL-30	Amendment No. 6
Exclusion criteria and text to provide greater clarity regarding the composition of Dose Escalation Committee and DEC decision making updated to meet country specific regulatory and ethics requirements.		
2014N192690_08	2015-SEP-22	Amendment No. 7
To modify study design to enable assessment of the impact of pre-existing anti-drug antibodies in healthy volunteers and psoriasis subjects. To clarify estimation of body surface area, extend review of psoriasis clinical response, define duration of extended screening for subjects undergoing vaccination and add		

flexibility to assays for ex vivo antigen stimulation and transcriptomics.		
2014N192690_09	2016-MAY-18	Amendment No. 8
Part B, Psoriasis: To include females of reproductive potential (FRP) and to modify other eligibility criteria (age, BMI, BSA, vaccination and liver function tests). Addition of causality requirement to adverse event reporting for safety review criteria.		
2014N192690_10	2017-MAR-09	Amendment No. 9
Remove requirement for 3 ADA+ve patients in Cohorts 8 and 9. Update Time and Events Table 9 and Table 10 to reflect: adjustment of PK schedule (one new visit for Cohort 8 [Day 36] and Cohort 9 [Day 71]; introduction of efficacy assessments at Day 85; removal of *Ex vivo* Antigen/Cytokine Stimulation Test and *in vitro* LAG-3+ activity assay; to state immunophenotyping methodology as chip cytometry; photography moved prior to biopsy; introduce possibility for additional interim analyses to inform internal development decisions, update medical monitor.		
2014N192690_11	2017-JUL-24	Amendment No. 10
Update pharmacokinetic predictions and data. Consolidate the follow-up and surveillance visits for subjects in Part B who have not already completed follow up, into a 6-month final visit and incorporate assessment of clinical response (Section 6.3.5.3). An additional PGA endpoint added to secondary endpoints. Minor corrections to Time and Event Tables. Update medical monitor details.		

SPONSOR SIGNATORY

PPD

24th July 2017

Caroline Savage Date

VP and Head Experimental Medicine Unit

Immuno-Inflammation Therapy Area Unit

PPD

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

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Regulatory Agency Identifying Number(s): EudraCT Number 2014-000312-33

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200630

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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LIST OF ABBREVIATIONS

%AUCex	Percentage of AUC(0-∞) obtained by extrapolation
µg	Microgram
ABC	airway, breathing, and circulation from Basic Life Support
aCCR4	Anti C-C chemokine receptor type 4
ADA	Anti-drug antibodies
ADCC	Antibody Dependent Cell Cytotoxicity
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-x)	Area under the concentration-time curve from zero (pre-dose) to some fixed nominal time x
BCG	Bacillus Calmette Guérin vaccine
BMI	Body mass index
BSA	Body Surface Area
BUN	Blood urea nitrogen
CI	Confidence Interval
CIL	Clinical Investigator Lead
CL	Systemic clearance of parent drug
Cmax	Maximum observed concentration
CMV	Cytomegalovirus
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation
CPR	Cardio-Pulmonary Resuscitation
CPSSO	Clinical Pharmacology Sciences and Study Operations
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTLA	Cytotoxic T-Lymphocyte Antigen
CXCR	CXC Chemokine Receptor
DC	Dendritic Cells
DEC	Dose Escalation Committee
DMPK	Drug Metabolism and Pharmacokinetics
DPT	Diphtheria, pertussis, tetanus
DTH	Delayed type hypersensitivity
EBV	Epstein-Barr Virus
EC50	Median Effective Concentration
EC90	90% Effective Concentration
ECG	Electrocardiogram
ECL	Immunoelectrochemiluminescent

eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
FCS	Foetal Calf Serum
FDA	Food and Drug Administration
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTIH	First Time In Human
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
h	Hour
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
Hep B	Hepatitis B
Hep C	Hepatitis C
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
IBS	Irritable Bowel Syndrome
ICU	Intensive Care Unit
ID	Intradermal
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IgM	Immunoglobulin M
IHC	Immunohistochemistry
ii TAU	Immuno-Inflammation Therapeutic Area Unity
IL2R	Interleukin 2 Receptor
ILH	Immediate local hypersensitivity
INR	International Normalised Ratio
IRB	Institutional Review Board
IV	Intravenous
KD	Dissociation constant
kg	Kilogram
L	Litres
LAG-3	Lymphocyte Activation Gene 3
LDH	Lactate dehydrogenase
LFA	Lymphocyte Function-associated Antigen
LLQ	Lower Limit of Quantification
mAb	Monoclonal Antibody

MABEL	Minimum Anticipated Biological Effect Level
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
mg	Milligram
MHCII	Major Histocompatability Complex II
MlU/mL	milli-international units per millilitre
ml	Millilitre
mm	Millimetre
MMR	Measles, mumps, rubella
mRNA	Messenger Ribonucleic Acid
MRT	Mean Residence Time
MSDS	Material Safety Data Sheet
MTB	Mycobacterium tuberculosis
NK	Natural Killer
nM	Nanomolar
NOAEL	No Observed Adverse Effect Level
OSL	Operations and Science Lead
PASI	Psoriasis Area Severity Index
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PGA	Physicians Global Assessment
PGx	Pharmacogenetics
PK	Pharmacokinetic
PLSS	Plaque Lesional Severity Score
PML	Progressive Multifocal Leukoencephalopathy
PPD	Tuberculin Purified Protein Derivative
PTS	Platform Technologies and Science
QSci	Quantitative Sciences
QTc	Electrocardiogram QT interval corrected for heart rate
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
RO	Receptor Occupancy
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event(s)
SC	Subcutaneous
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
sLAG-3	Soluble Lymphocyte Activation Gene 3
SPC	Summary of Product Characteristics
SPM	Study Procedures Manual
t½	Terminal phase half-life

TB	Tuberculosis
tlast	Time of last quantifiable concentration
tmax	Time of occurrence of Cmax
TNFα	Tumour necrosis factor alpha
Tregs	Regulatory T cells
TU	Tuberculin Unit
UK	United Kingdom
USA	United States of America
Vss	Volume of distribution at steady state
VZV	Varicella Zoster Virus
WBC	White blood cells
λz	Terminal elimination rate

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1. INTRODUCTION

1.1. Study Rationale

This study is the first administration of GSK2831781 in humans and will evaluate in two parts the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of single intravenous (IV) doses of GSK2831781 administered to healthy volunteers (Part A), including a cohort of those previously vaccinated with Bacillus Calmette Guérin (BCG) (Part A delayed type hypersensitivity [DTH] cohort) and patients with plaque psoriasis (Part B). Single dose escalation will allow for the identification of any immediate dose-limiting toxicities. Investigation of pharmacology in healthy subjects in the Part A DTH cohort will confirm whether the selected dose is likely to result in pharmacodynamic effects in immune-inflammatory diseases associated with the target Lymphocyte Activation Gene 3+ (LAG-3+) T cells, which are then tested in Part B. As there are very low levels of LAG-3+ T cells in blood it is necessary to monitor LAG-3+ cells at the site of antigen challenge or the disease site. The use of a DTH in healthy subjects in Part A allows investigations into the impact of GSK2831781 on immunological endpoints after a controlled challenge. The switch to patients with psoriasis in Part B, at a dose by which effects would be expected, then allows investigations of higher doses in a chronic disease setting. Measuring the pharmacology of GSK2831781 using the depletion of LAG-3+ T cells in skin biopsies from Tuberculin Purified Protein Derivative (PPD) skin challenge and lesional skin biopsies from patients with psoriasis, is an important component of the study and for the latter may enable an understanding of the dose response relationship, which will be important for decision making and the design of future studies in immuno-inflammatory diseases, including psoriasis. The use of DTH and psoriasis subjects to explore the mechanism in biopsies and clinical response endpoints in these populations, as well as investigate systemic biomarkers will also provide useful information before conducting studies in other immune-inflammatory disease where more invasive tissue biopsies would be required.

1.2. Brief Background

1.2.1. GSK2831781

GSK2831781 is a humanised Antibody Dependent Cell Cytotoxicity (ADCC) enhanced monoclonal afucosylated antibody (mAb) that is specific to the LAG-3 protein, and has demonstrated depletion of LAG-3+ cells *ex vivo* and *in vivo*. LAG-3 is predominantly expressed on recently activated T cells upon T cell receptor engagement.

In vitro pharmacology studies conducted with GSK2831781 demonstrate high binding affinity of GSK2831781 to LAG-3 (dissociate constant (KD) = 0.218 nanomolar [nM]) (GlaxoSmithKline Document Number 2011N130304_00). The biological activity of GSK2831781 was demonstrated *in vitro* showing ADCC activity on ARH-77, a human LAG-3 expressing cell line with median effective concentration (EC50) for killing activity 8.4 ng/ml. A 4 week IV or subcutaneous (SC) good laboratory practice (GLP) toxicity study in cynomolgus monkeys was used to provide the safety profile. In this study there were no consistent GSK2831781 related changes in plasma cytokine levels 6 or 24 hours after administration of GSK2831781 relative to baseline. Adverse

GSK2831781 related effects were limited to a marked decrease in absolute neutrophil count for two males given 100 mg/kg/week (one animal by each route of administration). Based on the GLP toxicity study, the no observed adverse effect level (NOAEL) for monkeys in this study was considered to be 30 mg/kg/week given intravenously. However, in two investigative studies, a reduction in neutrophil counts was observed in 1 monkey from each study dosed intravenously at 30mg/kg (n=7) but was not observed in monkeys dosed at 3 mg/kg (n=7).

Pre-existing anti-drug antibodies (ADA) that bind GSK2831781 have been noted in 36% and 37.5% of sera from healthy and psoriatic human subjects respectively. Analysis of ADA to GSK2831781 indicated they are generally low titre and low affinity, based on the IgM isotype. The relevance of pre-existing ADAs for biotherapeutics in general is poorly understood, but they may have an effect on pharmacological and clinical parameters (Xue *et al*, 2013).

Detailed information can be found in the Investigators Brochure (IB) for GSK2831781 [GlaxoSmithKline Document Number 2013N175515_01 and GlaxoSmithKline Document Number 2014N201916_00]

1.2.2. LAG-3 biology

The mode of action of GSK2831781 utilises the specific expression of LAG-3 on recently activated T cells as target to specifically deplete these potentially pathogenic T cells. This approach that has been utilised in the past with other agents, alefacept, that targets CD2 and denileukin diftitox which targets CD25+ T cells (Chaarani *et al,* 2010; Martin *et al*, 2001). *In vivo*, LAG-3 is a negative co-stimulatory receptor that modulates T cell homeostasis, proliferation and activation via its interaction with major histocompatability complex class II (MHCII). GSK2831781 is designed not to interfere with the MHCII binding of LAG-3 and does not increase T cell proliferation *ex vivo*. A monomeric soluble form of LAG-3 (sLAG-3) also exists and occurs at low levels in serum of healthy donors and patients.

LAG-3 is predominantly expressed on a low number of recently activated T cells (<1% in healthy volunteers) upon T cell receptor engagement, with very low expression on resting and naive/memory T cells and regulatory T cells (Tregs) in blood and secondary lymphoid tissue. This is supported by immunohistochemistry (IHC) data which demonstrate increased expression of LAG-3 on T cells in human tissue during the immune response to challenge antigens and in a growing number of immuno-inflammatory disorders, including psoriasis [GlaxoSmithKline Document Number 2013N184876_00]. It is hypothesised that in T cell driven immuno-inflammatory disorders, LAG-3+ T cells are pathogenic (having recently encountered self-antigen), and hence their depletion will reduce disease activity. The low level of expression of LAG-3 on other T cell sub-types (naive and memory) should allow preferential targeting of pathogenic/effector T cells while sparing memory and naive T cells and Tregs, which are key for the normal immune response to pathogens and immune homeostasis.

The key attribute of LAG-3 as a target antigen for an enhanced lymphocyte depletion agent is its relatively selective expression profile compared with other agents currently in

the clinic, i.e. Campath (T/B cells), alefacept (most CD45RO+ T cells) or rituximab (B-cells).

Data to support the hypothesis that depletion of LAG-3+ activated T cells will produce an inhibition of the immune response was generated by Immutep, the inventors of the parental non-enhanced mAb, IMP731. In a baboon tuberculin skin challenge model, IMP731 mediated depletion of LAG-3+ T cells, both in the periphery, including the lymph nodes and at the skin challenge site, and demonstrated a reduction in the tuberculin skin challenge response. LAG-3+ activated T cells have been quantified in biopsies of a delayed type hypersensitivity reaction following challenge with tuberculin purified protein derivative (PPD) in human healthy volunteers, at a time when the induration and erythema from the DTH reaction can also be measured (GSK unpublished data).

1.2.3. Psoriasis

Plaque psoriasis vulgaris is a chronic inflammatory skin disorder, affecting 1-3% of the population in Europe and the United States of America (USA) and represents one of the most prevalent immunoinflammatory diseases. The spread of psoriasis across the body can vary from minimal on elbows, knees and scalp (mild disease) to covering the entire body (severe).

There are two key abnormalities in psoriasis, hyperproliferation of keratinocytes and an inflammatory cell infiltrate, which includes; dendritic cells (DCs), macrophages, NK T cells, mast cells, T cells and neutrophils. There is strong evidence that T cells have an important role in psoriasis (Cai *et al*, 2012); this is supported by the clinical activity of multiple T cell targeted agents including: cyclosporine, anti-CD4 antibodies, anti-Cytotoxic T-Lymphocyte Antigen 4 Immunoglobulin (anti-CTLA4 Ig), alefacept (lymphocyte function-associated antigen 3 (LFA3)/CD2 fusion protein), efalizumab (anti-CD11a), siplizumab (anti-CD2) and DAB389IL-2 (diphtheria toxin-Interleukin 2 receptor fusion protein) (Kircik *et al*, 2009).

The number of T cells expressing LAG-3 are increased in lesional skin biopsies from patients with plaque psoriasis, when compared to non-involved skin from the same patients (GSK unpublished data). This increased LAG-3 expression, linked to the clear role of T cells in the pathogenesis of psoriasis warrant further investigation of GSK2831781 in patients with psoriasis.

2. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
To assess the safety and tolerability of single IV doses of GSK2831781 in healthy volunteers and psoriasis patients.	• Laboratory safety data (haematology, clinical chemistry, urinalysis) • Vital signs (blood pressure, heart rate, body temperature) • 12-lead ECGs • Adverse events • Inflammatory cytokine levels
Secondary	
To evaluate the pharmacology and clinical effect of a single IV dose of GSK2831781 in a DTH model in healthy volunteers.	• Change from baseline (PPD 1st challenge) of induration diameter from re-challenge at 3 days post-dose • Duration of induration in the re-challenge • Change from baseline (PPD 1st challenge) of LAG-3+ cells in biopsies of re-challenged skin at 3 days post-dose, measured by IHC
To evaluate the pharmacology of a single IV dose of GSK2831781 in psoriasis patients.	• Change from baseline in LAG-3+ cells in lesional biopsies at Day 29 measured by IHC
To evaluate the pharmacokinetics of single IV doses of GSK2831781 in healthy volunteers and psoriasis patients.	• GSK2831781 PK parameters following single intravenous dose: AUC(0-∞), AUC(0-t), AUC(0-Week4), %AUCex, Cmax, tmax, tlast, CL, Vss, MRT, λz and t ½ when assessable
To evaluate the immunogenicity of GSK2831781 administered as a single IV dose in healthy volunteers and psoriasis patients.	• Antibodies to GSK2831781 in serum
To evaluate the effect of a single IV dose of GSK2831781 on disease activity in psoriasis patients.	• Change from baseline and actual PASI scores at Day 15, 29, 43, 85, 121 and follow up • Proportion of subjects who achieve ≥50% and ≥75% improvement from baseline in PASI score at Day 15, 29,

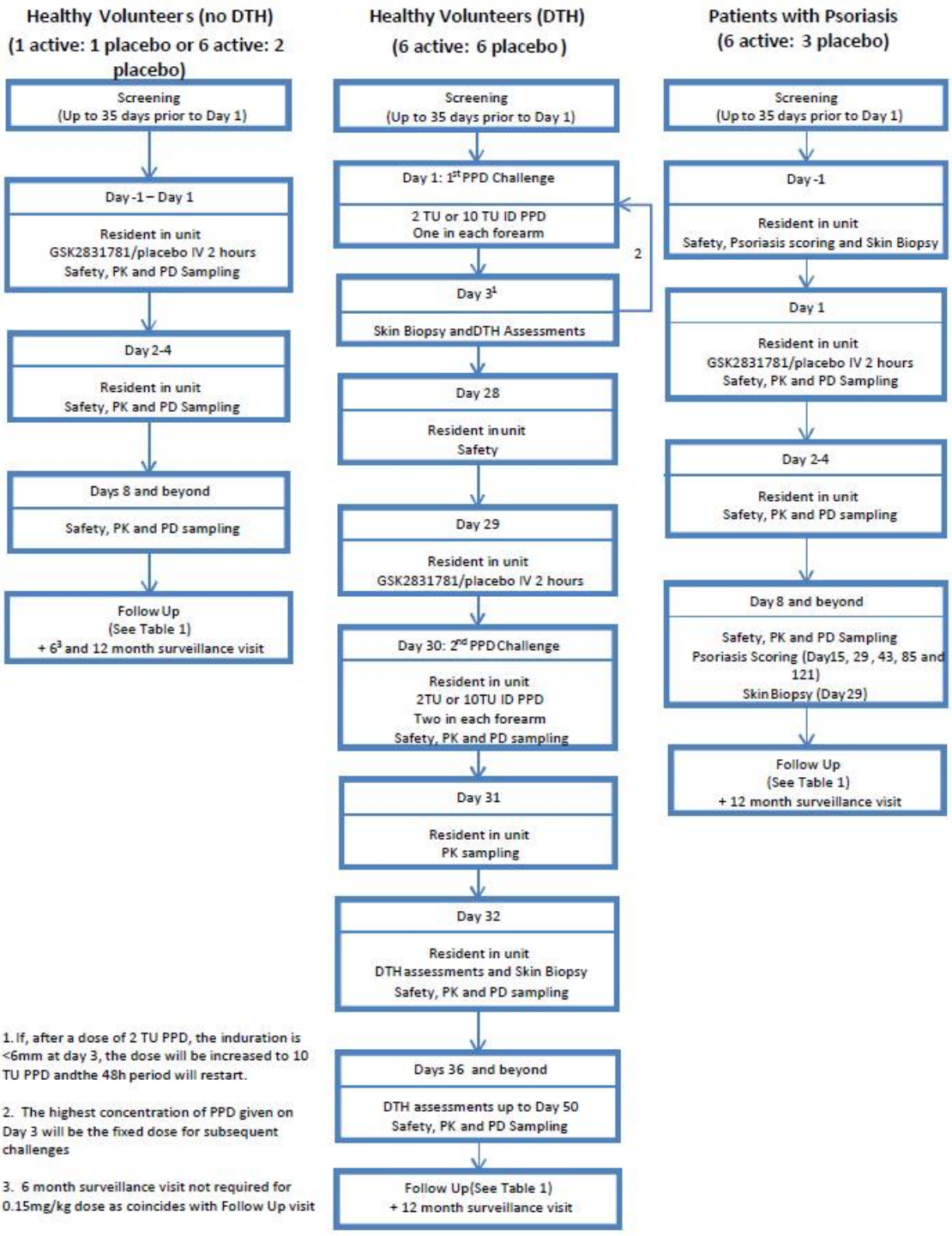
Objectives	Endpoints
	43, 85,121 and follow up (PASI 50 and PASI 75) • Change from baseline and actual PLSS scores at Day 15, 29, 43, 85 ,121 and follow up • Change from baseline and actual PGA scores at Day 15, 29, 43, 85 and 121 • Proportion of subjects in each PGA score category at Day 15, 29, 43, 85 and 121 • Proportion of subjects achieving PGA 0/1 and at least a 2 point improvement at Day 15, 29, 43, 85 and 121
Exploratory	
To evaluate the effect of a single IV dose of GSK2831781 in psoriasis patients on biomarkers.	• Histopathological scoring of psoriatic lesional biopsies in patients with psoriasis - Ki67, CD3 and epidermal thickness • Transcriptomic analysis of psoriatic lesional biopsies in patients with psoriasis

To evaluate the effect of a single IV dose of GSK2831781 in healthy volunteers and psoriasis patients on pharmacodynamic biomarkers.	• Proof of pharmacology biomarker endpoints may include, but not be limited to, the following as data permit:
	  • LAG-3 expression on different blood immune cell populations including T cells
	  • Transcriptomic profiling to assess mRNA levels in peripheral blood
	  • Quantification of LAG-3 mRNA in whole blood
	  • Inflammatory cytokine levels
	  • Free and GSK2831781 bound sLAG-3 concentrations
	  • NK cell CD16 receptor occupancy in whole blood
	  • NK cell activation marker expression in whole blood

Objectives	Endpoints
To explore the impact of pre-existing ADAs on the PK of GSK2831781	• GSK2831781 PK parameters following single intravenous dose: AUC(0-∞), AUC(0-t), AUC(0-Week4), %AUCex, Cmax, tmax, tlast, CL, Vss, MRT, λz and t ½ when assessable

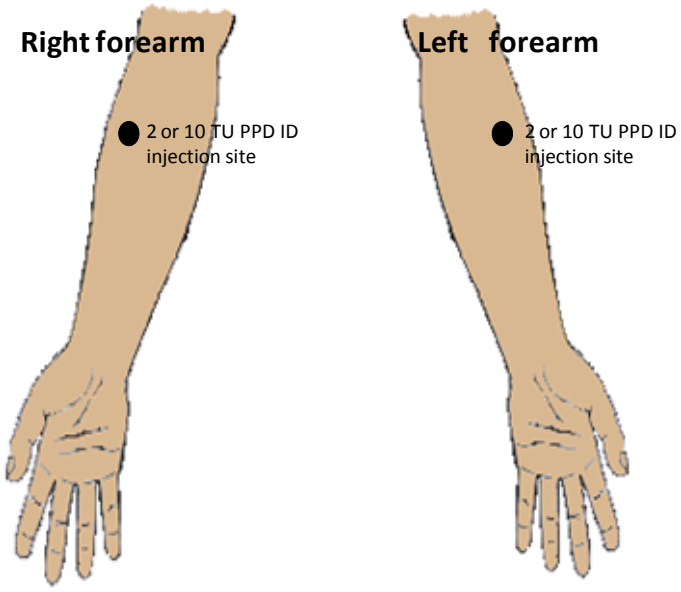
3. STUDY DESIGN

3.1. Study Schematic

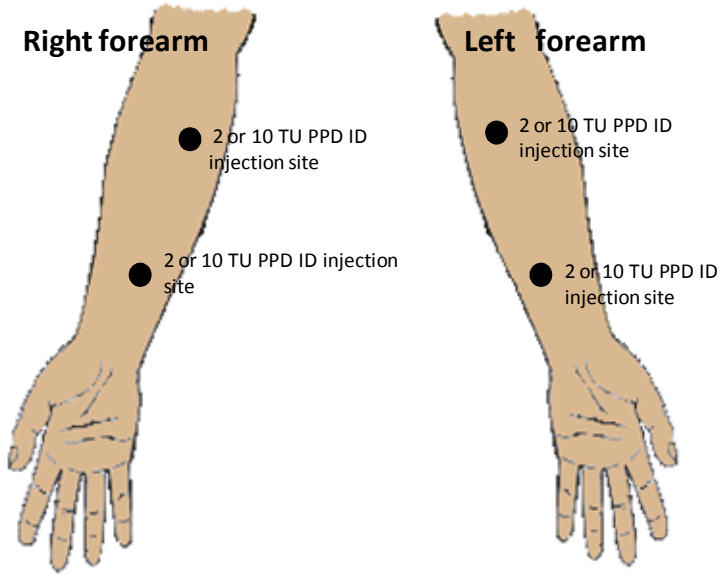


3.1.1. PPD injection sites

Day 1



Day 30



All injection sites should be 4 cm apart from each other and from Day 1 injection sites

3.1.2. Study Design Summary

Table 1 Dose escalation/Cohort Structure and Safety review periods

Planned Doses	**Number of subjects (active:placebo)**	**Safety Follow-up period to progress to next subjects/cohorts**	**PPD DTH Challenge if Healthy volunteer/ Biopsy if patient**	**Follow-up and end of exclusion of systemic immunosuppressives**
Healthy Volunteers				
0.0003mg/kg	1:1	1:1 wait 28 days post-dose	No DTH	Day 29 ± 1 day (28 days post-dosing)
0.0015mg/kg				Day 43 ± 1 day (42 days post-dosing)
0.0075mg/kg	6:2	1:1 wait 48 hours post-dose 5:1 wait 28 days post-dose	No DTH	Day 85 ± 2 days (84 days post-dosing)
0.04mg/kg				Day 147 ± 3 days (146 days post-dosing)
0.15mg/kg	6:6	1:1 wait 48 hours post-dose 5:5 wait 28 days post-dose	DTH	Day 219 ± 7 days (190 days post-dosing)
0.15mg/kg*	6:2	1:1 wait 48 hours post-dose 5:1 wait 28 days post-dose	No DTH	Day 189 ± 7 days (190 days post-dosing)
Note: Cohort with a DTH starts dosing on Day 29 *Note: No DTH cohort at dose level 0.15mg/kg is in subjects with pre-existing ADA. All previous cohorts are in subjects without pre-existing ADA Maximum dose for healthy volunteers may change based on emerging exposure (See Section 3.2.1)				
Psoriasis Patients (Pre-existing ADA- and ADA +)				
0.5mg/kg	6:3(ADA-ve 4:2 ADA+ve: 2:1)	1:1 ADA-ve wait 48 hours post-dose 5:2 wait 28 days post-dose*	Biopsy	230 days post-dosing ± 7† days
1.5mg/kg	6:3	Sentinel 1:1 - wait 48 hours post-dose 5:2 - then wait 28 days post-dose*	Biopsy	183 days post-dosing ± 7† days (prior to Amendment 10 was 270 days)

Planned Doses	**Number of subjects (active:placebo)**	**Safety Follow-up period to progress to next subjects/cohorts**	**PPD DTH Challenge if Healthy volunteer/ Biopsy if patient**	**Follow-up and end of exclusion of systemic immunosuppressives**
5mg/kg	6:3	Sentinel 1:1 - wait 48 hours post-dose 5:2	Biopsy	183 days post-dosing ± 7† days (prior to Amendment 10 was 300 days)

Note: All follow-up days may be increased or decreased during the study based on emerging data (See Section 3.3.1)

*Note: Progression to the next psoriasis cohort will be based on safety data and clinical measures of response at 28 days post-dose for a minimum of 8 out 9 subjects plus a minimum of 72 hours post-dose for all subjects.

† All subjects in Cohort 7 have already completed the day 230 ± 7 follow up visit. Any subjects in Cohort 7 who have not had a 12-month surveillance visit when the amendment is approved should instead have a surveillance telephone call as their last study visit (see Table 6), as soon as practically possible after the amendment is approved, rather than waiting to month 12 after dosing. Subjects in Cohort 8 who have already completed their follow up visit should also have a surveillance telephone call as soon as the protocol amendment is approved. Subjects in Cohort 8 and Cohort 9 who have not yet had a follow up visit when the protocol amendment is approved should have a combined follow up/surveillance visit at day 183 ± 7, or as soon as practically possible if they have already been monitored for longer than 183 ± 7 days after dosing.

3.2. Study Design Detail

This is a FTIH, phase I, randomised, double-blind (sponsor unblind), placebo-controlled, single ascending dose study in healthy volunteers and patients with plaque psoriasis. In Parts A and B of the study subjects will be screened for pre-existing ADA status and initially in Part A only subjects who do not have pre-existing ADAs will be randomised. A cohort (cohort 6) of subjects positive for pre-existing ADA at the maximum healthy volunteer dose of 0.15mg/kg will then be dosed. Part B will include subjects with both negative and positive pre-existing ADA status. In Cohort 7, randomisation was stratified by ADA status. as outlined in Table 1. In subsequent cohorts, the remaining subjects may be ADA+ve or ADA-ve.

The planned dosing schedule is provided in Table 1 to aid understanding, although this is subject to change dependent on emerging study data and DEC decisions after each dosing session (See Section 5.4). In summary the doses planned are 0.0003, 0.0015, 0.0075, 0.04, 0.15, 0.5, 1.5 and 5mg/kg.

The first healthy volunteer cohort will begin with the lowest dose. Healthy volunteers will be dosed up to a maximum dose of 0.15mg/kg (unless criteria in Section 3.2.1 are met). Once the last healthy volunteer cohort data has been reviewed by the DEC, the dose escalation will continue in patients with plaque psoriasis. The first cohort of patients with plaque psoriasis will begin at the next dose level after the maximum dose administered to healthy volunteers. The dose escalation will not exceed the maximum planned dose.

Based on the criteria which are defined in Section 5.4, 'Planned Dose Adjustments', Section 5.7 'Dose Adjustment/Stopping Pharmacokinetic Criteria' and the DEC Charter, the DEC may recommend that doses and intervals between dose levels are changed

within these limits based on any of the following emergent data: safety and tolerability, PK, clinical measures and PD.

All IV doses will be administered for 2 hours. However, dosing duration may be modified based on safety data with the approval of the PI and sponsor.

PART A

Healthy volunteers without DTH

In cohorts 1 and 2, one active and one placebo subject will be recruited.

For cohorts 3, 4 and 6, one active and one placebo subject will be recruited initially. After the GSK medical monitor and investigator have reviewed the safety data up to 48 hours post dose, an additional 5 active and 1 placebo subjects will be dosed (no more than 2 subjects per day with dosing separated by at least 1 hour).

After the DEC have reviewed the safety data up to 28 days on all subjects within the cohort along with the available PK data, a dose escalation may occur to the next planned dose. If safety findings are noted in the active subjects in cohorts with 2 subjects, the cohort may be expanded to a maximum cohort size of 6:3 (active:placebo) or the escalation stopped (See Section 5.5). Once data up to 28 days post dose has been collected for all subjects within cohort 6, the DEC will review the safety data along with the available PK data, available PD data from cohort 6 and also the DTH clinical response data from the Healthy Volunteer (DTH) cohort 5 (below), before switching to patients with plaque psoriasis.

A study schematic giving an overview of the visits is in Section 3.1.

Screening – Subjects will attend screening up to 35 days before dosing.

Day -1 – Day 4 – Subjects will attend the unit on Day -1 and will remain resident in the unit until Day 4. Provided that there are no safety issues on Day 4 (72 hours post dose) and there are no clinically significant haematology results from the 72 hour post-dose safety sample the subject will be discharged from the unit.

Days 8 and beyond - Subjects will attend the unit as an out-patient.

Follow-up - Subjects will return for a follow-up as specified in Table 1.

All subjects in cohorts 1, 2, 3 and 4 will attend a surveillance visit at 6 and 12 months. As the follow-up visit is at approximately 6 months (190 days post-dose, as per Table 1), subjects in the 0.15mg/kg cohort 6 do not require an additional post-dose surveillance visit at 6 months and will only attend a surveillance visit at 12 months.

Healthy volunteers with DTH

One active and one placebo subject will be recruited initially. After the GSK medical monitor and investigator have reviewed the safety data up to 48 hours post dose, an

additional 5 active and 5 placebo subjects will be dosed (no more than 2 subjects per day with dosing separated by at least 1 hour). Once data up to 28 days post dose has been collected for all subjects within the cohort, the DEC will review the safety data along with the available PD data, before dosing a cohort of healthy volunteers with pre-existing ADA, at the same dose, without DTH.

A study schematic giving an overview of the visits is in Section 3.1.

Screening - Subjects will attend screening up to 35 days before the first PPD challenge.

Day 1 to Day 3 - Subjects will attend the unit on Day 1 and will receive ID injections of PPD as per Section 5.10.1 and Section 6.5.1. A skin biopsy will be taken from one of the DTH sites as detailed in Section 6.8.1.

Day 28 to Day 32 - After a period of at least 28 days (± 3 days) from the first challenge, subjects will return to the unit and will remain resident in the unit from Day 28 (± 3 days) until at least 72 hours after dosing. Subjects will receive ID injections of PPD as per Section 5.10.1 and Section 6.5.1. A skin biopsy will be taken from one of the DTH sites as detailed in Section 6.8.1. Provided there are no safety issues and there are no clinically significant haematology results on Day 32 (72 hours post dose) the subject will be discharged from the unit.

Days 36 and beyond dependent on dose group - Subjects will attend the unit as an out-patient.

Follow-up - Subjects will return for a follow-up as specified in Table 1

As the follow-up visit is at approximately 6 months (190 days post-dose, as per Table 1), subjects in the 0.15mg/kg cohort do not require an additional post-dose surveillance visit at 6 months and will only attend a surveillance visit at 12 months.

PART B

Psoriasis patients

At the beginning of Cohort 7, sentinel dosing in subjects without pre-existing ADA will occur such that one subject will receive active and one subject will receive placebo. After review of the two sentinel subjects' safety data (Cohort 7) at 48 hours post-dose, an additional 5 active (3 without and 2 with pre-existing ADA) and 2 placebo subjects (1 with and 1 without pre-existing ADA) will be dosed (no more than 2 subjects per day with dosing separated by at least 1 hour).

All subsequent cohorts do not require stratification for pre-existing ADAs.

Once safety data and clinical measures of response (e.g. PASI) at 28 days post-dose have been completed for a minimum of 8 out of 9 subjects within the cohort and all subjects

have completed dosing and the inpatient monitoring until Day 4, the DEC will review the safety data, available PK data and clinical response data, and may consider the available PD data before proceeding to the next dose level.

A study schematic giving an overview of the visits is in Section 3.1.

Screening - Patients will attend screening up to 35 days before dosing.

Day -1 to Day 4 - Patients will attend the unit on Day -1. Two psoriatic plaques (index lesion and biopsy lesion) will be identified as per Section 6.4.4 and Section 6.8.2. The biopsy lesion will be photographed prior to biopsy. Patients will remain resident in the unit for at least 72 hours after dosing. Provided there are no safety issues and there are no clinically significant haematology results at 72 hours post-dose the patient will be discharged from the unit.

Day 8 and beyond - Patients will return to the unit as an out-patient. The biopsy lesion will again be photographed prior to biopsy on Day 29 (as specified in Section 6.8.2).

Follow-up and Surveillance - Patients will have a final combined follow-up and surveillance visit as specified in Table 1 and associated footnote.

3.2.1. Healthy Volunteer to Patient Switching

When the switch to psoriasis patients is made, no further dosing of healthy volunteers will occur. If the understanding of EC50 for LAG-3+ T cells depletion change and/or emerging PK profiles differs markedly from prediction, the maximum dose for healthy volunteers may also change. If GSK2831781 exposure is substantially less than predicted the maximum dose into healthy subjects would be increased to a dose predicted by the emerging pharmacokinetic data to provide a similar exposure as currently predicted at 0.15mg/kg (i.e. a target AUC of ~1800µg*h/mL [See Table 2]). If a dose switch then occurs later, psoriasis cohorts would start one dose higher than the last dose used in healthy volunteers. Details of dose adjustment can be found in Section 5.4.

3.3. Discussion of Study Design

3.3.1. Design Rationale

This study has been designed to be a 2-part study. Firstly, in Part A, a single ascending dose escalation will enrol healthy volunteers and then Part B will enrol patients with psoriasis.

The assessment of GSK2831781 pharmacology in healthy subjects is challenging due to the low numbers of LAG-3+ T cells in the blood of healthy volunteers which makes the monitoring of the depletion of this cell population technically difficult. To circumvent this issue, the last cohort of Part A of the study will employ a DTH model of a PPD intradermal injection, in healthy volunteers previously vaccinated with BCG to induce a DTH skin reaction and an increase of LAG-3+ T cells in the skin. GSK2831781

mediated LAG3+ T cell depletion can then be monitored. Intradermal DTH challenge results in accumulation of LAG-3+ T cells in the DTH site, as measured in biopsies from healthy volunteers previously vaccinated with BCG (GSK unpublished results). The acute synchronous activation of T cells in a DTH challenge site may facilitate the demonstration of GSK2831781 pharmacology by monitoring the LAG-3+ T cell depletion *in vivo*, using a single ascending dose design. By contrast, this T cell activation is likely to be chronic and asynchronous and hence potentially more difficult to detect after a single dose in an immuno-inflammatory condition like psoriasis.

In addition the DTH reaction will be used as a proof of mechanism, to test whether GSK2831781 affects the clinical immune response, as measured by the induration diameter. DTH skin reactions to intradermal injections of specific antigens have been used for decades in clinical studies to measure immune function. DTH reactions are strongly driven by T cells (Ahmed *et al*, 1983) and so are very suited for measuring the proposed mode of action of GSK2831781. Patient and healthy volunteer studies have demonstrated inhibition of the clinical induration response with T cell targeted agents such as cyclosporine, efalizumab, fingolimod and anti-IFNγ mAb (Palestine *et al,* 1985; Amlot *et al*, 1986; Ellis *et al*, 1991; Rentenaar *et al,* 2002; Krueger *et al,* 2008; Boulton *et al*, 2012; Dumont *et al*, 2005). By contrast, patient and healthy volunteer studies have demonstrated that inhibition of the B-cell immune response (Bingham *et al*, 2010) and the innate immune system (anti-Tumor Necrosis Factor alpha [TNFα] mAbs) have little or no effect on clinical DTH response (Moreland *et al,* 2002; Hatemi *et al*, 2007; Joven *et al*, 2006). In addition, LAG-3 T cell depletion with the parental molecule of GSK2831781 - IMP731- has demonstrated inhibition of the tuberculin DTH response in baboons (Poirier *et al, 2*011). Furthermore, a study with PPD ID challenge performed by GSK (GlaxoSmithKline Document Number 2012N150273_03) has demonstrated that the PPD challenge response has the operating characteristics to allow detection of a treatment response as well as showing the presence of LAG-3 cells at the challenge site by IHC (GSK unpublished data). It is therefore hypothesised that a DTH challenge should allow the assessment of both the pharmacology and the mechanism of action of GSK2831781.

A healthy volunteer population is believed to be the appropriate population for the initial (Part A) investigations of GSK2831781 to explore the safety and tolerability in a population not currently receiving concomitant therapeutic treatments, and in whom the impact on immune function could be assessed in a controlled manner (i.e. under controlled challenge conditions). The healthy volunteer population offers the potential to confirm the pharmacology observed in the baboon tuberculin skin challenge study with the parent mAb by using a well described PPD DTH challenge (Vukmanovic-Stejic *et al,* 2006). Furthermore, assessment of the pharmacokinetics and pharmacodynamics across a wide dose range is not practical in a patient population especially given the requirement for the patient population to be treatment free of systemic immunosuppressives, due to the theoretical risk of synergistic or additive immunosuppressive effects, or confounding of the results. In addition the recruitment of healthy volunteers at lower dose cohorts will mean that recruitment of patients with psoriasis will be focused on doses more likely to demonstrate clinical activity. These considerations justify clinical investigations in healthy subjects before dosing patients with psoriasis.

Proof of pharmacology and mechanism will be tested in healthy subjects up to 0.15mg/kg (to limit duration of exposure above the *in vitro* EC50 ADCC killing activity) before switching to psoriasis patients for further evaluation of pharmacology and mechanism (see Section 3.3.2.3 for dose rationale). This dose of 0.15 mg/kg might be altered if emerging PK profiles differ markedly from predictions (See Section 3.2.1). A number of factors support the selection of patients with psoriasis as the population for Part B of the study. It is well described that skin resident T cells are important drivers of psoriasis pathogenesis (Cai *et al,* 2012) and this has been demonstrated therapeutically, with a range of T cell targeted agents. In addition data generated in-house, has shown that LAG-3+ T cells are present in increased numbers in psoriatic plaques from patients with psoriasis and that LAG-3+ cells can be used as a biomarker in a first time in human (FTIH) study to measure depletion of LAG-3+ T cells in psoriatic lesions.

Measuring depletion of LAG-3+ T cells in psoriasis lesional biopsies is anticipated to be more challenging than in a PPD DTH challenge as T cell activation is asynchronous, hence the study in patients will be focused on doses at or above doses that are anticipated to demonstrate pharmacology in healthy volunteers following a DTH challenge.

Test of proof of mechanism in psoriasis patients will be carried out using psoriasis disease endpoints such as lesional plaque biomarkers like epidermal thickness and CD3+ T cell numbers. Clinical response in psoriasis patients will be measured using PASI and PLSS.

Dose escalation in psoriasis patients will be started at one dose higher than the maximum dose investigated in healthy volunteers following a DTH challenge. The overall total number of LAG-3+ cells in the whole body is not anticipated to be markedly different between healthy volunteers with a DTH challenge and patients with mild to moderate psoriasis. However, LAG3+ T cells in skin lesions of psoriasis patients are likely to be higher and that could result in the need for higher doses compared to the dose showing pharmacological activity in healthy volunteers following a DTH challenge. Dose escalation will therefore continue in psoriasis subjects until a significant clinical response is seen (Section 5.4) or the maximum dose is achieved.

Due to the presence of pre-existing ADA in a variable percentage in sera from both healthy and psoriatic human subjects, the initial investigation of GSK2831781 will be carried out initially in ADA negative subjects in Part A of the study to minimise the potential for diluting/confounding a signal of pharmacological or clinical response. However, for GSK2831781 to have development potential, it will need to be used in a mixed ADA population. Therefore, after initial 28 day safety information is available for the DTH cohort at the highest dose for healthy volunteers, an additional cohort of healthy volunteers (without DTH) with pre-existing ADA will be dosed at the same dose level. Subjects in the psoriasis Cohort 7 will be recruited according to the following stratification: 4 ADA negative on active: 2 ADA negative on placebo and 2 ADA positive on active: 1 ADA positive on placebo. Stratification for pre-existing ADAs in subsequent cohorts is not required. Subject follow-up visits will occur when GSK2831781 plasma concentrations are on average around the EC50 value of the *in vitro* depletion assay in human plasma (See Table 1 and Figure 1). This criteria was selected based on the theoretical possibility that GSK2831781 may still be able to deplete LAG-

3+ T cells and affect the immune system, requiring monitoring of infection risk and applying restrictions for immunosuppressives use and travelling to endemic areas. Thus the period between final dosing and follow up will vary depending on the dose received. The time of the follow-up may be revised based on emerging data collected during the study.

In addition, it is not known whether there will be any long term PD effect, beyond the follow-up time at which levels of GSK2831781 would be negligible, for example by prolonged activity due to slow repletion of LAG-3+ cells. Therefore all subjects in Part A will have a 12 month long term surveillance visit for assessment of safety and tolerability, as well as repeat of immune cell phenotyping and other pharmacodynamic assessments, which are still considered clinically abnormal at the follow-up visit. Subjects on lower doses, where follow-up is less than 6 months, will also have an interim 6 month long term surveillance visit. See Section 6.3.5.2 for repeat PPD challenge for subjects with persistent reduction of the DTH challenge.

In Part B, psoriasis patients will be assessed for clinical response to determine long term effect up to Day 121. Emerging pharmacokinetic data from subjects in Part A and in Part B (0.5 and 1.5mg/kg dose cohort) demonstrated a much more rapid clearance of GSK2831781 than previously predicted (see Figure 1 and Table 1). At the highest dose delivered (5mg/kg), levels of GSK2831781 are expected to be below the lower limit of quantitation by Day 85. Subjects in Part B receiving 1.5mg/kg and 5.0mg/kg will therefore have a combined final follow-up and surveillance visit at 6 months (183 days ± 7). If a follow-up visit has already taken place, a final surveillance telephone call will take place as soon as practically possible after the introduction of Amendment 10 (see Table 1). Lifestyle and medication restrictions are not mandated between the follow-up visit and final long-term surveillance visit, but use of any immunosuppressant or experimental medicine during this time, will be assessed for likelihood of confounding results. Subjects with abnormalities at the final study visit that can be reasonably attributed to GSK2831781, will be asked to return for continued surveillance visits until the abnormality has resolved or is no longer clinically significant.

3.3.2. Dose Rationale

3.3.2.1. Human PK prediction

The human PK profile of GSK2831781 was predicted using the monkey pharmacokinetic data collected during the safety assessment study, excluding the PK profiles with suspected immunogenicity. Analysis of the monkey pharmacokinetic data using a 2-compartment PK model provided estimates of PK parameters in this species. In these conditions, the clearance of GSK2831781 in the monkey was 0.000533 L/h or 4.42 mL/day/kg, the volume of distribution was 0.190 L or 65.6 mL/kg and the half-life was approximately 11 days. An allometric scaling approach was used to predict the PK parameters in humans, with powers of unity for volume and 0.75 for clearance. Assuming a bodyweight of 70 kg for humans, the predicted human clearance (CL) is 0.00581 L/h or 1.99 mL/day/kg, the volume of distribution (Vss) is 4.59 L or 65.6 mL/kg and the plasma elimination half-life is approximately 23 days, in the absence of target mediated disposition. Predicted human exposure at the proposed different doses (Figure 1), assuming a 2-hour infusion duration, as well as the comparison with monkey (cross-

reactive species) exposure was determined assuming no target mediated disposition and in the absence of soluble LAG-3 (most conservative case) (Table 2). Due to the small expected amount of target, target mediated disposition is not anticipated to be prominent even at the low doses. Furthermore, internalisation of the complex drug-LAG-3 receptor was found to be limited *in vitro*. The anticipated level of soluble LAG-3 in the plasma is also low.

The proposed dose escalation scheme used a cautious approach in light of the enhanced ADCC mechanism, the nature of the target and the observed neutropenia in monkeys with larger dose increments at the beginning after the starting dose has been tested and when the doses investigated are still low. Lower dose increments are then implemented when getting closer to the maximum dose to be tested in this study.

Table 2 Predicted human exposure versus monkey exposure at 30 mg/kg (cross-reactive species) at the proposed GSK2831781 doses administered IV with emerging actual exposure data and updated predictions also presented

Predicted Human Cmax and AUC			Comparison vs. Monkey (30 mg/kg)			Ratio of predicted human Cmax/EC50*	Updated actual or predicted human Cmax and AUC values based on emerging data**)	
Dose (mg/kg)	Cmax (µg/mL)	AUC (µg*h/mL)	Dose ratio	Cmax ratio	AUC ratio		Cmax (µg/mL)	AUC (µg*h/mL)
0.0003	0.00763	3.61	100000x	171791x	36802x	0.908x	NA	NA
0.0015	0.0381	18.1	20000x	34358x	7360x	4.54x	NA	NA
0.0075	0.191	90.3	4000x	6872x	1472x	22.7x	0.152	1.38
0.04	1.02	482	750x	1288x	276x	121x	0.861	25.4
0.15	3.81	1807	200x	344x	73.6x	454x	3.22	208
0.5	12.7	6023	60x	103x	22.1x	1514x	8.48	903
1.5	38.1	18069	20x	34.4x	7.4x	4541x	40.1	8250
5	127	60232	6.0x	10.3x	2.2x	15136x	95.6†	30700†

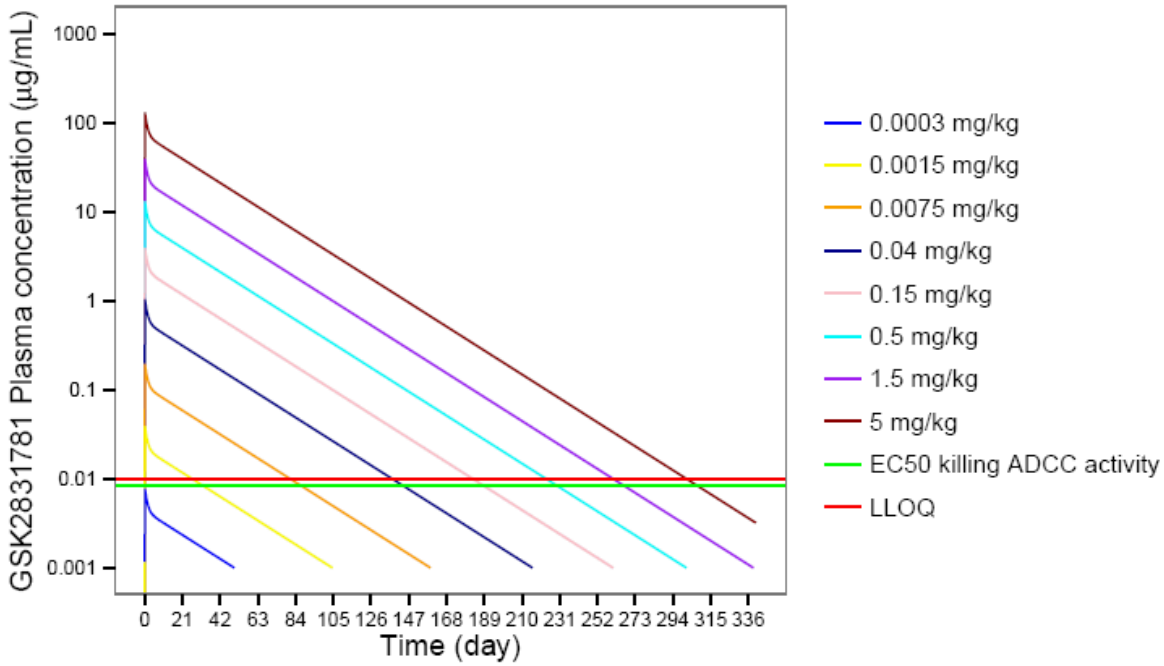
* EC50 = 8.4 ng/mL for depletion of LAG-3 + cells in human plasma

** For doses up to and including 1.5mg/kg calculations are based on actual PK interim data from dose escalation meetings (all concentrations, except for one, were below LLOQ of 10ng/mL after 0.0003 and 0.0015mg/kg, and therefore PK parameters could not be derived). For 5mg/kg dose: Cmax and AUC shown are predicted using a population PK model that was developed with data from 0.0075-1.5mg/kg GSK2831781

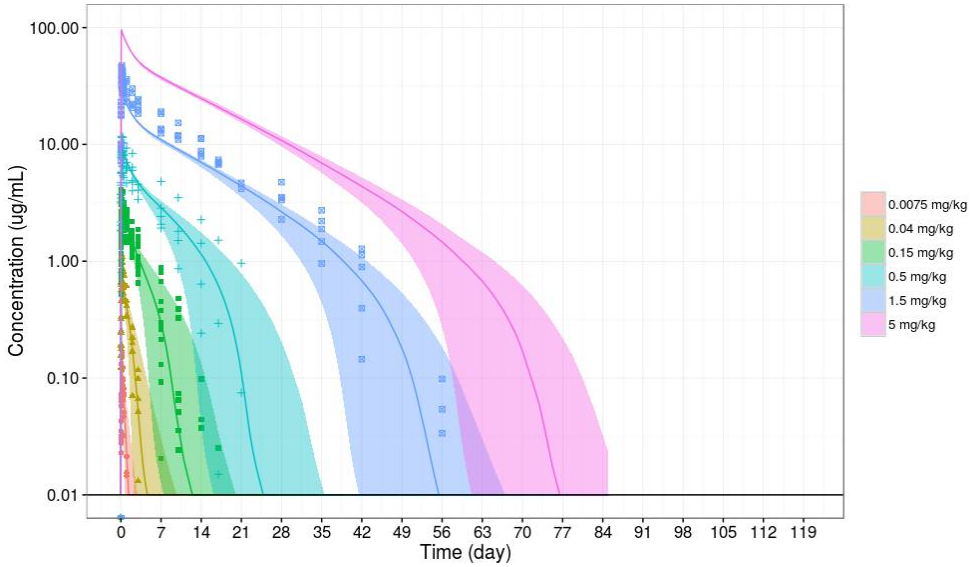
† Predicted values

Figure 1 **Predicted human GSK2831781 PK profiles at the proposed doses administered IV; predictions at beginning of study (a), and after 1.5mg/kg cohort, with preliminary PK data (b)**

a)



b)



Note: symbols are actual subject PK measurements observed during the study. Lines represent median drug concentrations per cohort based on the model predictions, and the shaded areas indicate the 95% confidence intervals of the model predications.

3.3.2.2. Starting dose determination (Minimum Anticipated Biologically Effective Level [MABEL] approach)

In order to investigate the pharmacology aspect of GSK2831781, predicted receptor occupancy (RO) in the plasma of healthy subjects, based on the binding affinity of the drug for its target and LAG-3 receptor concentration in the blood (Ganusov *et al*, 2007) at the predicted Cmax (assuming no target mediated disposition and in the absence of soluble LAG-3) of the proposed doses, were estimated and summarised in Table 3 below.

Table 3 Predicted receptor occupancy in the plasma at Cmax of the proposed GSK2831781 doses

Dose (mg/kg)	Cmax (µg/mL)	RO
0.0003	0.00763	19%
0.0015	0.0381	54%
0.0075	0.191	86%
0.04	1.02	97%
0.15	3.81	99%
0.5	12.7	100%
1.5	38.1	100%
5	127	100%

Furthermore, to incorporate the dynamic aspect, a drug-receptor binding PKPD model was developed incorporating the major elements believed to be involved in the drug disposition process (e.g. target load, number of LAG-3 receptors on T cells, internalisation rate and shedding rate of the LAG-3 receptors (soluble LAG-3)), based on pre-clinical data (*in vitro* and *in vivo*) generated in house, and assumptions supported by published data in the literature. The model simulates the predicted level of receptor occupancy achieved over time and the number of LAG-3+ T cells. Predicted Cmax and receptor occupancy at the proposed GSK2831781 doses are presented in Table 4 below. Prediction incorporates the presence of soluble LAG-3.

Table 4 Predicted receptor occupancy in the plasma at Cmax of the proposed GSK2831781 doses from the drug-receptor binding PKPD model

Dose (mg/kg)	Cmax (µg/mL)	RO
0.0003	0.00707	18%
0.0015	0.0375	52%
0.0075	0.184	84%
0.04	1.05	97%
0.15	3.67	99%
0.5	12.5	100%
1.5	37.7	100%
5	131	100%

Selection of starting dose:

In consideration of the enhanced ADCC mechanism of action of GSK2831781, the novelty of the target and the cell expressing the target (T cells), a starting dose (MABEL) at which the PK profile remains below the *in vitro* EC50 for depleting activity in human plasma was selected. A starting dose of 0.0003 mg/kg is therefore proposed (Figure 1). This dose is predicted to provide 18% receptor occupancy at Cmax in the plasma which is expected to translate into the depletion of approximately 10% of the LAG-3 + T cells in the systemic circulation. The proposed starting dose is in the same range as the starting dose investigated by another competitor ADCC enhanced molecule (e.g. siplizumab 0.0004mg/kg) albeit with different target. The proposed starting dose of 0.0003 mg/kg is 100000-fold lower than the 30 mg/kg dose investigated in the GLP toxicity study in monkey and the predicted AUC 36800-fold lower than the exposure observed at that dose. The predicted AUC would be 4081-fold lower than the exposure at the highest dose (3mg/kg) without neutropenia in the investigative study P70263N.

3.3.2.3. Assessment of GSK2831781 pharmacology in healthy volunteers

It is hypothesised that LAG-3+ T cells drive the clinical DTH response in humans, therefore an adequate depletion of LAG-3 expressing T cells by GSK2831781 should translate in the reduction of DTH induration. There is evidence in the literature that molecules with enhanced ADCC mechanism show pharmacology at very low doses (i.e. 0.03 mg/kg and below (benralizumab [Busse *et al,* 2010])).

To assess the pharmacology of GSK2831781 in healthy volunteers and confirm the findings in the baboon study conducted with the parent molecule IMP731 where a depletion of peripheral LAG-3 expressing T cells was associated with an inhibition of a DTH response (Poirier *et al*, 2011), a DTH challenge will be conducted at the 0.15 mg/kg proposed dose.

The difference in potency between the parent molecule IMP731 used in the baboon experiment and GSK2831781 using EL4 cells expressing human LAG-3 incubated with human peripheral blood mononuclear cells (PBMC) was about 20-fold in favour of GSK2831781. Assuming the same fold difference would also apply in the baboon *in vivo*, as inhibition of the DTH response was observed at a Cmax of 2.5 µg/mL with IMP731 (highest Cmax observed at 0.1 mg/kg), it could be reasonable to assume that an effect on the PPD challenge could be observed at a concentration around 0.125 µg/mL (2.5/20) with GSK2831781. At the proposed highest dose of 0.15 mg/kg in healthy subjects, human predicted concentrations are expected to be above 0.125 µg/mL for 98 days.

From the drug-receptor binding PKPD model adjusted for the DTH challenge component, a dose of 0.15 mg/kg is predicted to confer at least on average 80% RO in the skin over approximately 28 days which is expected to translate into a reduction in the DTH response.

There will be a maximum dose for healthy subjects of 0.15mg/kg (dose could be altered dependent on emerging PK data and/or PD data), to limit the duration of exposure above the *in vitro* EC50 ADCC killing activity (where there are lifestyle and medication restrictions), to no more than approximately 6 months (See Section 3.2.1 and Section 5.4 Planned Dose Adjustments).

3.3.2.4. Potential therapeutic dose determination

From the drug-receptor binding PKPD model, considering the presence of soluble LAG-3 and a skin compartment, doses in the range of 0.5-2 mg/kg, depending on the blood:skin ratio assumed for a monoclonal antibody and the body surface area involved with psoriasis, are anticipated to confer at least 90% RO in the skin over 28 days (an acceptable dosing interval). These doses would also provide a concentration in the skin above the EC90 from the assay depletion of LAG-3 + cells in human plasma. The maximum dose to be investigated in this study will not exceed 5 mg/kg. The decision to progress up to 5 mg/kg will be based on the emerging safety, tolerability, pharmacokinetic, pharmacodynamic data and clinical activity (PASI score and PLSS). If significant clinical activity is seen (see Section 5.4 Planned Dose Adjustments), but with no safety and tolerability signals, dose will be increased to one higher level than the dose with clinical activity, but not beyond the maximum 5mg/kg dose. The maximum dose is based on the predicted therapeutic dose range of 0.5-2 mg/kg in psoriasis patients derived from the receptor binding PKPD model, while also taking into account the maximum dose that can be delivered every 4 weeks by one subcutaneous injection and to also allow a fold factor above it to gather additional safety information.

The maximum dose proposed in this study is 6-fold lower than the 30 mg/kg dose investigated in the GLP toxicity study in monkey and the predicted AUC 4.3-fold lower than the exposure observed at that dose. The maximum dose proposed would be 1.7-fold higher than the dose (3 mg/kg) without neutropenia in the investigative study P70263N and the AUC 2-fold higher than the AUC at that dose. Although the maximum proposed dose exceeds the highest dose and exposure without neutropenia findings in the investigative monkey study, it will only be assessed providing the extensive within study monitoring has shown no clinically relevant safety findings at the lower doses.

3.4. Risk Management

Consistent with GlaxoSmithKline guidance for early phase studies, GSK2831781 will be administered in an in-patient setting (with sufficient overnight facilities) with appropriate monitoring.

In order to minimise the risk of the initial human administration of GSK2831781 monoclonal antibody, at the beginning of each cohort, 1 subject will receive GSK2831781 and 1 subject will receive placebo. After the GSK medical monitor and investigator have reviewed the safety data up to 48 hours, the remaining subjects (where appropriate) from that cohort will be dosed (see Section 3.2). Once safety data and clinical measures of response (e.g. DTH induration for healthy volunteers, PASI for psoriasis patients) at 4 weeks post-dose have been completed for all subjects in each cohort (Part B: minimum 8 of 9 subjects, but with all subjects completing 72 hours post dose), the DEC and the investigator will review the data along with the available PK data before proceeding to the next dose level. In Part A and B of the study, the in-house safety monitoring will be at least 72 hours after dosing.

A number of potential risks have been identified. Details of these risks and the proposed strategy to mitigate/monitor these risks are described in Table 5.

Table 5 Summary of Key Issues, Their Impact and Strategy to Mitigate Risk

Potential risk	Summary of data	Impact eligibility criteria	Strategy-monitoring criteria
IP risk			
Infusion-reaction/hypersensitivity	The first study in humans will be conducted by IV administration.	Subjects will be excluded if history of severe allergic reaction. (Exclusion #4) Initial cohorts (1-5) will exclude subjects with pre-existing ADA (Exclusion criteria #8)	Subjects will be in a phase 1 unit and closely monitored for 72 hours post dosing. IV doses will be administered for 2 hours. However, dosing duration may be modified based on safety data with the approval of the PI and sponsor. Guidelines for monitoring relevant adverse events encompassing hypersensitivity, angioedema and anaphylaxis and for management of acute anaphylactic shock and minor allergic episodes will be in place at investigational sites. Study sites will include facilities and expertise for emergency care/resuscitation, including access to hospital and Intensive Care Unit (ICU). Pre-medications are permitted at investigator's discretion (Section 6.3.4).
Cytokine release	Hyper-immune activation leading to activation of the innate immune system is only a theoretical safety concern, as there is no *in vitro* and *in vivo* evidence of cytokine release associated with LAG-3+ and T cell depletion mechanism, in the presence or absence of pre-existing ADA.	Initial cohorts (1-5) will exclude subjects with pre-existing ADA (Exclusion criteria #8)	Study sites will include facilities and expertise for emergency care/resuscitation, including access to hospital and ICU. Monitoring for clinical symptoms associated with cytokine release such as fever, nausea, chills, hypotension, tachycardia, asthenia, headache, rash, tongue and throat swelling, and dyspnea. Standard safety haematology and clinical chemistry assessments to include CRP will be performed. In addition limited cytokine analysis will be performed within 24 hours if any clinical signs suggest cytokine release syndrome (See Section 6.3.7)

Potential risk	Summary of data	Impact eligibility criteria	Strategy-monitoring criteria
Type III Hypersensitivity (Immune complex deposition in kidney, liver, skin)	Reactions due to immune complexes formed from pre-existing ADA and GSK2831781 are a theoretical risk. Risk is assessed as low as pre-existing ADAs are predominantly of low titre.	Initial cohorts (1-5) will exclude subjects with pre-existing ADA (Exclusion criteria #8)	Targeted clinical monitoring will include physical examination, urinalysis to detect haematuria and proteinuria, and clnical chemistry to monitor renal and liver function.
Risk of infection	No specific studies have been conducted in nonclinical species to investigate the effect of GSK2831781 on response to viral or bacterial infection. A significant proportion of newly activated T cells express LAG-3, and therefore T cell proliferation upon encounter with an infectious agent may be inhibited by GSK2831781 if exposure is at the same time. However, it has been demonstrated that in healthy volunteers only a small proportion of central memory T cells express LAG-3, so there is low risk of eliminating central memory of anti-infectious immune response against future encounter.	Subjects to be screened for HIV, Hep C and B prior to enrolment and excluded if positive. (Exclusion #13 and 15) Subjects with a history of tuberculosis (TB) (screening for latent infection included) or other relevant chronic diseases will be excluded. (Exclusion #2 and 7) Healthy volunteer subjects will need to be vaccinated against infectious agents (Inclusion #8). Psoriasis subjects: investigators are expected to assess vaccination status, according to local and/or national guidelines for patients with psoriasis during screening. Subjects with an acute illness or evidence of significant active infection, such as fever, will not be allowed on the study. (Exclusion #7)	Subjects will be advised not to travel to infection endemic countries up to the follow-up visit. Serology for Cytomegalovirus (CMV), and Epstein-Barr Virus (EBV) will be tested at baseline. Samples for CMV, EBV, Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) will be taken and stored at baseline. If signs or symptoms consistent with viral reactivation occur during the study further samples will be taken and analysed together with the baseline sample. Other immunosuppressive concomitant medications (See Section 5.14 are excluded up to follow-up (exposure above *in vitro* EC50 level for LAG-3 depletion) though low dose background therapies may be allowed depending on the immunosuppressive risk at the time of FTIH. Close monitoring of subjects for infections to follow-up visit with targeted surveillanceas specifed in the protocol. Subjects will not be allowed to receive live (attenuated) vaccine within the 4 weeks prior to Day 1 or during the study until the end of follow-up. A biomarker approach will be used to measure the duration of action of GSK2831781 in inhibiting the response to PPD challenge repeated at 3 month

Potential risk	Summary of data	Impact eligibility criteria	Strategy-monitoring criteria
			intervals until recovery of response, in healthy volunteers.
Risk of autoimmune-like reactions	Theoretical risk only. There are publications demonstrating a small subset of T-regulatory cells being LAG-3 positive.	Excluded: patients with history of other immune disorders. (Inclusion #3 and Exclusion #24) Excluded: patients with any acute or chronic clinical, even mild, GI upset. (Exclusion #6)	Targeted clinical monitoring of possible autoimmune-reactions, especially GI tract and thyroid diseases will be conducted at every visit. See Section 6.3.6.
Neutropenia	In the 1 month GLP toxicology study clinically significant decreases in neutrophil count, which were considered adverse, were observed in 2/12 monkeys which were administered 100 mg/kg/week SC or IV. Including separate single and repeat dose pharmacology studies, decreases in neutrophil count of a similar magnitude occurred in 2/15 animals at 30 mg/kg but not in 7 animals administered at 3 mg/kg.	Exclude subjects with neutrophils below normal range. (Exclusion # 5)	Neutrophil count is readily measurable in the clinic and both trends and changes outside normal range will be monitored as part of laboratory safety assessments. Subjects developing neutrophil counts <1.5x10^9/L will be followed up until levels are not clinically significant. Study stopping criteria are also in place (see Section 5.5). Supportive therapy (growth factors, transfusions, antibiotics, monitoring and active treatment of infections) may be provided if neutropenia is seen.
Hepatotoxicity	Minimal to mild Kupffer cell activation at doses >30mg/kg in primates.	Only subjects with liver chemistry results within the limits specified in the inclusion and exclusion criteria will be included (Inclusion #10; Exclusion #10, #25)	Standard GSK liver stopping applied for dosing new subjects, and monitoring guidance (See Section 5.5 and Section 5.6.1)
PPD ID risk			
Potential events associated with PPD ID injection: 1. Systemic Hypersensitivity (Anaphylaxis) for PPD 2. Immediate local hypersensitivity (ILH) after secondary intradermal	1 and 2 likely to occur <30 minutes post immunisation. 1. Systemic anaphylaxis' is characterised by any of the following: difficulty in breathing, stridor, hoarse voice, flushing, wheezing, rash, itching,	Subjects with a prior medical history of anaphylaxis, severe adverse reaction to vaccines, or history of sensitivity to any of the study challenge agents, or components thereof or a history of drug or other allergy will be excluded if in the opinion of the	Subjects will be observed for 30 minutes after the administration of PPD at the study unit at the investigators discretion. The study will be conducted in a unit where personnel is trained in immediate management of anaphylaxis Immediate assessment and

Potential risk	Summary of data	Impact eligibility criteria	Strategy-monitoring criteria
immunisation with PPD 3. Excessive DTH 4. Necrotic skin reaction	swelling of the lips or tongue, hypotension, confusion, diarrhoea). 2. ILH post challenge is defined as a wheal that is at least 5 mm larger than the original bleb 3. Excessive DTH: 30 mm or larger induration between 24-48 hours associated with inflammation and itching. Vesiculation is possible. Pain is possible with large reactions but significant pain is unlikely. 4. Necrotic skin reaction: characterised by severe pain, swelling, induration and possibly haemorrhage and necrosis.	investigator or GSK Medical Monitor, it contraindicates their participation.	management will be conducted according to the current guidelines from the Resuscitation Council (UK) on Emergency Treatment of Anaphylactic Reactions. Any subject requiring treatment for suspected anaphylaxis will be transferred to an acute medical unit for further observation as judged necessary by the medical team in charge of the clinical emergency situation Subjects will be advised to seek immediate medical attention if they develop these symptoms after leaving the unit and they will be issued with an information leaflet that details what these symptoms are. Any subject that exhibits an ILH after secondary ID immunisation can be reassured that their symptoms are likely to settle within a few hours, but if they consider this unacceptable they may be offered antihistamines at the discretion of the attending physician. Subjects receiving antihistamines will be continued in the trial but note will be made of their antihistamine use at the analysis stage. An excessive DTH or necrotic skin reaction in extreme cases and at the discretion of the attending physician treatment with glucocorticoids could be offered according to best clinical practice.
Procedure risk			
Punch Biopsy	Possible risks of the procedure are pain for the subject, a small infection risk after the Punch Biopsy and possible scarring, these will be minimised considerably by following the study procedures.	Subjects with keloids or a history of keloids will be excluded. (Exclusion #19 and 24)	Three mm (DTH) and 6 mm (Psoriasis plaques) punch skin Punch Biopsies will be performed under a local anaesthetic to reduce any discomfort for the subjects. The small risk of infection after Punch Biopsy will be minimised by cleaning of the site before Punch Biopsy and the addition of a steri-strip if required (or

Potential risk	Summary of data	Impact eligibility criteria	Strategy-monitoring criteria
			similar) on top of the Punch Biopsy site. For the 3mm biopsy a minute scar will be visible and will be minimised. Stitching and a small scar will occur for the 6mm biopsy.
Vaccination	As per Boostrix-IPV and/or M-M-RVAXPRO or equivalent SPC.	Subjects in Part A who are ineligible due to lack of history of vaccinations for diphtheria, tetanus, pertussis, measles, mumps or rubella, who consent to vaccination may only be vaccinated in accordance with the restrictions for these vaccines in the SPC. If such subjects are unable to be vaccinated, they will be ineligible for the study.	As per Boostrix-IPV and/or M-M-RVAXPRO or equivalent SPC.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 67 subjects will be enrolled to complete dosing and critical assessments. The subject numbers will be split to approximately 40 healthy volunteers and 27 patients with psoriasis.

Additional subjects/cohorts may be enrolled between the 0.0003mg/kg and 5mg/kg doses to allow for evaluation of additional dose levels but they will not exceed 5mg/kg (see Section 5.4).

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor in consultation with the investigator.

4.2. Eligibility Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigators Brochure [GlaxoSmithKline Document Number 2013N175515_01 and GlaxoSmithKline Document Number 2014N201916_00].

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Part A males aged between 18 and 65 years of age and Part B males and females aged between 18 and 75 years of age inclusive at the time of signing the informed consent.
2. Part A: A body weight ≤120 kg and BMI within the range 19 – 32 kg/m2 (inclusive). For healthy volunteer subjects participating in Germany the BMI must be within the range of 19 – 30 kg/m2 (inclusive). Part B: BMI within range 19-35 kg/m^2 (inclusive).
3. **Part A only:** Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and 12-lead ECGs. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the Investigator in consultation with the GSK Medical Monitor, if required, agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
4. **Part A DTH cohort only:** Subjects with a history of BCG vaccination as evidence by either:
   - A BCG scar and verbal confirmation of BCG vaccination
   - Or documented medical history of a BCG vaccination with or without a BCG scar
5. **Part B only:** Subject has psoriasis covering BSA ≥3% as assessed at Screening and Day -1.
6. **Part B only:** Subject has had a confirmed diagnosis of chronic plaque-type psoriasis (without recent documented flare within 30 days prior to screening) for at least 6 months.
7. **Part B only:** Subject has at least 2 stable plaques assessed at Screening and Day -1. One of a suitable size and in a site suitable for repeat biopsy, and one for index lesion PLSS scoring. Both must have a PLSS lesional score of ≥2 for the induration component (moderate or above), ≥1 for erythema and scaling with a total score of ≥5. The biopsy lesion must not be on the face, groin or scalp and must be protected from the sun.
8. Part A only: Subjects with a history of vaccination for Tetanus, diphtheria, measles, pertussis, mumps and rubella.
9. **Part B only:** A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test at screening and negative urine hCG test at Day -1 for FRP), not lactating, and at least one of the following conditions applies:
   a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
  - Documented tubal ligation
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Hysterectomy
  - Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to use a barrier method (male condom or female diaphragm) plus to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 5) from 28 days prior to the first dose of study medication and until completion of the follow-up visit.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. The investigator or designee should remind the subjects of the need to comply with these requirements approximately monthly, either at study visits or by telephone call until the follow-up visit.

10. ALT, alkaline phosphatase and bilirubin ≤ 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
11. Based on single or averaged QTc values of triplicate ECGs obtained over a brief recording period:

    -QTcF < 450 msec
12. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form, and has provided written informed consent.

4.2.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Received live vaccine(s) (attenuated or recombinant) within 4 weeks of Day 1 or plan to receive a live vaccination during the study until follow-up.
2. Subjects who have history of tuberculosis or have close family members with confirmed MTB infection or who are positive at screening by Quantiferon testing.

3. Subject is unable to abstain from travelling to areas with high endemic rates of infectious diseases until the end of the follow up period.
4. A medical history of severe allergic reaction, angio-edema, anaphylaxis or immunodeficiency.
5. Subjects with neutrophil results below the normal range at screening and baseline.
6. Subjects with any clinical, even mild, GI upset such as, but not limited to, diarrhea or abdominal cramping during the previous week before dosing, as well as history of more chronic GI upset, e.g. IBS
7. Current evidence of ongoing or acute infection within 3 months prior to the first dose of study drug, such as:
    - Serious local infection (e.g. cellulitis, abscess)
    - Systemic infection (e.g. pneumonia, septicaemia, TB)
8. **Part A (only cohorts, 1-4 without DTH challenge, and DTH cohort 5) only:** Subjects who test positive for pre-existing ADA to GSK2831781 at screening.
9. History of malignancy.
10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). **Part A only:** Subjects with an aspartate aminotransferase and/or gamma glutamyltransferase level above the upper limit of normal at screening and/or baseline will be excluded.
11. History of regular alcohol consumption within 6 months of the study defined as:

    an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
12. History of sensitivity to any of the study medications or PPD challenge agent, or components thereof or a history of drug (or IgG therapeutic antibodies) or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.
13. A positive pre-study Hepatitis B surface antigen or Hepatitis B core antibody, or positive Hepatitis C antibody result within 3 months of screening.
14. A positive pre-study drug/alcohol screen.
15. A positive test for HIV antibody.
16. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period.
17. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
18. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

19. **Part A (only cohort with DTH challenge) only:** Presence of tattoos, naevi or other skin abnormalities such as keloids (or a history of keloids) that may, in the opinion of the investigator, interfere with DTH assessments.
20. **Part A (only cohort with DTH challenge) only:** Use of nicotine patches on the arm at screening that would interfere with the injection sites.
21. **Part A (only cohort with DTH challenge) only:** Subjects participating, within seven days of screening, in recreational sun-bathing, or the use of a sun-bed, on the area of the skin from the wrist to the shoulder (inclusive).
22. **Part A only:** Use of prescription drugs or non-prescription drugs, if in the opinion of the investigator (in consultation with the GSK medical monitor), the medication will interfere with the study procedures or compromise subject safety.
23. **Part A only:** Subjects must not currently be taking any of the following: topical steroids on the arms, oral or systemic steroids or any other immune-modulators (the washout period will be determined, on a case by case basis, by the investigator in consultation with the GSK medical monitor).
24. **Part B only:** History of significant cardiac, endocrinologic, haematologic, pulmonary, metabolic, renal, hepatic, immunologic (excluding psoriasis and psoriatic arthritis), urologic, neurologic, dermatologic (except psoriasis), psychiatric or gastrointestinal conditions that, in the opinion of the investigator and/or GSK medical monitor, places the subject at unacceptable risk.
25. **Part B only:** Clinically significant abnormalities of laboratory assessments (not related to disease) as judged by the investigator and/or GSK medical monitor.
26. **Part B only:** All systemic psoriasis medications, including psoralen long-wave ultraviolet radiation treatments, or other systemic immunosuppressives, are not allowed within 5 half lives prior to Day -1 (Methotrexate and cyclosporin are not allowed within 8 weeks of Day -1; Psoralen long-wave UV is not allowed within 4 weeks of Day-1). Subjects should not be included if the investigator considers that the subject is at high risk of requiring rescue with prohibited medication (see Section 5.14.2.3) for duration of study up to follow-up. This assessment should be based on current disease activity or a history of frequent and/or severe flares requiring systemic immunosuppression.
27. **Part B only:** The use of single treatment phototherapy (ultraviolet B or self treatment with tanning beds) is not allowed within 14 days prior to Day -1.
28. **Part B only:** The use of topical therapies for psoriasis are not allowed with 7 days prior to Day -1 on the index lesion or biopsy plaque.
29. **Part B only:** Previous treatment with anti-TNF/IL-12/IL-23 or any other monoclonal antibodies is not allowed within 12 weeks prior to Day -1.
30. **Part B only:** Patients that require narrow therapeutic index medications from Screening to Follow-up.
31. Vulnerable subjects (e.g. person kept in detention).

32. Subjects who are not able to understand and communicate in the native language of the country where the study is conducted.

33. Subjects who work for the Sponsor or CRO.

4.3. Lifestyle Restrictions

4.3.1. Dietary requirements

Subjects must fast overnight before screening for the glucose blood test. If the subject has not fasted then they may return before baseline to have the glucose blood test taken.

4.3.2. Alcohol

Subjects will abstain from alcohol for 24 hours prior to each visit to the clinical unit. Additionally they should refrain from alcohol for 7 days after dosing. Thereafter an average weekly intake of <21 units alcohol.

4.3.3. Activity

Part A and B: Subjects will abstain from strenuous exercise for 48 hours prior to dosing and prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

Part B: Subjects must not sunbathe or use a tanning device (e.g. sunbed or solarium) whilst taking the study medication and until Day 43. Subjects will be advised that when they are outdoors they should wear protective clothing (e.g. sun hat, long sleeves) and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors.

4.4. Screen and Baseline Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including, but not limited to, Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

4.5. Withdrawal Criteria and Procedures

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons.

Refer to Section 5.4 or planned dose adjustment and Section 5.5 for subject specific dose adaptation including Liver Chemistry and QTc.

Liver chemistry threshold monitoring criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). See Section 5.6.1 for details.

4.6. Subject Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit (which will be a combined follow-up/surveillance visit or a surveillance telephone call if the subject has already completed Follow Up, as specified in Table 1).

5. STUDY TREATMENT

5.1. Investigational Product and Other Study Treatment

	Study Treatment		
Product name:	GSK2831781	Diluent	Placebo
Formulation description:	50mM Na Acetate, 51mM NaCl, 0.05mM EDTA, 0.02% Polysorbate 80, and 57mM Arginine at pH 5.5	0.9% NaCl solution containing 0.015% PS80	Commercial saline solution
Dosage form:	Solution	Solution	Commercial saline solution
Unit dose strength(s)/Dosage level(s):	100mg/mL SD of 0.0003-5mg/kg	N/A	Saline Placebo
Route/ Administration/ Duration:	IV over approximately 2 hours	N/A	IV over approximately 2 hours
Dosing instructions:	Infuse over approximately 2 hours via an infusion pump	N/A	Infuse over approximately 2 hours via an infusion pump
Physical description:	Clear or opalescent, colourless, yellow to brown liquid that is essentially free from particles.	Clear, Colourless to pale yellow, sterile solution	Commercial presentation
Manufacturer/ source of procurement:	GSK Parma, Italy	GSK Parma, Italy	Supplied by site

5.2. Challenge Agents

	Challenge Agent
Product name:	Challenge agent PPD
Formulation description:	Tuberculin PPD RT23
Dosage form:	Solution
Unit dose strength(s)/Dosage level(s):	ID 2TU / 0.04μg ID 10TU / 0.2μg
Route/ Administration/ Duration:	Part A DTH cohorts: 1x ID injection/single dose

	Challenge Agent
Dosing instructions:	Part A DTH cohorts: 1 x ID injection left forearm 1 x ID injection right forearm Followed by 4x ID injection 28 days later: 2 x ID injection left forearm 2 x ID injection right forearm
Manufacturer/ source of procurement:	Staten Serum Institut

5.3. Treatment Assignment

Subjects will be assigned to receive GSK2831781 or placebo in accordance with the randomisation schedule generated by Clinical Statistics, prior to the start of the study, using the validated internal software RandAll NG.

The randomisation schedule will be generated to account for the sentinel subjects. Where the first two subjects dosed for any given cohort will be randomised so that 1 subject will receive GSK2831781 and 1 subject will receive matching placebo. In Part B, the sentinel subjects will be required to be ADA negative and subsequent subjects will be stratified by ADA status (ADA negative or ADA positive) as applicable (see Section 3.1.2).

Eligible subjects will receive a unique subject number which will be assigned in chronological order. Once a subject number has been assigned to a subject, it cannot be reassigned to another subject.

Each subject scheduled to receive study drug will also receive a treatment allocation number when randomised. The treatment number will indicate if the subject is to receive the scheduled dose of GSK2831781 or placebo at each dosing occasion.

A description of the projected regimens based on available data is provided in the table below:

Regimen	Description	Ratio (Active:Placebo)
A	0.0003mg/kg GSK2831781 IV single dose	1:1
B	0.0015mg/kg GSK2831781 IV single dose	1:1
C	0.0075mg/kg GSK2831781 IV single dose	3:1
D	0.04mg/kg GSK2831781 IV single dose	3:1
E	0.15mg/kg GSK2831781 IV single dose	1:1 for HV DTH (ADA-) 3:1 for HV No DTH (ADA +)
F	0.5mg/kg GSK2831781 IV single dose	4:2 for psoriasis (ADA-) 2:1 for psoriasis (ADA+)
G	1.5mg/kg GSK2831781 IV single dose	6:3 for psoriasis
H	5mg/kg GSK2831781 IV single dose	6:3 for psoriasis
P	Placebo IV single dose	N/A

5.4. Planned Dose Adjustments

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum single dose will not exceed 5 mg/kg (to ensure about a 2.2 fold ratio with regard to the exposure (AUC) observed at 30 mg/kg in the cynomolgus monkey GLP toxicity study). The maximum dose exceeds the highest dose without neutropenia findings in the investigative monkey study, but will only be assessed providing the extensive within study monitoring has shown no clinically relevant safety findings at the lower doses.

Safety/tolerability data monitoring and the decision to proceed to the next dose level of GSK2831781 will be made by the DEC, consisting of the Principal Investigators (or appropriate designees), GSK Medical Monitor, GSK Study Team Leader (either Clinical Investigator Lead [CIL] and/or Operations and Science Lead [OSL]), GSK CPMS representative, a GSK GCSP representative, GSK Statistician and an independent GSK expert on FTIH studies. The DEC may also call on *ad hoc* internal/external members with specific expertise. DEC meetings will have open and closed sections. During the open section, the Principal Investigators will be present to provide additional information on patient assessment if required, and the data will be blinded. In the closed section, the Principal Investigators will not be present and if required data will be presented in an

unblinded manner. A DEC charter will be agreed between GSK and the principal investigator before the first DEC meeting.

For healthy volunteer cohorts, once safety data up to 28 days post-dose has been collected in all subjects for that cohort, the DEC will review the safety/tolerability data (including trends in neutrophil counts), the available PK data and for the DTH cohort, the clinical DTH response (induration diameter), before proceeding to the next dose level (See Section 3.2.1). The DEC may also consider available biomarker/PD data (including immune cell phenotyping) in considering the escalation. Outcomes of DEC review include escalation to the next dose, stopping the escalation, switching escalation to psoriasis patients, altering the next dose level, altering the subject numbers in a cohort. If emerging PK data departs from prediction, outcomes may also include continuing dose escalation in healthy volunteers beyond the maximum of 0.15mg/kg up to a maximum duration of exposure above EC50 of approximately 6 months, if there are no other safety/tolerability findings or reduction of DTH response (See Section 3.2.1).

For the psoriasis cohorts, once safety data and clinical measures of response (PASI and PLSS) at 28 days post-dose have been completed for a minimum of 8 out of 9 subjects, and all subjects have completed dosing and the inpatient monitoring until Day 4, the DEC will review the safety/tolerability data (including trends in neutrophil counts), the available PK data and the clinical response (PASI and PLSS) before proceeding to the next dose level. The DEC may also review the other measures of clinical response and available biomarker/PD data (including immune cell phenotyping) in considering the escalation. Outcomes of DEC review include escalation to the next dose, stopping the escalation, altering the next dose level or altering the subject numbers in a cohort. Definition of significant change in PLSS and/or PASI or strong trends in clinical response, leading to stopping of dose escalation at same or one higher dose will be discussed in the DEC Guidance/Charter document.

Apart from stopping of the dose escalation, alterations to the planned dose levels and intervals between dose levels will be limited to the following. Other changes will require a substantial amendment:

- Reduction in the dose increment to the next dose level (based on higher exposure than predicted and/or safety data of clinical significance).
- Introduction of an additional dose level cohort between the current and next planned dose level (based on higher exposure than predicted and/or safety data of clinical significance).
- Replacement of the highest dose level in psoriasis cohorts with a lower dose than the scheduled starting dose for psoriasis cohorts

For both healthy volunteers and psoriasis patients, the DEC will ensure that data from the ongoing cohort as well as accumulated data from all previous cohorts is reviewed. Decisions may be modified if subjects on placebo have findings. The dosing schedule may also add cohorts to evaluate 2 additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

5.5. Dose Adjustment/Stopping/Monitoring Criteria

If one or more subject experiences an Serious Adverse Event (SAE) that can be reasonably attributed to GSK2831781, the dose escalation will be halted and no further subject will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the DEC, (which must include the GSK medical monitor), relevant GSK personnel, and with the Ethics Committee and Regulatory Agency will then take place. If following the safety review a decision is made to restart dose escalation, this may be allowed after approval of a substantial amendment.

If two or more subjects experience a severe or significant non-serious AE that can be reasonably attributed to GSK2831781, the dose escalation will be halted and no further subject will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the DEC (which must include the GSK medical monitor), relevant GSK personnel, and with the Ethics Committee and Regulatory Agency will then take place. If following the safety review a decision is made to restart dose escalation, this may be allowed after approval of a substantial amendment.

Events of note across the cohorts (unless otherwise stated) that will also result in the study being temporarily halted and reviewed by the DEC include:

NOTE: If any of the below occur in the single active subject in the first 2 healthy volunteer cohorts the study will also be reviewed by the DEC.

1. Infusion Reaction/Hypersensitivity: Infusion reactions requiring termination of infusion/dosing in 2 or more subjects.
2. Cytokine Release Syndrome (CRS): Evidence of CRS leading to moderate clinical symptoms in 2 or more subjects, based on modified NCI-CTC Criteria (see Section 12.3, Appendix 3). Symptoms include: Headache, fever, chills/rigors, nausea, vomiting, diarrhoea, arthalgia, myalgia, hypotension.
3. Neutropenia (the following must be confirmed by repeat samples):
    - If one subject experiences neutrophil count $<1.5 \times 10^9$/L for >7 days for the first 28 days for the first 2 healthy volunteer cohorts.
    - If one or more subjects experiences neutrophil count $<0.5 \times 10^9$/L for >7 days
    - If 2 or more subjects experience neutrophil count $<0.5 \times 10^9$/L for <7 days.
    - If 2 or more subjects experience clinically significant neutropenia for >7 days.
4. Infections: If one or more subjects experiences an infection SAE, regardless of initial assessment of causality.
5. Liver event in one or more subjects:
    - a Hy's law liver SAE as characterised by ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin*); or ALT ≥ 3xULN and INR** > 1.5 (*serum bilirubin fractionation should be performed if testing is available; if unavailable, withdraw subject (if ALT ≥ 3xULN and total bilirubin ≥ 2xULN) and measure urinary bilirubin via dipstick.** INR testing not required per protocol and the

threshold value does not apply to subjects receiving anticoagulants). The study will be also put on hold if one subject experiences

- ALT ≥ 5xULN.
- ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
- ALT ≥ 3xULN persists for ≥ 4 weeks.

QTC criteria: if 2 or more subjects demonstrate

- QTcF > 500 msec or,
- QTcF increase >60 msec from baseline

This assessment is to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTc values of the 3 ECGs to determine whether the subject should meet these criteria.

If safety findings are noted in the active subject in cohorts with a single active subject, the cohort may be expanded to a maximum cohort size of 6:3 (active:placebo) or the escalation stopped.

To enable appropriate investigation of potential issues, the DEC will review data prior to continued dosing, if any of the following occur:

1. PPD challenge; if one or more subjects experience persistent reduction of the PPD challenge for ≥3 months after rechallenge.
2. Moderate or severe adverse events of the same nature (including infections) in 2 or more subjects in the same cohort which can be reasonably attributed to dosing with GSK2831781, within 28 days of dosing (Appendix 4 and specific criteria at individual subject level in Section 5.6).
3. For a cohort of patients with psoriasis, if 2 or more subjects in a dose cohort experience a worsening of their psoriasis symptoms which can be reasonably attributed to dosing with GSK2831781, which requires treatment with prohibited concomitant medication.

The above criteria will apply regardless of whether pharmacokinetics are less than the PK stopping criteria described in Section 5.7 and every effort will be made to take a blood sample at the time of the event for pharmacokinetics analysis in the presence of any of the above events.

5.6. Subject Specific Dose Adjustment/Stopping Safety/Monitoring Criteria

5.6.1. Liver Chemistry Monitoring Criteria

Liver chemistry threshold monitoring criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

In addition to any liver safety criteria (Section 5.5, bullet point 5), subjects meeting the following liver chemistry criteria will have enhanced monitoring:

- ALT ≥ 3xULN

NOTE: Refer to Appendix 1 for details of the required assessments if a subject meets the above criteria**.**

5.6.2. QTc Monitoring Criteria

For subjects that meet either criterion below, additional monitoring will be required. The same QT correction formula, QTcF, should be used to determine inclusion and enhanced monitoring for any individual subject throughout the study.

- QTcF > 500 msec,
- Change from baseline: QTcF >60 msec

Monitoring of subjects is to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTc values of the 3 ECGs to determine whether the subject should return for further monitoring of ECG one week later, and should be followed up until values are not clinically significant.

If an abnormality is noted during dosing the infusion may be halted.

5.6.3. Renal Function Monitoring Criteria

If a subject experiences a serum creatinine increase of ≥30% from baseline (Pre-dose Day 1) the patient should be followed up until values are not clinically significant.

5.6.4. Haematological Monitoring Criteria

If any of the following haematological criteria is met the patient should be followed up until values are not clinically significant:

- Haemoglobin <10 g/dL or an absolute decrease of ≥3 g/dL from baseline (pre-dose Day 1)
- White blood count <2.5 x 10^9/L
- Neutrophils <1.5 × 10^9/L

- Lymphocytes <0.85 × 10^9/L
- Platelets <125 × 10^9/L

5.6.5. Febrile Monitoring Criteria

Any unexplained febrile illness/episode will be considered a significant medical event. The patient should be followed up until the event is resolved. If the subject demonstrates any clinical symptoms consistent with viral reactivation e.g. fever, a blood sample will be taken and analysed for viral reactivation and/or other appropriate medical investigations as suggested by the clinical context.

5.6.6. Other Dose Adjustment/Stopping Safety Criteria

Symptoms of hypersensitivity which require stopping of infusion, together with appropriate management are described in Section 6.3.4.

The reason(s) for discontinuation of the study treatment must be recorded in the subject's electronic case report form (CRF). Subjects whose infusion is terminated prematurely will be expected to complete the remainder of the study visits so that study data are collected.

5.7. Dose Adjustment/Stopping Pharmacokinetic Criteria

Pre-defined dose will be altered or dose escalation stopped if the average predicted exposure AUC and/or Cmax at the next dose reaches 66.5 mg.hr/mL and/or 0.66 mg/mL respectively (AUC and Cmax values 2-fold lower than the observed values at the 30 mg/kg dose from the GLP repeat dose toxicity study in monkey).

See also Section 3.3.2.4 for comparisons with predicted exposure at maximum dose.

5.8. Blinding

This will be a double-blind (sponsor unblind) study.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, or in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator. Investigators have direct access to the subject's individual study treatment. It is preferred (but not required) that the investigator first contact the GSK Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment. If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding. The date and reason for the unblinding must be fully documented in the appropriate data collection tool.

A subject may continue in the study if that subject's treatment assignment is unblinded as subjects will only receive a single dose.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff will unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

When the DEC convenes the investigator will only attend the open (blinded) portion of the meeting.

5.9. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

5.10. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of GSK2831781 can be found in the Technical Terms of Supply document.

Study treatment must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study treatment. Only authorized site staff may supply or administer study treatment. An un-blinded pharmacist will perform the dilutions and preparation of the IV bags for active and placebo subjects. The un-blinded pharmacist must ensure that the blind is maintained. All study treatment must be stored in a secure area with access limited to the investigator and authorized site staff. Study treatment is to be stored at -40°C (±10°C) and protected from light. Maintenance of a temperature log (manual or automated) is required.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance. The investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from GSK and destroyed by the site and the amount administered to the subjects. The required accountability unit for this study will be a vial. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study treatment are listed in the SPM.

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or study manager. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator.

5.10.1. PPD 2TU and 10TU Dose

In Part A Healthy volunteers DTH cohort only

See PPD injection sites diagram in Section 3.1.1.

In the Part A DTH cohort, on Day 1, 0.1ml of PPD 2 TU (0.04 µg/0.1ml) will be injected intradermally into the volar aspect of the left forearm and the volar aspect of the right forearm. On Day 3 the injection sites will be inspected. If the induration is less than 6mm on Day 3, the subject will be re-challenged with 10 TU PPD in both arms (0.2 µg/0.1ml).

The subject will then return 48 hours later and the Day 3 assessments will be repeated. If subjects do not have an induration of 6mm or more after the 10 TU ID PPD dose on day 3, they will be withdrawn and replaced.

On Day 30, 0.1ml of PPD 2 or 10 TU will be injected intradermally into the volar aspect of the left forearm and the volar aspect of the right forearm, twice in each forearm (at least 4cm apart from each other and the Day 1 injection sites).

5.11. Assessment of Compliance

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When subjects are dosed at the study site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

5.12. Treatment of Study Treatment Overdose

For this study, any dose of GSK2831781 > the planned single dose for that cohort will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The investigator or physician in charge of the subject at the time will use clinical judgment to treat any overdose.

5.13. Treatment After the End of the Study

Healthy volunteers will not receive any additional treatment from GSK after completion of the study nor will the patients with psoriasis because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition, whether or not GSK is providing specific post-study treatment.

5.14. Concomitant Medications and Non-Drug Therapies

It is recommended that a subject's vaccination record and the need for immunisation prior to Day 1 should be carefully investigated in all subjects prior to entering the study. In those who are likely to require immunisation in the period up to the follow up visit for non-study reasons, such as subjects requiring vaccinations or boosters for their professional activity, the administration of any required vaccination/booster should be given at least 4 weeks prior to Day 1. For subjects with psoriasis, if indicated as part of standard of care, non live vaccines (e.g., inactivated influenza vaccines) may be administered during the study based on an assessment of the benefit:risk (e.g. risk of theoretical decreased responsiveness).

5.14.1. Permitted Medications

5.14.1.1. Part A and Part B

Occasional paracetamol or NSAIDs, at prescribed doses, are permitted for use during the study. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

5.14.1.2. Part B

Medicinal shampoos that contain tar and/or salicylic acid, but not corticosteroid containing, are permitted at any time during the study for use on the scalp area.

Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

5.14.2. Prohibited Medications and Non-Drug Therapies

5.14.2.1. Part A

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

Exceptions to the above are detailed in Section 5.14.1.

5.14.2.2. Part A and B

Live vaccine(s) (attenuated or recombinant) within 4 weeks of Day 1 and until completion of the follow up visit.

5.14.2.3. Part B

Use of the following prescription and non-prescription drugs are not permitted for the following periods a detailed below:

Restricted Medication	**Restricted Time Period**	**Details**
Low potency local corticosteroid "rescue" treatment for psoriasis flares may be used, but not at or near the index plaque being used to assess efficacy or the biopsy plaque. Worsening of the psoriasis may, if needed, be managed by introducing topical steroid therapy (if not already in use) or increasing the strength of topical steroid being used or using a higher potency steroid.	7 days prior to Day -1 to Day 43	As a rescue medication only upon discussion with investigator. **Example medications:** Weak topical steroids (class VI or VII only) for use limited to the face, axillae, or genitalia as required except on the lesions of interest. Alclometasone dipropionate 0.05% cream and 0.05% ointment Desonide 0.05% cream, 0.05% foam, 0.05% gel and 0.05% lotion Fluocinolone acetonide 0.01% shampoo and 0.01% solution Flurandrenolide 0.025% cream Triamcinolone acetonide 0.025% cream and 0.025% lotion
Over-the-counter non-medicated, topical emollients/moisturizers	24hr prior to Day -1 to Day 43	Not allowed within 24hrs before assessment visit
Topical Vitamin D analogues High dose topical corticosteroids Topical coal tar	7 days prior to Day -1 to Day 43	Always
Single-treatment phototherapy (ultraviolet B or self-treatment with tanning beds).	14 days prior to Day-1 to Day 43	Always
Anti-TNF/IL12/23 or other monoclonal antibodies.	12 weeks prior to Day -1 to Follow up[1]	Always

Restricted Medication	**Restricted Time Period**	**Details**
Systemic therapies including oral steroids, Fumaric acid esters, Oral retinoids Acitretin, Oral steroid.	5 half lives prior to Day -1 to Follow-up[1]	Always
Methotrexate and Cyclosporine	8 weeks prior to Day -1 to Follow-up[1]	
PUVA with psoralen	4 weeks prior to Day -1 to Follow-up[1]	
Narrow therapeutic index medications	Screening to Follow-up[1]	Always

1. Follow-up varies with dose (See Table 1).

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 6.1. Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or others assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The change in timing or addition of time points for any planned study assessments must be approved and documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form. No more than 600 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

6.1. Time and Events Table

Informed consent for optional PGx (pharmacogenetics) research must be obtained before collecting a sample

Table 6 Screening and Follow-Up

Protocol Activity	Screening[f]	Combined Follow Up/Surveillance Visit[a]	Surveillance telephone call[b]
	Up to 35 Days prior to Day 1	Day 183+/-7 days	
Informed Consent Process	X		
Subject Demography	X		
Full Physical Exam	X	X	
Medical/Disease History	X		
Urine Drug and Alcohol Screen	X		
Quantiferon TB Test	X		
Pregnancy Test (FRP)	X (serum)	X (urine)	
Safety Assessments			
Vital Signs	X	X	
12 - Lead ECG	X[c]	X	
Concomitant Medications	X	X	X[d]
Adverse Events Assessment / SAE's	X	X	X[e]
Laboratory Assessments			
Haematology	X	X	
Chemistry	X	X	
Urinalysis	X	X	
Hep B(HBsAg), Hep C (HCVAb) and HIV Ab Screen	X		
Serology to confirm vaccination status (if required)	X[g]		
Thyroid Function Test	X		
Vaccination for MMR and/or DPT (only if required)[g]	X[f]		
Identify 2 target psoriatic lesions	X[i]		

Protocol Activity	**Screening[f]**	**Combined Follow Up/Surveillance Visit[a]**	**Surveillance telephone call[b]**
	Up to 35 Days prior to Day 1	**Day 183+/-7 days**	
Psoriatic Body Surface Area	X[i]	X[h]	
Psoriatic Lesion Severity Score	X[i]	X[h]	
Psoriasis Area Severity Index		X[h]	
Immune Cell Phenotyping		X	
Immunogenicity Sample	X	X	
PK Sample		X	
G-CSF Sample		X	
sLAG-3 Sample		X	
Blood transcriptomics sample		X	

a. Required for subjects who have not yet had a follow-up visit at the time of approval of Protocol Amendment 10. If the subject has already been monitored for more than 183 days at the time of the Protocol amendment, but have not yet had a follow-up visit, this combined follow-up/surveillance visit should be conducted as soon as practically possible.
b. Required for subjects who completed their follow-up visit prior to amendment 10, but have not completed a 12-month surveillance visit. This call should be conducted as soon as practically possible.
c. Triplicate.
d. Only immunosuppressants and experimental medicines will be collected.
e. Only relevant AEs and SAEs as defined in Section 7.
f. Screening can be longer, up to a maximum of 42 days if vaccinations are required prior to dosing.
g. Part A only: See Section 6.3.8 for more details.
h. Subjects with psoriasis will be assessed for BSA, PASI and for index lesion PLSS at follow-up (See Section 6.3.5.3 and Table 1)
i. Psoriasis patients only.

Table 7 Healthy Volunteers (No DTH)

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits										
		Day 1						Day 2	Day 3	Day 4	Day 8										
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 hour post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25[a]	Day 29[k]	Day 43	Day 57[l]	Day 85	Day 121
Window											±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±3d
Admission to the unit	X																				
Discharge from the unit										X											
Brief physical	X																				
Urine Drug and Alcohol Screen	X																				
Administer IV Dose (2 hour infusion)			◄---------► [i]																		
Safety Assessments																					
Vital Signs	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X	X	X
12 - Lead ECG	X[j]	X	◄---------► [b]			X				X											
Concomitant Medications	◄----------																				----------►
Adverse Events Assessment / SAE's[c]	◄----------																				----------►
Laboratory Assessments																					
Haematology	X					X	X			X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X					X[d]	X[d]			X	X		X		X		X	X	X	X	X
Urinalysis	X					X	X			X	X		X		X		X	X	X	X	X

Protocol Activity	**Base-line**	**In Clinic Period**									**Out Patient Visits**										
		Day 1						**Day 2**	**Day 3**	**Day 4**	**Day 8**										
	Day -1	**Pre-dose**	**0 hour**	**2 hour post-infusion start**	**4 hour post-infusion start**	**6 hour post-infusion start**	**12 hour post-infusion start**	**24 hour post-infusion start**	**48 hour post-infusion start**	**72 hour post-infusion start**	**168 hour post-infusion start**	**Day 11**	**Day 15**	**Day 18**	**Day 22**	**Day 25[a]**	**Day 29[k]**	**Day 43**	**Day 57[l]**	**Day 85**	**Day 121**
Window											**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±2d**	**±2d**	**±2d**	**±3d**
CMV and EBV serology sample	X																				
Viral load sample (CMV, EBV, HSV, VZV)[e]	X																				
PK Sample[f]		◄----------													----------►						
Immunogenicity Sample		X									X						X			X	
Immune Cell Phenotyping[g]		X				X		X		X	X		X				X		X	X	X
CD16 and LAG-3 Receptor occupancy		X				X		X		X	X		X				X		X	X	X
Cytokine Sample		X				X	X	X	X												
G-CSF Sample		X				X		X		X	X		X				X	X	X	X	X
sLAG-3 Sample		X				X		X		X	X		X				X	X	X	X	X
Blood Transcriptomics Sample		X						X													
Ex Vivo Antigen/Cytokine Stimulation Test		X						X													

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits										
		Day 1						Day 2	Day 3	Day 4	Day 8										
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 hour post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25[a]	Day 29[k]	Day 43	Day 57[l]	Day 85	Day 121
Window											±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±3d
In vitro LAG-3+ activity		X		X							X										
PGx Sample	X[h]																				

a. Cohort 0.0003mg/kg last out patient visit will be on Day 25.
b. Continuous 2-lead ECG during infusion. Only significant abnormalities during this time will be databased.
c. A targeted physical examination may take place if guided by AE reporting relating to Section 6.3.4, Section 6.3.5 and Section 6.3.6..
d. Liver Chemistry and CRP only
e. Viral load sample for storage as baseline. If symptoms suggestive of viral infection develop then a sample will be taken and analysed with the baseline sample (See Section 6.3).
f. See Pharmacokinetic time and events table for dose specific timepoints.
g. Additional blood samples may be taken during the study if subject develops infection in order to measure LAG-3+ cells or other parameters as may be clinically or immunologically indicated.
h. Pharmacogenetics sample can be taken any time after consent is signed.
i. To calculate the correct dose, weight must be measured on Day -1 or Day 1 pre-dose.
j. Triplicate. Only required if screening ECG not within 35 days of Day 1.
k. Cohort 0.0015mg/kg last out patient visit will be on Day 29.
l. Cohort 0.0075mg/kg last out patient visit will be on Day 57.

Table 8 Healthy Volunteers (DTH)

Protocol Activity	1st Challenge		In Clinic Period										Out Patient Visits										
			Day 28	Day 29 (Day 1)						Day 30 (Day 2 post-dose)	Day 31 (Day 3 post-dose)	Day 32 (Day 4 post-dose)											
	Day 1	Day 3	Day 28	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hours post-infusion start	72 hour post-infusion start	Day 36 (Day 8 post-dose)	Day 39 (Day 11 post-dose)	Day 43 (Day 15 post-dose)	Day 46 (Day 18 post-dose)	Day 50 (Day 22 post-dose)	Day 53 (Day 25 post-dose)	Day 57 (Day 29 post-dose)	Day 71 (Day 43 post-dose)	Day 85 (Day 57 post-dose)	Day 113 (Day 85 post-dose)	Day 149 (Day 121 post-dose)
Window			±3d										±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±3d
Admission to the unit			X																				
Discharge from the unit												X											
Brief Physical	X		X																				
Urine Drug and Alcohol Screen	X																						
Administer IV Dose (2 hour infusion)					◄----------► n																		
Safety Assessments																							
Vital Signs	X	X		X		X	X	X	X	X	X	X	X		X		X		X	X	X	X	X
12 - Lead ECG	X[a]			X	◄----------► [b]		X					X											
Concomitant Medications	◄----------																						----------►
Adverse Events Assessment / SAE's[c]	◄----------																						----------►

Protocol Activity	1st Challenge		In Clinic Period										Out Patient Visits										
			Day 28	Day 29 (Day 1)						Day 30 (Day 2 post-dose)	Day 31 (Day 3 post-dose)	Day 32 (Day 4 post-dose)											
	Day 1	Day 3	Day 28	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hours post-infusion start	72 hour post-infusion start	Day 36 (Day 8 post-dose)	Day 39 (Day 11 post-dose)	Day 43 (Day 15 post-dose)	Day 46 (Day 18 post-dose)	Day 50 (Day 22 post-dose)	Day 53 (Day 25 post-dose)	Day 57 (Day 29 post-dose)	Day 71 (Day 43 post-dose)	Day 85 (Day 57 post-dose)	Day 113 (Day 85 post-dose)	Day 149 (Day 121 post-dose)
Window			±3d										±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±3d
Efficacy Assessments																							
Visual Arm Inspection	X[d]									X[e]													
ID PPD Challenge	X[f]									X[f]													
Bleb/ILH Assessment	X[e]									X[e]													
Ball Point Pen Technique		X										X	X		X		X						
Skin Biopsy		X[g]										X[g]											

Protocol Activity	1st Challenge		In Clinic Period										Out Patient Visits										
			Day 28	Day 29 (Day 1)						Day 30 (Day 2 post-dose)	Day 31 (Day 3 post-dose)	Day 32 (Day 4 post-dose)											
	Day 1	Day 3	Day 28	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hours post-infusion start	72 hour post-infusion start	Day 36 (Day 8 post-dose)	Day 39 (Day 11 post-dose)	Day 43 (Day 15 post-dose)	Day 46 (Day 18 post-dose)	Day 50 (Day 22 post-dose)	Day 53 (Day 25 post-dose)	Day 57 (Day 29 post-dose)	Day 71 (Day 43 post-dose)	Day 85 (Day 57 post-dose)	Day 113 (Day 85 post-dose)	Day 149 (Day 121 post-dose)
Window			±3d										±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±3d
Laboratory Assessments																							
Haematology	X[h]		X					X	X			X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X[h]		X					X[i]	X[i]			X	X		X		X		X	X	X	X	X
Urinalysis	X[h]		X					X	X			X	X		X		X		X	X	X	X	X
CMV and EBV serology sample			X																				
Viral load sample (CMV, EBV, HSV, VZV)[j]			X																				
Immunogenicity Sample				X									X						X			X	
PK Sample[k]				◄----------																	----------►			
Immune Cell Phenotyping[l]				X				X		X		X	X		X				X		X	X	X
CD16 and LAG-3 Receptor occupancy				X				X		X		X	X		X				X		X	X	X
Cytokine Sample				X				X	X	X	X												
G-CSF Sample				X				X		X		X	X		X				X	X	X	X	X

Protocol Activity	1st Challenge		In Clinic Period										Out Patient Visits										
			Day 28	Day 29 (Day 1)						Day 30 (Day 2 post-dose)	Day 31 (Day 3 post-dose)	Day 32 (Day 4 post-dose)											
	Day 1	Day 3	Day 28	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hours post-infusion start	72 hour post-infusion start	Day 36 (Day 8 post-dose)	Day 39 (Day 11 post-dose)	Day 43 (Day 15 post-dose)	Day 46 (Day 18 post-dose)	Day 50 (Day 22 post-dose)	Day 53 (Day 25 post-dose)	Day 57 (Day 29 post-dose)	Day 71 (Day 43 post-dose)	Day 85 (Day 57 post-dose)	Day 113 (Day 85 post-dose)	Day 149 (Day 121 post-dose)
Window			±3d										±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±3d
sLAG-3 Sample				X				X		X		X	X		X				X	X	X	X	X
Blood Transcriptomics Sample				X						X													
Ex vivo antigen/cytokine stimulation				X						X													
In vitro LAG-3+ activity				X		X							X										
PGx Sample	X^m																						

a. Triplicate. Only required if screening ECG not within 35 days of Day 1.
b. Continuous 2-lead ECG during infusion. Only significant abnormalities during this time will be databased.
c. A targeted physical examination may take place if guided by AE reporting relating to Section 6.3.4, Section 6.3.5 and Section 6.3.6..
d. Must be performed before ID PPD Challenge
e. Bleb is assessed 5 minutes after ID injection and the immediate local hypersensitivity assessment 15-30 minutes after ID injection.
f. See Section 5.10.1 for details.
g. Only biopsy from one of the PPD sites preferably from the subjects non-dominant arm.
h. If safety labs have been taken ≤7 days prior to challenge then these safety labs are not required. These samples can be taken on Day 1 or Day -1.
i. Liver Chemistry and CRP only
j. Viral load sample for storage as baseline. If symptoms suggestive of viral infection develop then a sample will be taken and analysed with the baseline sample (See Section 6.3).
k. See Pharmacokinetic time and events table for dose specific timepoints.
l. Additional blood samples may be taken during the study if subject develops infection in order to measure LAG-3+ cells or other parameters as may be clinically or immunologically indicated.
m. Pharmacogenetics sample can be taken any time after consent is signed.
n. To calculate the correct dose, weight must be measured on Day 28 or Day 29 pre-dose.

Table 9 Psoriasis Patients

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits [l]												
		Day 1						Day 2	Day 3	Day 4	Day 8												
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 36 [n]	Day 43	Day 57	Day 71 [n]	Day 85	Day 121
Window											±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±2d	±3d
Admission to the unit	X																						
Discharge from the unit										X													
Reassess 2 target lesions for suitability	X																						
Brief physical	X																						
Urine Drug and Alcohol Screen	X																						
Administer IV Dose (2 hour infusion)			◄------► [j]																				
Safety Assessments																							
Vital Signs	X	X		X	X	X	X	X	X	X	X		X		X		X		X	X		X	X
12 - Lead ECG	X [k]	X	◄------► [a]			X				X													
Concomitant Medications			◄----------																				
Adverse Events / SAEs [b]			◄----------																				

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits [l]												
		Day 1						Day 2	Day 3	Day 4	Day 8												
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 36 [n]	Day 43	Day 57	Day 71 [n]	Day 85	Day 121
Window											±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±2d	±3d
Efficacy Assessments																							
Psoriatic Body Surface Area	X												X				X		X			X	X
Psoriasis Area Severity Index	X												X				X		X			X	X
Psoriatic Lesion Severity Score	X [c]												X [c]				X [c]		X [d]			X [d]	X [d]
Phys. Global Assessment Scale	X												X				X		X			X	X
Skin Biopsy	X																X						
Photograph of index lesion	X												X				X		X			X	X
Photograph of biopsy lesion [e]	X																X						

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits [l]												
		Day 1						Day 2	Day 3	Day 4	Day 8												
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 36 [n]	Day 43	Day 57	Day 71 [n]	Day 85	Day 121
Window											±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±2d	±3d
Laboratory Assessments																							
Haematology	X[o]					X	X[o]			X[o]	X[o]	X	X	X	X	X	X		X	X		X	X
Chemistry	X					X [f]	X [f]			X	X		X		X		X		X	X		X	X
Urinalysis	X					X	X			X	X		X		X		X		X	X		X	X
Urine Pregnancy Test (FRP)	X																X			X		X	X
CMV and EBV serology sample	X																						
Viral load sample (CMV, EBV, HSV, VZV) [g]	X																						
Immunogenicity Sample		X									X						X					X	
PK Sample [h]				◄----------																			----------►
Immune Cell Phenotyping [i] (Flow)		X				X		X		X	X		X				X		X	X		X	X
Immune Cell Phenotyping [m] (Chip)		X		◄----------																			----------►
CD16 and LAG-3 Receptor occupancy		X				X		X		X	X		X				X		X	X		X	X

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits [l]												
		Day 1						Day 2	Day 3	Day 4	Day 8												
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 36 [n]	Day 43	Day 57	Day 71 [n]	Day 85	Day 121
Window											±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±2d	±3d
Cytokine Sample		X				X	X	X	X														
G-CSF Sample		X				X		X		X	X		X				X		X	X		X	X
sLAG-3 Sample		X				X		X		X	X		X				X		X	X		X	X
Blood Transcriptomics Sample		X						X															
PGx Sample	X																						

a. Continuous 2-lead ECG during infusion. Only significant abnormalities during this time will be databased.
b. A targeted physical examination may take place if guided by AE reporting relating to Section 6.3.4, Section 6.3.5 and Section 6.3.6..
c. PLSS will be recorded for the index lesion and the biopsy lesion (prior to the biopsy being performed).
d. Index lesion only.
e. Photographs of the biopsy lesion will be taken before the skin biopsy.
f. Liver Chemistry and CRP only
g. Viral load sample for storage as baseline. If symptoms suggestive of viral infection develop then a sample will be taken and analysed with the baseline sample (See Section 6.3).
h. See Pharmacokinetic time and events table for dose specific timepoints.
i. Additional blood samples may be taken during the study if e.g. subject develops infection (measure LAG-3+ cells), hypersensitivity reactions (serum tryptase), signs/symptoms suggestive of viral reaction, or other parameters as may be clinically or immunologically indicated (See Section 6.3).
j. To calculate the correct dose, weight must be measured on Day -1 or Day 1 pre-dose.
k. Triplicate. Only required if screening ECG not within 35 days of Day 1.
l. Investigator/designee should remind subjects to comply with contraception requirements on an ~ monthly basis until Follow-Up (either at study visits or by telephone call).
m. Immune Phenotyping (Chip) Cohort 7: at Baseline, 6 hours post-start of infusion, Day 8 and 15. Cohorts 8 and 9: at Baseline, 6 hours post start of infusion, Day 43 and 85.
n. Additional visit introduced at Day 36 (Cohort 8 only) and Day 71 (Cohort 9 only).
o. Samples taken for haematology at Day -1, 12 hours, 72 hours and 168 hours are to include analysis for CD3, CD4 and CD8 lymphocyte subsets.

Table 10 Pharmacokinetics

Dose Level Cohort	In-clinic period [a]											Out-patient visits [a]											
	Day 1								Day 2	Day 3	Day 4	Day 8	Day 11	Day 15	Day 18	Day 22	Day 29	Day 36	Day 43	Day 57	Day 71	Day 85	Day 121
	Pre-dose	0.5 h	1 h	2 h [b]	4 h	6 h	8 h	12 h	24 h	48 h	72 h	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±2d	±3d
	◄----------hours post-start of infusion----------►											◄----------visit window----------►											
0.0003mg/kg Cohort **1**	X	X	X	X	X	X	X	X	X														
0.0015mg/kg Cohort **2**	X	X	X	X	X	X	X	X	X	X	X												
0.0075mg/kg Cohort **3**	X	X	X	X	X	X	X	X	X	X	X	X		X									
0.04mg/kg Cohort **4**	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X		X	X			
0.15mg/kg Cohort **5 & 6**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X	
0.5mg/kg Cohort **7**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X	X
1.5mg/kg Cohort **8**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
5mg/kg Cohort **9**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X

a. When PK is taken in the healthy volunteer DTH cohort all PK times are relative to the start of the infusion on Day 29.

b. The PK sample taken at the time coinciding with the end of infusion should be collected just before the end of the infusion. Timing for PK collection post infusion may be adjusted in particular if the infusion duration were to be modified during the course of the study.

6.2. Demographic/Medical History Assessments

The following demographic parameters will be captured: year of birth, gender, race and ethnicity.

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2. Cardiovascular medical history/risk factors including height, weight, blood pressure, smoking history, medical conditions will also be assessed at baseline.

6.3. Safety

Planned timepoints for all safety assessments are listed in the Time and Events Table (Section 6.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

6.3.1. Physical Exams

- A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.
- A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- A targeted physical examination may take place if guided by AE reporting relating to Section 6.3.4, Section 6.3.5 and Section 6.3.6.

6.3.2. Vital Signs

- Vital sign measurements to be measured in semi-supine position after 5 minutes rest will include systolic and diastolic blood pressure, pulse rate and temperature.

6.3.3. Electrocardiogram (ECG)

- Triplicate 12-lead ECGs will be obtained at screening and single 12-lead ECGs will be obtained thereafter during the study, using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.6.2 for QTc monitoring criteria and additional QTcF readings that may be necessary.
- ECG to be measured in semi-supine position after 5 minutes rest.
- 2-lead ECG will be measured continuously during the IV infusion (0-2 hours). Only abnormalities during this time will be databased. If abnormalities are detected a 12-lead ECG will be obtained.

6.3.4. Infusion-related Reactions and Hypersensitivity Reactions

Subjects with a history of allergies or urticaria, allergic responses to foods, drugs, or insects may receive diphenhydramine and paracetamol (acetaminophen) prior to dosing at the discretion of the Principal Investigator or as a result of emerging data.
Subjects will be closely monitored for signs of infusion-related reactions and acute allergic reactions and/or anaphylaxis following the administration of GSK2831781. If an infusion-related reaction occurs during administration, the infusion rate will be reduced or halted. The subject will receive appropriate medical treatment. When the subject's condition is stable, the infusion may be restarted and the infusion rate will be half of the infusion rate at the time the infusion was paused. Severe hypersensitivity reactions such as anaphylaxis, will result in immediate termination of the infusion and the infusion will not be restarted.

As GSK2831781 is a fully humanized monoclonal antibody, it is considered unlikely for acute allergic reactions to occur in response to GSK2831781 exposure; however, all subjects will be monitored carefully for evidence of allergic response. A subject that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and remain on study at the discretion of the investigator and after discussion with the GSK medical monitor. In the event of a suspected acute hypersensitivity reaction a blood sample should be taken between 30 minutes – 3 hours of the event for serum tryptase analysis.

In accordance with the preparedness for treatment of anaphylaxis, emergency resuscitation equipment, advanced cardiac life support equipment, and medications must be readily accessible during GSK2831781 administration.

If more severe clinical signs arise, immediate assessment of the ABC's (airway, breathing, and circulation from Basic Life Support) will be done in all suspected anaphylactic reactions. Cardio-Pulmonary Resuscitation (CPR) will be initiated if needed. Epinephrine will be given by injection without delay. Emergency interventions may include endotracheal intubation or tracheostomy. Treatment for shock will include IV fluids and medications that support the actions of the heart and circulatory system.

6.3.5. Immunosuppression, Infections and Malignancies

As with other immunomodulating agents, the mechanism of action of GSK2831781 could increase the possibility of immunosuppression resulting in an increase in the frequency and/or severity of infection and/or an increased risk of malignancy. Therefore, the protocol will exclude subjects who may be at increased risk of infection or malignancy based on medical/medication history and screening physical examination or laboratory findings. During the trial, subjects will be questioned at all study visits about adverse events and results recorded in the electronic case report form (eCRF). Specific attention will be given to monitoring for infection, although the single dose design with limited follow-up means that specific monitoring for malignancies is not supported.

Examinations and laboratory evaluations will be performed routinely and the results, including markers of potential immunosuppression, will be reported to the investigators. Blood samples may be collected from subjects with infections, including flu like

symptoms, during the study for analysis of LAG-3+ cells. Serology for CMV and EBV will be performed at baseline to identify subjects with potential risk of viral reactivation for these viruses. Blood samples for viral load monitoring (CMV, EBV, HSV, VZV) will be taken at baseline and archived. If the subject demonstrates any clinical symptoms consistent with viral reactivation e.g. fever, then another sample would be taken and this and the baseline sample sent for analysis and/or other appropriate medical investigations as suggested by the clinical context.

6.3.5.1. Progressive Multifocal Leukoencephalopathy (PML)

PML has been found as a very rare occurrence in certain other immunosuppressive agents with different mechanisms of action. The most common signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and mental status changes such as disorientation or confusion. If these are found, the investigator must exercise best judgment in further workup and clinical intervention as appropriate. If PML is suspected this should be promptly reported to the sponsor.

6.3.5.2. Follow-up of healthy volunteers who exhibit reduction of PPD challenge

Healthy volunteers will undergo a first PPD DTH ID challenge on Day 1 and then on Day 30 (24 hours post GSK2831781 infusion) as described in Section 3.2. Healthy volunteers who produce an induration of ≥ 6 mm in the post dose challenge, will not require further PPD DTH ID re-challenges. However, subjects who produce a DTH induration of < 6 mm (i.e. exhibit reduction), will have a PPD DTH ID re-challenge after a further 3 months. If they still produce an induration of < 6 mm, it is likely that they will be PPD ID re-challenged every 3 months until the DTH induration is ≥ 6 mm dependent on review by the DEC.

6.3.5.3. Follow-up of subjects with psoriasis

All subjects in Part B will have assessments of clinical response (BSA, PASI, PLSS) carried out on Day 121 and follow-up visits.

6.3.6. Autoimmunity

There is a theoretical risk that subjects could develop autoimmunity following GSK2831781 as there are a small percentage of T-regulatory cells which are LAG-3+ (Gagliani *et al*., 2013; Camisaschi *et al*, 2010; GSK internal data). Subjects will therefore be monitored for evidence of possible auto-immune reactions.

6.3.6.1. Monitoring for thyroid complications and other endocrine complications

Subjects will be excluded with a history of other significant immune disorders (apart from psoriasis), including diabetes, if places subject at unacceptable risk. Investigators and subjects will be told to monitor for constant or unusual headaches, fatigue or the subjects feeling cold at all the time, dizziness, as well as for weight, change in mood and personality and change in the pattern of your bowel movements. Subjects will be tested for thyroid function at screening for comparison, if thyroid clinical symptoms occur during the study.

6.3.6.2. Monitoring for colitis

Subjects will be excluded, and/or not be dosed if they experience gastrointestinal (GI) upset, but not limited to diarrhoea or abdominal cramping, during the previous week before dosing, as well as if they have a history of more chronic GI upset e.g. Irritable Bowel Syndrome (IBS). Investigators and subjects will be told to monitor GI symptoms and to seek medical advice as soon as these symptoms appears, including continuous abdominal pain, fever, blood in the stools, or dark coloured stools.

6.3.7. Clinical Laboratory Assessments

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below. Details for the preparation and shipment of samples will be provided by the local laboratory. Reference ranges for all safety parameters will be provided to the site by the laboratory.

If additional non-protocol specified laboratory assessments are performed at the site's local laboratory and result in a change in subject management or are considered clinical significant by the Investigator (for example SAE or AE or dose modification) the results must be captured and sent to GSK along with other study data as defined in Appendix 4.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

Haematology

Platelet Count	RBC Indices:	Automated WBC Differential:
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes***
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry

BUN	Potassium	AST (SGOT)**	Total and direct bilirubin**
Creatinine	Chloride	ALT (SGPT)**	Uric Acid
Glucose, fasting*	Bicarbonate	GGT**	Albumin
Sodium	Calcium	Alkaline phosphatase**	Total Protein
C-reactive protein (CRP)			

***Fasting glucose only screening. Glucose non-fasting at all other timepoints.**
**** Liver Chemistry parameters**
***** CD3, CD4 and CD8 lymphocyte subsets will be analysed for subjects in Part B at Day -1, 12, 72 and 168 hours**

Cytokines for safety assessment may include but are not limited to IL-6, TNFα, IL-8, IFN-γ. Analysis will be performed within 24 hours **if** any clinical signs suggest cytokine release syndrome.

NOTE: Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Section 5.6.1

Routine Urinalysis (minimum requirements)

Specific gravity
pH, glucose, protein, blood, leucocytes, nitrites and ketones by dipstick
Microscopic examination (if blood or protein is abnormal)
Urine pregnancy test

Other screening tests

HIV
Hepatitis B (HBsAg, HBcAb)
Hepatitis C (Hep C antibody)
FSH and estradiol (as needed in women of non-child bearing potential only)
Serum pregnancy test
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).
Thyroid Function Test
Quantiferon test
Serology to confirm vaccination status (if required)

Baseline only tests

CMV, EBV serology
Viral load: CMV, EBV, HSV, VZV (sample for storage only unless clinical symptoms during study)

All laboratory tests with values that are significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.

6.3.8. Vaccination

6.3.8.1. Part A: Healthy Volunteers

Subjects who have no history of vaccination for diphtheria, pertussis, and tetanus may consent to receive a booster of an appropriate licensed combined vaccine at least 2 weeks prior to dosing (If a suitable serology test is available to confirm vaccination status then this may be used prior to vaccinating).

Subjects who have no history of vaccination for measles, mumps and rubella may consent to receive a booster of an appropriate licensed combined vaccine (M-M-RVAXPRO or similar) at least 4 weeks prior to dosing which will be given after serology results are available to assess levels of antibodies.

It has been reported that live attenuated measles, mumps, and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity (PPD challenge). Therefore, for this study, vaccination using M-M-RVAXPRO (or similar) should be administered a minimum of 28 days (4 weeks) before the first PPD challenge (based on advice in SPC). When a serology sample to assess MMR vaccination status is taken, results must be obtained and interpreted prior to administering MMR vaccination. If required, MMR vaccination will be administered at a separate visit during the screening period.

For further details refer to the SPM.

6.3.8.2. Part B: Psoriasis subjects

Investigators are expected to assess vaccination status according to local and/or national guidelines for patients with psoriasis during screening.

6.4. Efficacy

6.4.1. Body Surface Area (BSA)

This should be performed by the same qualified dermatologist at all timepoints as detailed in the Time and Events table.

The BSA will be estimated by the 'palm method' whereby the palm to the proximal interphalangeal (PIP) joints, including the thumb, of the patient represents 1% of the total BSA) (Christensen *et al*, 2006).

Calculate the number of palm areas affected for the following areas:

- Head
- Upper extremities
- Trunk
- Lower extremities

The sum of these areas is the % BSA affected.

6.4.2. Psoriasis Area and Severity Index (PASI) Assessment

The PASI assessment will be performed by the investigator or a suitably trained delegate, and whenever possible, the PASI assessments for an individual subject will be completed by the same assessor at all time-points.

Each area of the body (head, upper extremities, trunk, lower extremities) will be assessed for the following symptoms: erythema, induration, scaling.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

After calculating the BSA as detailed above, use the multiplier for that body region to calculate the area score for each region as detailed below:

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

The area of psoriatic involvement for each area of the body (head, upper extremities, trunk, lower extremities) will be assessed using a 0–6 point rating scale, as follows:

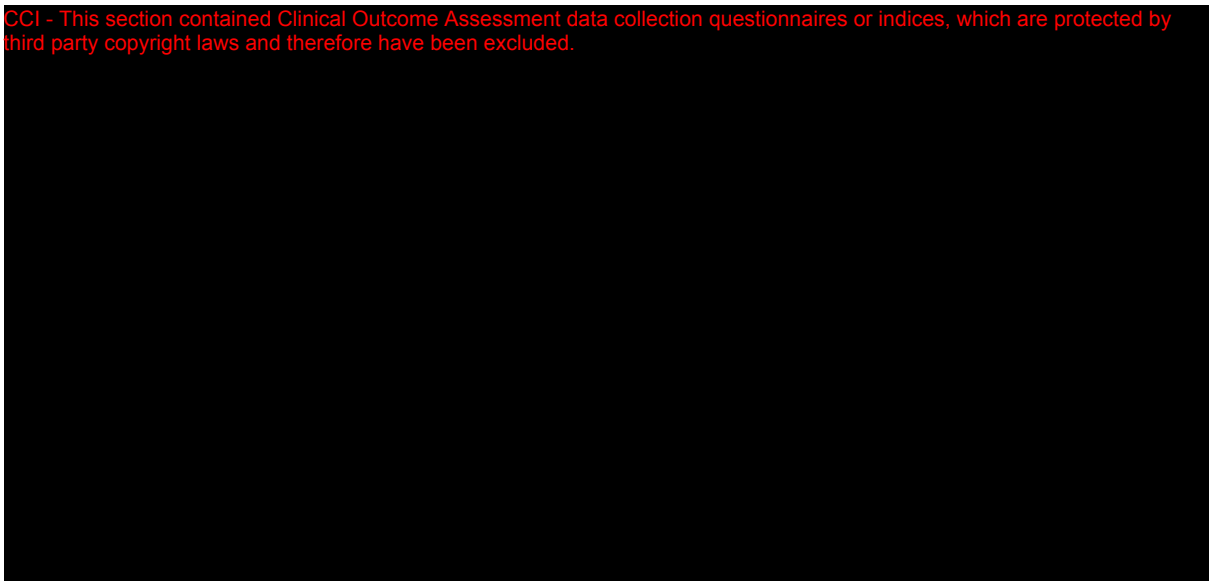
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Further details including the formula for calculating the PASI are included in the SPM.

6.4.3. Physician Global Assessment (PGA)

Psoriatic lesions will be assessed using the PGA (Langley *et al*, 2004). The PGA assessment will be performed wherever possible by the same qualified dermatologist at all timepoints (either the investigator or a suitably trained delegate).

A 7-point scoring system will be used to measure the severity of psoriatic lesions over the whole body, at the time of the evaluation:



6.4.4. Plaque Lesional Severity Score (PLSS) and index plaque selection

Two plaques will be selected at Day -1, one for clinical assessment (index plaque) and one for biopsy. Ideally the index plaque should be the most severe plaque. At a minimum each plaque will have an induration score of ≥2 (moderate or above) and a score of ≥1 in erythema and scaling, as detailed in the scoring list below. Each lesion must have a PLSS score of ≥5. The PLSS is the sum of the erythema, scaling and induration. The PLSS assessment will be performed by the same qualified dermatologist throughout, wherever possible and will be scored using the same scale (0-4 point rating scale) as the PASI (Section 6.4.2).

6.4.5. Photograph of the psoriasis plaques

A photograph of the index lesion and the biopsy lesion will be taken at each timepoint as detailed in the Time and Events table (Section 6.1).

6.4.6. Histology-Psoriasis skin biopsy evaluation and scoring

Skin biopsies will be analysed histologically for psoriasis disease activity biomarkers by a central reader. The biopsy tissue may be evaluated for general appearance, epidermal thickness, total inflammatory infiltrate, expression of Ki67. Specific cell numbers may also be analysed (which may include but not limited to CD163+ monocytes, CD11c+ dendritic cells, CD83+and/or CD206+ cells, and CD3+ T cells).

6.5. Other measures of clinical response

6.5.1. PPD Intradermal injections

Healthy volunteers will receive one PPD injection into each forearm on Day 1 and 2 injections into each forearm on Day 30.

- 0.1mL is administered with a 1mL graduated syringe fitted with a short bevel needle.

- The injection should be given strictly intra-dermally in the middle third of the forearm. Administration near the wrist or the elbow joint may weaken the reaction.
- The skin is slightly stretched, and the needle is held almost parallel with the skin surface with bevel upwards. The tip of the needle is inserted into the superficial layer of the dermis.
- The needle should be visible through the epidermis during insertion. The 0.1mL is slowly injected and a small blanched papule of 8 – 10 mm in diameter appears. This papule will disappear after approximately ten minutes.
- If a papule does not appear, the injection has been given too deep, and the skin test should be repeated on the other arm or on the same arm, separated at least 4 cm from the first injection site.

Subjects will be observed at the research unit for 30 minutes after any administration of PPD (ID).

6.5.1.1. Bleb

In order to assess whether a negative DTH reaction is due to a poor intradermal technique, a bleb assessment will be made within 5 minutes of administering a challenge agent. The length (diameter) and width of the bleb (raised area) that develops following an ID injection will be measured with a plastic flexible millimetre (mm) ruler.

6.5.1.2. ILH

An immediate local hypersensitivity assessment will take place 15-30 minutes after each ID challenge immunisation. The assessment will involve examining the injection site for evidence of immediate local hypersensitivity/wheal (erythema or induration will not be taken into consideration for this assessment). The diameter of the wheal (central swelling/raised skin) at the immunisation site, if that is present at the time of the hypersensitivity assessment, will be measured in the vertical and horizontal plane using a plastic flexible millimetre (mm) ruler. The 2 measurements will be added and divided by 2 to get the diameter value.

The recognition and management of immediate local hypersensitivity is summarised in Section 3.4.

6.5.2. DTH

6.5.2.1. Ball Point Pen Technique

PPD induced DTH response will be assessed by the ball point pen technique. The induration of wheals (defined as elevation and induration that are palpable in the skin) that develop as a result of intradermal immunisation with PPD will be measured in the vertical and horizontal plane using the ball point pen technique.

Only the induration, which is a hard, dense, raised formation, will be measured, even if there is soft swelling or redness (erythema). The diameter of the induration is measured by rolling a medium ball point pen from 10 to 20 mm outside the edge of the induration and toward the centre with just enough pressure to indent the skin slightly. When the

induration is met the investigator (or designee) will feel a change in resistance as the biro is advanced. At this point they should immediately remove the biro from the surface of the skin.

6.5.2.2. Photograph of DTH reaction

Photographs of any abnormal skin reactions may be taken if they are clinically significant.

6.6. Pharmacokinetics

6.6.1. Blood Sample Collection

Blood samples for pharmacokinetic analysis of GSK2831781 will be collected at the time points indicated in Section 6.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the SPM.

6.6.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the SPM. Concentrations of GSK2831781 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SPM).

6.7. Immunogenicity

6.7.1. Blood Sample Collection

Serum samples for determination of anti-GSK2831781 antibodies will be taken from all subjects in this study at the time-points specified in the Time and Events Tables in Section 6.1.

In Parts A cohorts 1-5, only subjects with a negative pre-existing ADA status at screening will be included.

6.7.2. Sample Analysis

Immunogenicity assays will be performed by Clinical Immunology, GSK. ADAs to GSK2831781 will be detected using a validated bridging electrochemiluminescent (ECL) immunoassay. This assay will be used both to prospectively define subjects' pre-existing ADA status and to evaluate post-dose ADA responses. The bioanalytical cut points of screening and confirmation for a positive antibody response will be determined statistically during ADA assay validation from drug-naive human serum samples. Samples will be directly tested in confirmatory ADA assay to define subjects' pre-existing ADA status for subject screening if required. An ADA assay involving

screening, confirmation and titration steps (tiered-testing approach) will be adopted for study samples. Confirmed positive samples will be titrated to obtain the titre of the anti-GSK2831781 antibodies. Samples testing positive for anti-GSK2831781 antibodies may be further characterised for the presence of GSK2831781 neutralizing activity (NAb) using a validated ADCC reporter gene assay, if needed. Details on sample preparation, storage and analysis will be given in the SPM.

6.8. Biomarkers/Pharmacodynamic Markers

6.8.1. LAG-3+ cells in DTH challenge site skin biopsies (Part A)

A punch biopsy will be taken from one of the challenge sites after each challenge. A 3mm skin punch biopsy will be taken from all subjects at the timepoints specified in Section 6.1, under local anaesthetic.

Biopsies will be taken from the middle of the induration as detailed in the SPM.

Biopsies will always be taken after the relevant DTH assessments have been completed.

The biopsy will be placed in formalin and subsequently processed for analysis by immunocytochemistry or other techniques to characterise and count the LAG-3+ and CD3+ cells in the biopsy. These sections may also be analysed for histology including but not limited to the number of perivascular infiltrates and mRNA transcriptome analysis for novel biomarkers (see Section 6.8.7 and SPM).

6.8.2. LAG-3+ cells in psoriasis lesion biopsies (Part B)

At baseline (pre-dose Day 1), a target lesion suitable for repeat biopsies will be identified on the trunk or extremities that protected from the sun. The same target lesion will be used for the baseline lesion biopsy and post treatment biopsy. Lesions on palms, soles, face and groin will not be used as the target biopsy lesion site. Ideally the most severe plaque, after the index lesion, should be selected and the severity of the erythema, scaling and induration of the plaque will be assessed as detailed in the PLSS scoring (Section 6.4.4).

Six mm punch biopsies will be taken from the active leading edge of the lesion using standard methodology. Local anaesthetic will be administered before each biopsy, and only suitably experienced personnel, trained in aseptic technique, will take the biopsies.

The 6mm biopsy will be split with a scalpel into 2, one sample will be placed in formalin and used to quantify CD3+ and LAG-3+ immune cells by IHC or similar techniques and also for histology assessment (see SPM). The 2nd half of the biopsy will be frozen for mRNA transcriptome analysis for novel biomarkers (see Section 6.8.7 and SPM).

6.8.3. Immune Cell Phenotyping

To address the effects of GSK2831781 on the LAG-3 expressing cells in the T cell compartment, regulatory, memory and effector T cells may be assessed.

Markers may include but are not restricted to: CD3, CD4, CD8, CD14, CD16, CD19, CD25, CD45, CD56, CD45RA, CD95, CD127, CD197 (CCR7), CCR6, CXCR3 and LAG-3 as data permit.

CD107a, CD69, CD11b expression may be explored on NK cells to investigate the effect of GSK2831781 on NK cell function.

To monitor effects on specific blood leukocytes absolute counts for T, B and NK cells may be measured by flow cytometry or other technologies (e.g. chip cytometry).

6.8.4. LAG-3 Cell Receptor Occupancy

The binding of GSK2831781 to cell surface LAG-3 may be measured (bound and free) using competitive and non-competitive anti-LAG3 antibodies.

6.8.5. NK CD16 Cell Receptor Occupancy

The binding of GSK2831781 to CD16 may be measured (bound and free).

6.8.6. Serum Protein Analysis

6.8.6.1. Assessment of serum cytokines

Pro- and anti-inflammatory cytokine production will be assessed at the end of the study or may be assessed at the end of each cohort.

Granulocyte-Colony Stimulating Factor [G-CSF] samples may be taken and analysed as an exploratory biomarker.

6.8.6.2. Assessment of sLAG-3 receptor occupancy

Levels of sLAG-3 bound and unbound to GSK2831781 may be measured using ECL assays.

6.8.7. Novel Biomarkers

With the subject's consent, skin tissue and blood sample(s) will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence psoriasis or the DTH challenge immune response, and/or medically related conditions, as well as the biological and clinical responses to GSK2831781. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Samples will be collected at the timepoints indicated in Section 6.1. The timing of the collections may be adjusted on the basis of emerging PK or PD data from this study or other new information in order to ensure optimal evaluation of the PD endpoints.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with psoriasis or the DTH challenge immune response or medically related conditions and/or the action of study treatment may be identified by application of

- RNA transcriptome analysis of blood and skin tissue samples.
- Measurement of the levels of a subset of RNA species on blood and skin tissue samples.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

6.8.7.1. RNA Transcriptome Research

An exploratory whole human genome expression array analysis may be conducted on blood and the punch skin biopsies from the DTH biopsies and from psoriasis patients using RNA sequencing, microarray, and/or alternative equivalent technologies, which facilitates the simultaneous measurement (and confirmation) of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each skin sample. That will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to the DTH immune challenge or psoriasis (Part A and Part B respectively) or the action of GSK2831781.

The same samples may also be used to confirm findings by application of alternative technologies.

6.8.7.2. RNA Expression Research of a Subset of RNA Species

RNA expression studies may be conducted using quantitative RT-PCR, and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of hundreds of RNA species resulting in a RNA expression profile for each blood and skin tissue sample. The RNAs assayed may include LAG-3 itself and other mRNAs that maybe involved with the pathogenesis of psoriasis or the DTH challenge immune response, the absorption, distribution, metabolism, or excretion of GSK2831781, or in the subject's response to GSK2831781. In addition continuing research may identify other proteins or regulatory RNAs that may be involved in response to GSK2831781 or the pathogenesis of psoriasis or the DTH challenge immune response. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to psoriasis or the DTH challenge immune response and medically related conditions or the action of GSK2831781.

In part B the samples expression of specific genes may include, but not limited to, Ki67, K16, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17, IL-22, IL-23, INF-γ, TNF-α, iNOS, IL-1R antagonist, PGC-1α, NCoR, NFκβ, FOXO, p300, PPARα, PPAR-delta, and p53.

6.9. Pharmacogenetics

Information regarding pharmacogenetic (PGx) research is included in Appendix 2 Pharmacogenetic research. The IRB/IEC and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and in most cases, the study, except for PGx

assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

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

7.1.1. Time period for collecting AE and SAE information

AEs will be collected from the start of Study Treatment and until the follow-up contact.

Between follow-up and the surveillance visits only listed targeted medical events (see Section 3.4) will be reported and databased as SAEs/AEs.

Subjects will be issued with a diary to record adverse events and concomitant medications during the study. This document will be used to assist subject recall in discussions with the investigator, for site staff to then enter as appropriate into the eCRF.

Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions CRF.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator would promptly notify GSK.

NOTE: The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.1.3. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE **include**:

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

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

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.1.4. Definition of Serious Adverse Events

If an event is not an AE per Section 7.1.3, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Is associated with liver injury **and** impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), or
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

- Refer to Appendix 1 for the required liver chemistry follow-up instructions.

7.1.5. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thrombosis
- Deep Venous Thrombosis
- Revascularization

This information should be recorded within one week of when the AE/SAE(s) are first reported.

7.1.6. Death Events

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded within one week of when the death is first reported.

7.1.7. Prompt Reporting of SAEs to GSK

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to GSK within 24 hours. Any follow-up information on a previously reported SAE will also be reported to GSK within 24 hours.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Appendix 4.

7.1.8. Regulatory Reporting Requirements For SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Hypotheses and Treatment Comparisons

The primary objective is to determine the safety and tolerability of single IV Doses of GSK2831781 in healthy volunteers and in patients with mild to moderate psoriasis.

There are no formal hypotheses planned.

An assessment of dose proportionality of AUC and Cmax, following single dosing, will be conducted separately for healthy volunteers and patients with psoriasis.

Where appropriate, an estimation approach will be used to address the study objectives where point estimates and corresponding confidence intervals will be constructed to provide a plausible range of values for the comparison of interest.

Exploratory comparisons will be conducted to investigate the effect of ADA status at baseline on the pharmacokinetics of GSK2831781.

9.2. Sample Size Considerations

The sample size is based on feasibility, and therefore there have been no formal sample size calculations

9.2.1. Sample Size Assumptions

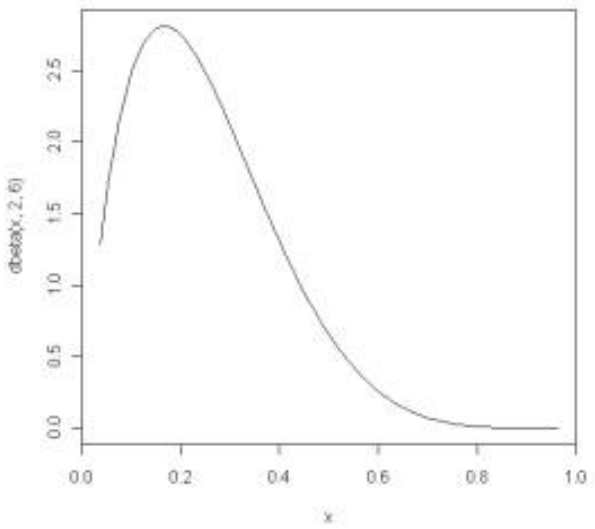
The sample size is based on feasibility, and therefore there have been no formal sample size calculations conducted.

It is anticipated that sufficient number of healthy volunteers and patients will be enrolled in the study so that data are obtained from approximately 40 healthy subjects (26 on active, 14 on placebo) and approximately 27 psoriasis patients (18 on active, 9 on placebo).

Part A and Part B - Safety

The primary objective of the study is safety, where a number of safety events are of interest. A maximum of 6 subjects will receive each active dose and therefore if 0/6 of a particular safety event in the GSK2831781 group is observed, the upper limit of the exact 95% Confidence Interval (CI) indicates that a true incidence rate of 46.5% could not be ruled out. Whereas if 1/6 of the same safety event in the GSK2831781 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 62.9% could not be ruled out.

Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe 1 safety event in 6 then the posterior distribution would be Beta (2, 6), as outlined below:



Where we can be 95% certain that the true probability of the safety event lies between 0.04 and 0.58.

Efficacy Assessment in Psoriasis Patients

The percentage change from baseline in PLSS in psoriasis patients can vary, with standard errors ranging from 6.9% to 11.1% (Boy *et al*, 2009). Assuming the greatest variability from this tofacitinib data and a sample size of 6 for each cohort, the 95% CI around the percentage change from baseline in PLSS point estimate would be plus or minus 26%, assuming a standard deviation of 24.8%.

9.2.2. Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates. If the number of subjects who completed each active dose is lower than 6, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 9.2.1) would change. These changes are outlined in the table below:

N completing cohort	Number of particular a safety event observed with GSK2586184	Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out
6	2 / 6	75.2%
6	3 / 6	84.9%
5	0 / 5	51.8%
5	1 / 5	69.1%
4	0 / 4	58.4%
4	1 / 4	76.4%
4	2 / 4	88.6%

N completing cohort	Number of particular a safety event observed with GSK2586184	Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out
2	0 / 2	76.8%
2	1 / 2	93.4%

9.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

Statistical analyses will be performed by, or under the auspices of, Clinical Statistics, QSci, GlaxoSmithKline.

Complete details of the planned statistical analyses will be provided in the Reporting and Analysis Plan (RAP).

9.3.1. Interim Analysis

Dependant on the dose cohorts reached in the escalation, formal interim analyses may be performed after the last subject in the Healthy Volunteer DTH cohort has completed their 4 week post dose assessment visit, and also after the last subject in the Psoriasis group has completed the final PK assessment visit, to inform internal development decisions. If required, additional interim analyses to contribute to internal development decisions may also be performed during Part B (psoriasis cohorts). Full details of interim analysis will be documented in a RAP addendum.

For Parts A and B of the study, review of safety, tolerability, available pharmacokinetic and DTH induration for healthy volunteers or PASI and PLSS for psoriasis patients will be performed by DEC to aid decisions to proceed to higher dose strengths or, between cohorts 5 and 6 to subjects with pre-existing ADA. This analysis can include review of individual subject data, summaries, graphical presentations and/or statistical analysis. Owing to the modest time intervals involved, all data to be used for dose escalation decisions will be preliminary, non-quality-controlled (non-QC'ed), data.

Safety/tolerability data monitoring and the decision to proceed to the next dose level of GSK2831781 will be made by the DEC (see Section 5.4 for more details).

The GSK Clinical Pharmacology Modeling and Simulation (CPMS) representative will extract PK data (including treatment information) from SMS2000 using unscrambled subject IDs. PK data will provide supporting evidence for each dose modification decision. Importantly, if the emerging PK data is significantly different from the predicted values, adjustment may have to be made to the planned doses (see Section 5.4). Dose modification decisions will take into account the emerging PK data, new PK prediction for the next dose and thus the expected safety cover for the next dose.

Standard Pharmacokinetic parameters will be derived for each subject by the GSK CPMS representative when possible. These parameters will be summarised by planned dose.

The criteria for switching from healthy volunteers to psoriasis patients are outlined in Section 3.2.1.

9.3.2. Final Analyses

Final analysis for all endpoints will be reported when all subjects in all groups have completed their final scheduled visits (Table 6).

9.3.2.1. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.3.2.2. Pharmacokinetic Analyses

Raw Plasma Concentrations
Blood sampling time will be related to the start of dosing. Linear and semi-logarithmic individual plasma concentration-time profiles and mean and median profiles by GSK2831781 dose will be plotted for each population (healthy volunteers or patients). Plasma concentrations of GSK2831781 will be listed and summarised by dose and nominal time for each population.

Derived Plasma Pharmacokinetic Parameters
Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, QSci, GSK. Plasma concentration time data for GSK2831781 will be analyzed by non-compartmental methods according to GlaxoSmithKline guidance document, GUI_00000051487 and using Phoenix. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration time data, the following pharmacokinetic parameters will be determined, as data permit, for each dose of GSK2831781 and for each subject in both population:

• maximum observed plasma concentration (Cmax)

• time to Cmax (tmax)

• area under the plasma time curve [AUC(0-t), AUC(0-week4) and AUC(0-∞)]

• %AUCextrapolated

• Last time point where the concentration is above the limit of quantification (tlast)

• Systemic clearance (CL)

• Volume of distribution at steady state (Vss)

• Mean residence time (MRT)

• terminal phase elimination rate constant (λz)

• the number of points used to determine λz

• the terminal phase half-life (t1/2).

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline.

Descriptive statistics (n, arithmetic mean, standard deviation, 95%CI, minimum, median and maximum,) will be calculated for all pharmacokinetic parameters by treatment and pre-existing ADA status, where applicable.

In addition, for $\log_e$-transformed variables geometric mean, 95% confidence interval and %CVb ($100 * \sqrt{(\exp(SD^2) - 1)}$) will be provided, where the SD is the standard deviation of log-transformed data.

Dose Proportionality

Separately for Parts A and B, dose proportionality across the single dose cohorts of $\log_e$-transformed parameters AUC(0-∞) (or if not available AUC(0-t)) and Cmax will be assessed using the power model for of data permit, as described below:

$y = \alpha * dose^{\beta}$

where y denotes the PK parameter being analysed and α depends on subject. Dose proportionality implies that $\beta=1$ and will be assessed by estimating β along with its confidence interval. The exponent, β, in the power model will be estimated by regressing the $\log_e$-transformed PK parameter on $\log_e$ dose:

$\log(y) = \log(\alpha) + \beta * \log(dose)$

The power model will be fitted by restricted maximum likelihood (REML), for all groups across the single dose cohorts. Both the intercept and slope will be fitted as random effects. If this model fails to converge, the model will be refitted with slope as a fixed effect. If the mixed effects model does not converge then a fixed effects power model will be fitted. The slope will be estimated from the power model and the corresponding 90% confidence interval calculated.

If the log transformed models are not proportional and sufficient data are available, loge transformed dose-normalised AUC(0-∞) (or if not available AUC(0-t)) and Cmax will be analysed using a suitable mixed effects model, fitting regimen as a fixed effect and subject as a random effect. Point estimates and corresponding 90% confidence intervals for the ratios of each dose level to the reference dose will be determined.

All other data will be summarised and listed.

9.3.2.3. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory plots will be presented for individual and/or pooled plasma GSK2831781 concentrations versus serum soluble LAG-3 and/or drug bound soluble LAG-3 levels, if appropriate.
Exploratory plots for PD/clinical activity variables (e.g. receptor occupancy, LAG3+ cells count and PASI, PLSS and PGA scores in patients) will be presented for individual and/or pooled plasma GSK2831781 concentrations and/or exposure versus corresponding PD/clinical activity variables. If deemed appropriate, further PK/PD modelling might be performed on those PD/clinical activity variables selected based on the results of the exploratory graphical analysis showing obvious relationships or trends between plasma GSK2831781 concentration/exposure and corresponding PD/clinical activity variables. The choice of the structural pharmacokinetic/pharmacodynamic models will be dependent on the emerging data. More details of any exploratory pharmacokinetic/pharmacodynamic analysis will be provided in the RAP.

9.3.2.4. Pharmacodynamic/Biomarker Analyses

For Parts A and B, descriptive statistics, where appropriate, (n, arithmetic mean, geometric mean, standard deviation, minimum, median and maximum) will be calculated for the pharmacodynamic endpoints and the biomarkers and summarized by time for GSK2831781. Graphical displays will be produced over time if deemed appropriate. All data will be listed.

For Parts A and B, appropriate secondary pharmacodynamic/biomarker endpoints will be separately analysed using suitable mixed models repeated measures (MMRM) analysis, if deemed appropriate. Point estimates and their associated 95% confidence intervals will be constructed for the adjusted mean differences between “GSK2831781-placebo”. Further details of the model terms (random and repeated effects), possible covariates and interactions between treatment and covariates will be included in the RAP.

Additional exploratory statistical analyses may also be performed to further characterise the pharmacodynamic/biomarker endpoints. Further details of the analyses will be provided in the RAP.

9.3.2.5. Efficacy Analyses

For Part B, secondary endpoints including those related to PASI, PGA and PLSS will be summarised and graphically represented appropriately. Formal statistical analysis may be conducted if deemed appropriate. Further details are outlined in the RAP. All data will be listed appropriately.

9.3.2.6. Immunogenicity Analyses

For Parts A and B, the immunogenicity assessment will include the incidence (confirmed positive results only) and titres of anti-GSK2831781 binding antibodies at each time

point and at any time point post baseline. Further details of the statistical analyses will be provided in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 1996 (Germany) and 2008 (UK) Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from each subject prior to participation in the study.

Information regarding pharmacogenetic research is included in Appendix 2) . In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency must also approve the PGx assessments (i.e., approval of Appendix 2)), unless otherwise indicated. Where permitted by regulatory authorities, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

10.2.1. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the study treatment, and this new event is likely to affect the safety of subjects, the sponsor and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The sponsor will work with the investigator to ensure the IEC/IRB and regulatory authorities are notified, according to local regulatory requirements.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK procedures.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or

severe non-compliance. For multicenter studies, this can occur at one or more or at all sites. If GSK determines such action is needed, GSK will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform investigators or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the

opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

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12. APPENDICES

12.1. Appendix 1: Liver Safety Process

The procedures listed below are to be followed if a subject meets the liver chemistry monitoring criteria defined in Section 5.5 and Section 5.6.1:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 7.1.4), the SAE data collection tool will be completed separately with the relevant details.
- Refer to the Flow chart for a visual presentation of the procedures listed below.

Safety Follow-Up Procedures for subjects with ALT ≥ 3xULN:

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects with ALT ≥3xULN and total bilirubin ≥2xULN (>35% direct bilirubin); or ALT ≥ 3xULN and INR[1] > 1.5:

- This event is considered an SAE (see Section 7.1.4). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

In addition, for all subjects with ALT ≥ 3xULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  - Hepatitis C RNA.
  - Cytomegalovirus IgM antibody.

[1] INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.

  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody.
- Blood sample for pharmacokinetic (PK) analysis, obtained within one week of the liver event. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected within a week of the liver event, **do not obtain a PK sample**. Instructions for sample handling and shipping are included in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 2xULN.
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.

The following are required for subjects with ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James *et al*, 2009]).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

12.2. Appendix 2: Pharmacogenetic research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington *et al*, 2002; Mallal *et al*, 2002; Mallal *et al*, 2008]	HLA-B* 57:01 (Human Leukocyte Antigen B)	Carriage of the HLA-B*57:01 variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B*57:01 screening and exclusion of HLA-B*57:01 positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B*57:01 screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B*57:01 screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung *et al*, 2010; Ferrell *et al*, 2008]	HLA-B*15:02	Independent studies indicated that patients of East Asian ancestry who carry HLA-B*15:02 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*15:02 prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti *et al*, 2004; Liu *et al*, 2008; Schulz *et al*, 2009]	UGT1A1*28	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no a priori hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to GSK2831781.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to GSK2831781. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK2831781 the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety and/or tolerability
- Efficacy

Study Population

Any subject who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

In addition to any blood samples taken for the clinical study, a whole blood sample (~6ml) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomised and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

- The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of GSK2831781 has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to GSK2831781.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time

when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to GSK2831781. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood/saliva being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarize the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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12.3. Appendix 3: Cytokine Release Syndrome AE Grading

Symptom/Sign	Severity Grade 0 None	1 Mild	2 Moderate	3 Severe	4 Disabling/Life-threatening
Headache	None	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	Severe pain: pain or analgesics severely interfering with activities of daily living	Disabling
Fever	None	38.0 - 39.0°C (100.4 - 102.2°F); Grade 1 after antipyretics or resolves	39.1 - 40.0°C (102.3 - 104.0°F); remains Grade 2 with or without antipyretics	> 40.0°C (>104.0°F) for < 24hrs despite antipyretics	> 40.0°C (>104.0°F) for > 24hrs despite antipyretics
Chills/Rigors	None	Mild, transient, requiring no or symptomatic treatment (e.g., blanket); remains at Grade 1 or resolves after non-narcotic medication	Moderate, requiring non-narcotic medication; lasts several hours before resolution	Severe and/or prolonged, requiring narcotic medication	Not responsive to narcotic medication
Nausea	None	Mild, but able to eat	Mild but oral intake significantly decreased	Moderate; no significant intake, requiring IV fluids; <24 hrs duration	Severe; prolonged, requiring IV fluids; ≥ 24 hrs duration
Vomiting	None	1 episode in 24 hours; antiemetics resolve or keep at Grade 1	2-5 episodes in 24 hours despite antiemetics	≥6 episodes in 24 hours; despite antiemetics or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic compromise
Diarrhea	None	Increase of < 4 stools/day over pre-treatment	Increase of 4-6 stools/day, or nocturnal stools	Increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; or hemodynamic compromise

Symptom/Sign	Severity Grade 0 None	1 Mild	2 Moderate	3 Severe	4 Disabling/Life-threatening
Arthralgia (joint pain)	None	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	Severe pain: pain or analgesics severely interfering with activities of daily living	Disabling
Myalgia (muscle pain)	None	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	Severe pain: pain or analgesics severely interfering with activities of daily living	Disabling
Hypotension	None	BP changes, but not requiring therapy (including transient orthostatic hypotension)	Requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	Requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	Shock (associated with acidemia; impairing vital organ function due to tissue hypoperfusion)

Modified from NCI-CTC.

12.4. Appendix 4: Procedures for Detection, Evaluation, Follow-Up and Reporting of Adverse Events and Medical Device Incidents

Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the appropriate data collection tool.

It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE data collection tool. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

Subject-completed health outcomes questionnaires and the collection of AE data are independent components of the study. Responses to each question in the health outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed data collection tool. The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Reporting of SAEs to GSK

The primary mechanism for reporting SAEs to GSK will be the electronic data collection tool. If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the GSK Medical Monitor or protocol

contact. Then the site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to their GSK protocol contact by telephone.

GSK contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

12.5. Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.5.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher *et al*, 2011])
4. Injectable progestogen [Hatcher *et al*, 2011]
5. Contraceptive vaginal ring [Hatcher *et al*, 2011]
6. Percutaneous contraceptive patches [Hatcher *et al*, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher *et al*, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- Will be withdrawn from the study.

REFERENCES

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3 2

12.6. Appendix 6: Protocol Amendment Changes

AMENDMENT 10

Summary and rationale for the changes

1. **Additional sub-analysis of PGA scores added to secondary endpoints (see Section 2).**
2. **Including emerging PK data into the Study Design explanation (see Section 3.3.2, Table 2 and Figure 1).**
    a. Pre-clinical pharmacokinetic (PK) data generated in non-human primates had predicted the half-life of GSK2831781 was such that at the highest dose (5mg/kg), the time taken for drug levels to drop below the lower limit of quantitation (LLOQ, 10ng/ml) would be approximately 300 days. Preliminary human PK data from Cohorts 1-8 has now been included in the protocol, together with updated predictions for Cohort 9 (5mg/kg), in which drug plasma concentration is predicted to drop below the LLOQ by Day 85 (Table 2 and Figure 1).
3. **Changing the study duration and structure to take account of this emerging PK data (see Section 3.1.2, Section 3.3.1, Table 1 and Table 6)**
    a. The duration of subject participation in the Phase I study was based on predictions, from non-human primate data, of the time taken to clear GSK2831781 from the circulation. As human PK has dramatically reduced these predictions, duration of subject participation has been amended
    b. Psoriasis patients in 0.5mg/kg, 1.5mg/kg and 5mg/kg dosing cohorts (7-9) will have a final combined follow-up and surveillance visit at Day 183± 7 due to emerging PK data that demonstrated more rapid clearance of GSK2831781 than previously predicted. Some subjects in Part B treated prior to Amendment 10 will have progressed beyond Day 183 ± 7. If they have already had their follow-up visit, they should have a final surveillance telephone call as soon as practically possible after Amendment 10 regulatory approval. If they have not already had their follow-up visit, a combined follow-up and surveillance visit should be completed as soon as practically possible after Amendment 10 regulatory approval. to reflect this change.
4. **Consolidation of previously enacted File Notes since Protocol Amendment #9 (See Time and Events Table 9).**
    a. **File Note [Jun 9th 2017]** – In Section 6.3.5.3, the protocol originally stated that clinical response would be assessed at follow-up and surveillance if clinical response was maintained at Day 121. This was amended via the file note to mandate response assessment (BSA, PASI, PLSS) at follow and surveillance visits for cohort 7, 8 and 9 subjects

irrespective of clinical response on Day 121. Protocol amendment 10 will include response assessments at follow-up visits (for some subjects, the follow-up and surveillance visit will occur at the same time, as detailed in Table 1).

b. **File Note [Jun 9th 2017] (2)** – Table 6 corrected, by removing ex vivo Antigen Stimulation Testing for cohorts 8 and 9, to reflect approved Protocol Amendment 09 text. Table 9 corrected to include assessment of CD16 and LAG3 receptor occupancy at Day 43 as per approved Protocol Amendment 09 text. Table 9 updated to clarify and reflect the routine analysis of CD3, CD4 and CD8 lymphocyte subsets for cohorts 7, 8 and 9 on samples taken for haematology at Day -1, 12h, 72h (Day 4) and 168h.

5. Updating medical monitor details

AMENDMENT 9

Summary and rationale for the non-substantial changes

Amendment 9 consolidates non-substantial changes to date. It serves to 1) remove the requirement for 3 ADA +ve patients in Cohorts 8 and 9, 2) introduce flexibility to conduct additional analyses to enable internal development decisions and 3) to incorporate previously enacted non-substantial changes captured in File Notes (8th Aug 2016, 7th Nov 2016 and 12th Dec 2016) so as to ensure clarity of and adherence to the protocol (detailed below).

The primary objectives and endpoints of the protocol remain unchanged and none of the changes were/are considered to impact on either safety or safety management or were/are considered to affect the overall scientific value of the study.

Briefly:-

1. Removal of the stratification of psoriasis patients according to their pre-existing anti-drug antibody (ADA) status, and to recruit "all-comers" into the remainder of Cohort 8 and into Cohort 9. The justification is based upon de-escalation of concerns regarding the theoretical impact of pre-existing ADAs following the review of Cohort 7 data and their substantially lower frequency in the patient population than predicted (patient pool has been screened to exhaustion). None of the events listed here have been observed following a single 0.5 mg/kg intravenous infusion: serious adverse event, immediate hypersensitivity, infusion reaction, cytokine release syndrome, type III hypersensitivity any other safety concern or any impact of ADA on pharmacokinetics. Importantly, enrolling patients at higher doses (1.5 or 5.0 mg/kg) is no longer considered necessary to test for overt risk of immediate hypersensitivity, infusion reactions, cytokine release or type III hypersensitivity.

2. Introduce the possibility of additional Interim Analyses to enable internal development decisions (See Section 9.3.1)

3. Consolidation of previously enacted File Notes since Protocol Amendment #8 (See Time and Events Table 9 and Table 10).
   a. File Note [12th Dec 2016] - Following the blinded review of Cohort 7 data, the following changes (permitted by the protocol) were deemed necessary to both bridge the anticipated shortfall in the critical portion of the kinetic profile and to secure the utility of this study to inform the next steps in rational clinical development (e.g. definition of the dose regimen):-
   - Adjustment of the pharmacokinetic sampling schedule (additional sample Days 29 and 57).
   - Introduction of one new (different) visit per each Cohort 8 [Day 36] and Cohort 9 [Day 71] to enable capture of important pharmacokinetic time points.
   - Adjustment to the timing of immunophenotyping (chip cytometry).
   - Introduction of psoriasis efficacy assessments at Day 85 (non-invasive).

   The overall blood volume (484 mL) remains below that approved (600 mL).

b. **File Note [7th Nov 2016]** - Downward adjustment of the overall blood volume (minus 44 mL) as a result of the following:-
   i) Difficulty in the development of bioanalytical assays for two exploratory pharmacodynamic biomarker objectives/endpoints (*Ex vivo* Antigen/Cytokine Stimulation Test and *in vitro* LAG-3+ activity), justified that blood should no longer be collected for such purposes in Cohorts 8 and 9.
   ii) Adjustment of the blood volume for immunophenotyping (chip cytometry), as permitted by the protocol.
c. **File Note [8th Aug 2016]** – Change the timing of photography of the biopsy lesion from post- to pre-biopsy.

AMENDMENT 8

Summary of Amendment Changes with Rationale

This amendment has been introduced to make the eligibility criteria more suitable for recruitment for psoriasis subjects in Part B of this study. This includes permitting the inclusion of females of reproductive potential (FRP) and modification of other eligibility criteria including age, BMI, BSA, vaccination and liver function tests that are more appropriate for the recruitment of psoriasis patients. The addition of a causality requirement to adverse event reporting for safety review criteria has also been introduced.

This amendment will also aim to improve operations by reducing number of biopsies required (from 3 to 2) in psoriasis subjects and modifying requirements for DEC review of psoriasis cohorts. Indeed dose escalation to the next psoriasis cohort will be based on safety data and clinical measures of response at 28 days post-dose for a minimum of 8 out 9 subjects plus a minimum of 72 hours post-dose for all subjects.

List of Specific Changes

CHANGE 1

Synopsis, 2nd and 3rd paragraph

REVISED/ADDED TEXT

Part A of the study will be a single dose escalation in healthy volunteers. The first 4 cohorts will be given an intravenous (IV) dose of GSK2831781 or placebo over approximately 2 hours on Day 1. The ~~last~~ **5th** healthy volunteer cohort will receive a skin challenge of 2 Tuberculin Unit (TU) or 10TU Purified Protein Derivative (PPD) on Day 1. Twenty-eight days later the subjects will be given an intravenous (IV) dose of GSK2831781 or placebo over approximately 2 hours. Twenty-four hours after dosing they will be re-challenged with either 2TU or 10TU PPD. Biopsies will be taken from one of the challenge sites after each challenge for measurement of LAG-3+ T cells. **A cohort (cohort 6) of subjects positive for pre-existing anti-drug antibodies (ADA) at the maximum healthy volunteer dose will then be dosed.**

Part B of the study will be a single dose escalation in patients with plaque psoriasis. Two lesions with a plaque lesional severity score (PLSS) of ≥5 will be identified. One will be used as an index lesion and the other will be used for skin biopsies on Day -1~~, Day 15~~ and Day 29. The biopsies will be used to quantify CD3+ and LAG-3+ immune cells. On Day 1 patients will be given an intravenous (IV) dose of GSK2831781 or placebo over approximately 2 hours. **Part B cohorts will be stratified to include subjects with negative or positive pre-existing ADA.**

CHANGE 2

Objectives and Endpoints table

REVISED TEXT

Change from baseline in LAG-3+ cells in lesional biopsies at ~~Day 15 and~~ 29 measured by IHC

CHANGE 3

3.1. Study Schematic

REVISED SCHEMATIC

Day 15 skin biopsy removed.

CHANGE 4

3.1.2. Study Design Summary

Footnote added to psoriasis section: ***Note: Progression to the next psoriasis cohort will be based on safety data and clinical measures of response at 28 days post-dose for a minimum of 8 out 9 subjects plus a minimum of 72 hours post-dose for all subjects.**

CHANGE 5

Section 3.2. Study Design Detail, Part B, Psoriasis Patients, 1st paragraph, 6th line

REVISED TEXT

Once safety data and clinical measures of response (e.g. PASI) at 28 days post-dose have been completed for **a minimum of 8 out of 9 subjects** ~~all subjects~~ within the cohort **and all subjects have completed dosing and the inpatient monitoring until Day 4**, the DEC will review the safety data, available PK data and clinical response data, and may consider the available PD data before proceeding to the next dose level.

CHANGE 6

Section 3.4. Risk Management, 2nd paragraph

ADDED TEXT

Once safety data and clinical measures of response (e.g. DTH induration for healthy volunteers, PASI for psoriasis patients) at 4 weeks post-dose have been completed for all subjects in each cohort **(Part B: minimum 8 of 9 subjects, but with all subjects completing 72 hours post dose)**, the DEC and the investigator will review the data along with the available PK data before proceeding to the next dose level.

CHANGE 7

Section 3.4. Risk Management, Table 5

AMENDED TEXT

Risk of infection section: **Healthy volunteer** subjects will need to be vaccinated against infectious agents (Inclusion #8).

Psoriasis subjects: investigators are expected to assess vaccination status, according to local and/or national guidelines for patients with psoriasis during screening.

Neutropenia section: Exclude subjects with neutrophils ~~outside of~~ **below** normal range. (Exclusion # 5).

Hepatotoxicity section: Only subjects with liver chemistry results within the limits specified in the inclusion and exclusion criteria will be included (Inclusion #10; Exclusion #10, **#25**)

Punch biopsy section: For the 3mm biopsy a minute scar will be visible and will be minimised ~~as it will not require stitching.~~ Stitching and a small scar will occur for the 6mm biopsy.

Vaccination section: Subjects **in Part A** who are ineligible due to lack of history of vaccinations for diphtheria, tetanus, pertussis, measles, mumps or rubella, who consent to vaccination may only be vaccinated in accordance with the restrictions for these vaccines in the SPC.

CHANGE 8

Section 4.2.1. Inclusion Criteria

AMENDED TEXT

1. Part A males **aged between 18 and 65 years of age** ~~only~~ and Part B males and females ~~of non-child bearing potential~~ aged between 18 and ~~65~~**75** years of age inclusive at the time of signing the informed consent.

2. **Part A:** A body weight ≤120 kg and BMI within the range 19 – 32 kg/m2 (inclusive). For healthy volunteer subjects participating in Germany the BMI must be within the range of 19 – 30 kg/m2 (inclusive). **Part B: BMI within range 19-35 kg/m^2 (inclusive).**

5. **Part B only:** Subject has psoriasis covering BSA **≥3**~~10~~% as assessed at Screening and Day -1.

6. **Part A only:** Subjects with a history of vaccination for Tetanus, diphtheria, measles, pertussis, mumps and rubella.

7. **Part B only:** A female subject is eligible to participate if she is ~~of:~~ **not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test at screening and negative urine hCG test at Day -1 for FRP), not lactating, and at least one of the following conditions applies:**

~~9. Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy [for this definition, "documented" refers to the outcome of the investigator's/designee's review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records]; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MlU/ml and estradiol < 40 pg/ml (<147 pmol/L) is confirmatory]. [Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study.]~~

a. Non-reproductive potential defined as:

- **Pre-menopausal females with one of the following:**
  - **Documented tubal ligation**
  - **Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion**
  - **Hysterectomy**
  - **Documented Bilateral Oophorectomy**
- **Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.**

b. Reproductive potential and agrees to use a barrier method (male condom or female diaphragm) plus to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 5) from 28 days prior to the first dose of study medication and until completion of the follow-up visit.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. The investigator or designee should remind the subjects of the need to comply with these requirements approximately monthly, either at study visits or by telephone call until the follow-up visit.

CHANGE 9

Section 4.2.2. Exclusion Criteria

AMENDED TEXT

1. Received live vaccine(s) **(attenuated or recombinant)** within 4 weeks of Day 1 or plan to receive a **live** vaccination during the study until follow-up.
5. Subjects with neutrophil results ~~outside of~~ **below** the normal range at screening and baseline.
10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). **Part A only:** Subjects with an aspartate aminotransferase and/or gamma glutamyltransferase level above the upper limit of normal at screening and/or baseline will be excluded.
26. **Part B only:** All systemic psoriasis medications, including psoralen long-wave ultraviolet radiation treatments, or other systemic immunosuppressives, are not allowed within 5 half lives prior to Day -1 (Methotrexate and cyclosporin are not allowed within 8 weeks of Day -1; Psoralen long-wave UV is not allowed within 4 weeks of Day-1). **Subjects should not be included if the investigator considers that the subject is at high risk of requiring rescue with prohibited medication (see Section 5.14.2.3) for duration of study up to follow-up. This assessment should be based on current disease activity or a history of frequent and/or severe flares requiring systemic immunosuppression.**

CHANGE 10

Section 5.4. Planned Dose Adjustments, 2nd paragraph, 10th line

ADDED TEXT

In the closed section, the Principal Investigators will not be present and **if required** data will be presented in an unblinded manner.

CHANGE 11

Section 5.4. Planned Dose Adjustments, 4th paragraph, 1st line

AMENDED TEXT

For the psoriasis cohorts, once safety data and measures of clinical response (PASI and PLSS) up to 28 days post-**dose have been completed for a minimum of 8 out of 9 subjects, and all subjects have completed dosing and the inpatient monitoring until Day 4**,~~has been collected in all subjects for that cohort,~~ the DEC will review the safety/tolerability data (including trends in neutrophil counts), the available PK data and the clinical response (PASI and PLSS) before proceeding to the next dose level.

CHANGE 12

Section 5.5. Dose Adjustment/Stopping/Monitoring Criteria

ADDED TEXT

2. Moderate or severe adverse events of the same nature (including infections) in 2 or more subjects in the same cohort **which can be reasonably attributed to dosing with GSK2831781,** within 28 days of dosing (Appendix 4 and specific criteria at individual subject level in Section 5.6).
3. For a cohort of patients with psoriasis, if 2 or more subjects in a dose cohort experience a worsening of their psoriasis symptoms **which can be reasonably attributed to dosing with GSK2831781**, which requires treatment with prohibited concomitant medication.

CHANGE 13

Section 5.14. Concomitant Medications and Non-Drug Therapies, 6th line

ADDED TEXT

For subjects with psoriasis, if indicated as part of standard of care, non live vaccines (e.g., inactivated influenza vaccines) may be administered during the study based on an assessment of the benefit:risk (e.g., risk of theoretical decreased responsiveness).

CHANGE 14

Section 5.14.2.2 Part A and B

ADDED TEXT

Live vaccine(s) **(attenuated or recombinant)** within 4 weeks of Day 1 and until completion of the follow up visit.

CHANGE 15

Section 6.1. Time and Events table

AMENDED TEXT

Table 6 - Pregnancy test added to screening and follow-up table.

Table 6 - Footnote J. **Part A only:** See Section 6.3.8 for more details.

Table 9 – Day 15 skin biopsy and photograph of biopsy lesion timepoints removed.

Table 9 – Pregnancy test added at Day-1, Days 29, 57, 85 and 121

Table 9 – **Footnote L. The investigator or designee should remind subjects of the need to comply with contraception requirements on an approximately monthly basis until Follow-Up (either at study visits or by telephone call).**

Table 10 – PK timepoints on Day 29 and 57 removed and added on Day 11 and 18 (for healthy volunteer Cohorts 5 & 6 and all psoriasis cohorts).

CHANGE 16

Section 6.3.7. Clinical Laboratory Assessments

Reason for cytokine change due to assay and validation availability.

AMENDED TEXT
Cytokines for safety assessment may include but are not limited to IL-6, TNFα, IL-8, ~~IL-1b~~ **IFN-γ**. Analysis will be performed within 24 hours **if** any clinical signs suggest cytokine release syndrome.

CHANGE 17

Section 6.3.7. Clinical Laboratory Assessments

ADDED TEXT

Urine pregnancy test added to Routine Urinalysis table.

Serum pregnancy test added to Other Screening Tests table.

CHANGE 18

Section 6.3.8. Vaccination

ADDED HEADINGS AND TEXT

Section 6.3.8.1 Part A: Healthy Volunteers

Section 6.3.8.2 Part B: Psoriasis subjects

Investigators are expected to assess vaccination status according to local and/or national guidelines for patients with psoriasis during screening.

CHANGE 19

Section 6.8.1. 4th paragraph

ADDED TEXT

The biopsy will be placed in formalin and subsequently processed for analysis by immunocytochemistry or other techniques to characterise and count the LAG-3+ **and CD3+** cells in the biopsy.

CHANGE 20

Section 6.8.3. Immune Cell Phenotyping, final paragraph

AMENDED TEXT

To monitor effects on specific blood leukocytes absolute counts for T, B and NK cells ~~will~~ **may** ~~also~~ be measured by flow cytometry **or other technologies**.

CHANGE 21

Section 9.3.2. Final Analyses

TEXT REMOVED

~~Final analysis of Part A will be reported when after all subjects in Part A have completed their follow-up visit.~~ Final analysis for all endpoints will be reported when all subjects in all groups have completed their 12 month surveillance visit.

CHANGE 22

Section 12.5. Appendix 5

APPENDIX ADDED

Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. **Contraceptive subdermal implant**
2. **Intrauterine device or intrauterine system**
3. **Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])**
4. **Injectable progestogen [Hatcher, 2011]**
5. **Contraceptive vaginal ring [Hatcher, 2011]**
6. **Percutaneous contraceptive patches [Hatcher, 2011]**
7. **Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.**

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Collection of Pregnancy Information

- **Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study**
- **Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.**
- **Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.**
- **Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.**
- **While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.**
- **A spontaneous abortion is always considered to be an SAE and will be reported as such.**
- **Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to**

GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- **Will be withdrawn from the study.**

REFERENCES

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3 2

AMENDMENT 7

Summary of Amendment Changes with Rationale

This amendment has been introduced to modify the study design to enable assessment of the impact of pre-existing anti-drug antibodies in healthy volunteers and psoriasis subjects.

The opportunity has been taken to modify text on BSA and screening requiring clarification, maximize utility of psoriasis clinical response assessments and add flexibility to assays for exploratory biomarkers.

List of Specific Changes

CHANGE 1

Change to describe rationale to including subjects with pre-existing ADAs

Section 1.2.1 GSK2831781, 3rd paragraph

REVISED/ADDED TEXT

Pre-existing anti-drug antibodies (ADA) that bind GSK2831781 have been noted in ~~approximately 10-32~~ **36**% and ~~6 – 45~~ **37.5**% of sera from healthy and psoriatic human subjects respectively. **Analysis of ADA to GSK2831781 indicated they are generally low titre and low affinity, based on the IgM isotype.** The relevance of pre-existing ADAs for biotherapeutics in general is poorly understood, but they may have an effect on pharmacological and clinical parameters (Xue *et al*, 2013).

Section 2 Objective(s) and Endpoint(s). Exploratory. 4nd row

ADDED TEXT

To explore the impact of pre-existing ADAs on the PK of GSK2831781	• **GSK2831781 PK parameters following single intravenous dose: AUC(0-∞), AUC(0-t), AUC(0-Week4), %AUCex, Cmax, tmax, tlast, CL, Vss, MRT, λz and t ½ when assessable**

Section, 3.3.1 Design Rationale, 9th paragraph

ADDED TEXT

Due to the presence of pre-existing ADA in a variable percentage in sera from both healthy and psoriatic human subjects, the initial investigation of GSK2831781 will be carried out **initially** in ADA negative subjects in Part A of the study to minimise the potential for diluting/confounding a signal of pharmacological or clinical response. **However, for GSK2831781 to have development potential, it will need to be used in a mixed ADA population. Therefore, after initial 28 day safety information is available for the DTH cohort at the highest dose for healthy volunteers, an additional cohort of healthy volunteers (without DTH) with pre-existing ADA will be dosed at the same dose level. Subjects with psoriasis in Part B of the study will then be from a mixed population with and without pre-existing ADAs, after initial sentinel dosing in subjects without pre-existing ADA. Subjects in the psoriasis cohorts will be recruited according to the following stratification: 4 ADA negative on active: 2 ADA negative on placebo and 2 ADA positive on active: 1 ADA positive on placebo. This will support a comparison of the effects of GSK2831781 at each dose level irrespective of ADA status, and will allow an exploration of the effect of ADA on PK across the dose levels.**

CHANGE 2

To correct typographical error in assessment day for an endpoint.

Section 2 Objective(s) and Endpoint(s). Secondary. 2nd row

REVISED TEXT

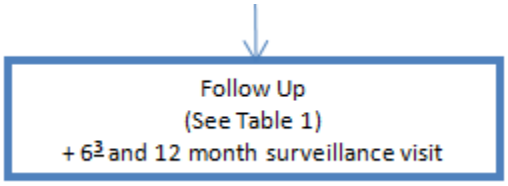
To evaluate the pharmacology of a single IV dose of GSK2831781 in psoriasis patients.	• Change from baseline in LAG-3+ cells in lesional biopsies at Day ~~1~~**15** and 29 measured by IHC

CHANGE 3

Change to indicate change in study design - that subjects with pre-existing ADA will now be recruited.

Section 3.1 Study Schematic

REVISED/ADDED TEXT



1. If, after a dose of 2 TU PPD, the induration is <6mm at day 3, the dose will be increased to 10 TU PPD and the 48 period will restart.

2. The highest concentration of PPD given on Day 3 will be the fixed dose for subsequent challenges

3. 6 month surveillance visit not required for 0.15mg/kg dose as coincides with Follow Up visit

Patients with Psoriasis
(6 active: ~~2~~3 placebo)

Section 3.1.2 Study Design Summary, Table 1

REVISED/ADDED TEXT

Planned Doses	**Number of subjects (active:placebo)**	**Safety Follow-up period to progress to next subjects/cohorts**	**PPD DTH Challenge if Healthy volunteer/ Biopsy if patient**	**Follow-up and end of exclusion of systemic immunosuppressives**
0.15mg/kg	6:6	1:1 wait 48 hours post-dose 5:5 wait 28 days post-dose	DTH	Day 219 ± 7 days (190 days post-dosing)
0.15mg/kg*	**6:2**	**1:1 wait 48 hours post-dose** **5:1 wait 28 days post-dose**	**No DTH**	**Day 189 ± 7 days** **(190 days post-dosing)**
Note: Cohort with a DTH starts dosing on Day 29 ***Note: No DTH cohort at dose level 0.15mg/kg is in subjects with pre-existing ADA. All previous cohorts are in subjects without pre-existing ADA** Maximum dose for healthy volunteers may change based on emerging exposure (See Section 3.2.1)				
Psoriasis Patients (Pre-existing ADA- and ADA +)				
~~0.15mg/kg~~	6:2**3** **(ADA-ve 4:2** **ADA+ve: 2:1)**	1:1 **ADA-ve** wait 48 hours post-dose 5:~~1~~**2** wait 28 days post-dose	Biopsy	~~190 days post-dosing ± 7 days~~
0.5mg/kg				230 days post-dosing ± 7 days
1.5mg/kg				270 days post-dosing ± 7 days
5mg/kg				300 days post-dosing ± 7 days

Section 3.2 Study Design Detail. 1st paragraph 2nd and 3rd sentences

ADDED TEXT

In Parts A and B of the study subjects will be screened for pre-existing ADA status and **initially in Part A** only subjects who do not have pre-existing ADAs will be randomised. **A cohort (cohort 6) of subjects positive for pre-existing ADA at the maximum healthy volunteer dose of 0.15mg/kg will then be dosed. Part B will include subjects with both negative and positive pre-existing ADA status, stratified by their ADA status, as outlined in Table 1**.

Section 3.2 Study Design Detail. 3rd paragraph 4th sentence

REVISED TEXT

The first cohort of patients with plaque psoriasis will begin at the ~~same dose as~~**next dose level after** the maximum dose administered to healthy volunteers.

Section 3.2 Study Design Detail. PART A Healthy volunteers without DTH, 2nd paragraph 1st sentence, 3rd paragraph 3rd sentence, 10th paragraph 1st and 2nd sentences

REVISED

For cohorts 3 ~~and,~~4 **and 6**, one active and one placebo subject will be recruited initially.

ADDED TEXT

Once data up to 28 days post dose has been collected for all subjects within cohort 6, the DEC will review the safety data along with the available PK data, available PD data from cohort 6, and also the DTH clinical response data from the Healthy Volunteer (DTH) cohort 5 (below), before switching to patients with plaque psoriasis.

REVISED/ADDED TEXT

All subjects **in cohorts 1, 2, 3 and 4** will attend a surveillance visit at 6 and 12 months. **As the follow-up visit is at approximately 6 months (190 days post-dose, as per Table 1), subjects in the 0.15mg/kg cohort 6 do not require an additional post-dose surveillance visit at 6 months and will only attend a surveillance visit at 12 months.**

Section 3.2 Study Design Detail. PART A Healthy volunteers with DTH, 1st paragraph 3rd sentence

REVISED/ADDED TEXT

Once data up to 28 days post dose has been collected for all subjects within the cohort, the DEC will review the safety data along with ~~theavailable PK data, the DTH clinical response and~~ available PD data, before ~~switching to patients with plaque psoriasis~~ **dosing a cohort of healthy volunteers with pre-existing ADA, at the same dose, without DTH.**

Section 3.2 Study Design Detail. PART B Psoriasis patients, 1st paragraph 1st and 2nd sentences

REVISED TEXT

At the beginning of each cohort **sentinel dosing in subjects without pre-existing ADA will occur, such that** one subject will receive active and one subject will receive placebo. After review of the safety data at 48 hours post-dose an additional 5 active **(3 without and 2 with pre-existing ADA)** and ~~1~~**2** placebo subject**s (1 with and 1 without pre-**

existing ADA) will be dosed (no more than 2 subjects per day with dosing separated by at least 1 hour).

Section 4.1 Number of Subjects, 1st paragraph

REVISED TEXT

Approximately ~~64~~**67** subjects will be enrolled to complete dosing and critical assessments. The subject numbers will be split to approximately ~~32~~**40** healthy volunteers and ~~32~~**27** patients with psoriasis.

Section 4.2.2 Exclusion Criteria #8

ADDED TEXT

8. **Part A (only cohorts, 1-4 without DTH challenge, and DTH cohort 5) only:**Subjects who test positive for pre-existing ADA to GSK2831781 at screening.

Section 5.3 Treatment Assignment, 2nd paragraph 3rd sentence

ADDED TEXT

In Part B, the sentinel subjects will be required to be ADA negative and subsequent subjects will be stratified by ADA status (ADA negative or ADA positive).

Section 5.3 Treatment Assignment, Table

REVISED TEXT

Regimen	Description	Ratio (Active:Placebo)
E	0.15mg/kg GSK2831781 IV single dose	1:1 for HV **DTH (ADA-)** 3:1 for ~~Psoriasis patients~~ **HV No DTH (ADA +)**
F	0.5mg/kg GSK2831781 IV single dose	**4:2 for psoriasis (ADA-)** **2:1 for psoriasis (ADA+)** ~~3:1~~
G	1.5mg/kg GSK2831781 IV single dose	**4:2 for psoriasis (ADA-)** **2:1 for psoriasis (ADA+)** ~~3:1~~
H	5mg/kg GSK2831781 IV single dose	**4:2 for psoriasis (ADA-)** **2:1 for psoriasis (ADA+)** ~~3:1~~

Section 6.7.1 Blood Sample Collection, 2nd paragraph

REVISED TEXT

In Parts A **cohorts 1-5** ~~and B~~, only subjects with a negative pre-existing ADA status at screening will be included.

Section 9.1 Hypothesis and Treatment Comparisons, 4th paragraph

ADDED TEXT

Exploratory comparisons will be conducted to investigate the effect of ADA status at baseline on the pharmacokinetics of GSK2831781.

Section 9.2.1 Sample Size Assumptions, 2nd paragraph

REVISED TEXT

It is anticipated that sufficient number of healthy volunteers and patients will be enrolled in the study so that data are obtained from approximately ~~32~~**40** healthy subjects (~~20~~**26** on

active, ~~12~~ **14** on placebo) and approximately ~~32~~**27** psoriasis patients (~~24~~**18** on active, ~~8~~**9** on placebo).

Section 9.3.1 Interim Analysis, 1st paragraph 1st sentence, 2nd paragraph 1st sentence

ADDED TEXT

Dependant on the dose cohorts reached in the escalation, formal interim analyses may be performed after the last subject in the Healthy Volunteer **DTH** ~~group~~ **cohort** has completed their 4 week post dose assessment visit, and also after the last subject in the Psoriasis group has completed the final PK assessment visit, to inform internal development decisions.

For Parts A and B of the study, review of safety, tolerability, available pharmacokinetic and DTH induration for healthy volunteers or PASI and PLSS for psoriasis patients at the end of each cohort will be performed by DEC to aid decisions to proceed to higher dose strengths **or, between cohorts 5 and 6 to subjects with pre-existing ADA**.

Section 9.3.2.2 Pharmacokinetic Analysis, Derived Plasma Pharmacokinetic Parameters, 15th paragraph

ADDED TEXT

Descriptive statistics (n, arithmetic mean, standard deviation, 95%CI, minimum, median and maximum,) will be calculated for all pharmacokinetic parameters **by treatment and pre-existing ADA status, where applicable**.

CHANGE 4

Change to indicate removal of psoriasis cohort which is the same as the top dose level for healthy volunteers

Section 3.2.1 Study Design Detail, 1st paragraph 4th sentence

ADDED TEXT

If a dose switch then occurs later, psoriasis cohorts would start **one dose higher than** ~~at~~ the last dose used in healthy volunteers.

Section 3.3.1 Design Rationale, 8th paragraph 1st sentence

REVISED TEXT

Dose escalation in psoriasis patients will be started at ~~the same dose as~~ **one dose higher than** the maximum dose investigated in healthy volunteers following a DTH challenge.

Section 5.4 Planned Dose Adjustments, 5th paragraph 3rd bullet

ADDED TEXT

- **Replacement of the highest dose level in psoriasis cohorts with a lower dose than the scheduled starting dose for psoriasis cohorts**

CHANGE 5

Change in risk mitigation activities to support inclusion of subjects with pre-existing ADA

Section 3.4 Risk Management, Table 5, IP risk

ADDED TEXT

Potential risk	Summary of data	Impact eligibility criteria	Strategy-monitoring criteria
IP risk			
Infusion-reaction/hypersensitivity	The first study in humans will be conducted by IV administration.	Subjects will be excluded if history of severe allergic reaction. (Exclusion #4) **Initial cohorts (1-5) will exclude subjects with pre-existing ADA (Exclusion criteria #8)**	Subjects will be in a phase 1 unit and closely monitored for 72 hours post dosing. IV doses will be administered for 2 hours. However, dosing duration may be modified based on safety data with the approval of the PI and sponsor. Guidelines for monitoring relevant adverse events encompassing hypersensitivity, angioedema and anaphylaxis and for management of acute anaphylactic shock and minor allergic episodes will be in place at investigational sites. Study sites will include facilities and expertise for emergency care/resuscitation, including access to hospital and Intensive Care Unit (ICU). **Pre-medications are permitted at investigator's discretion (Section 6.3.4).**

Potential risk	Summary of data	Impact eligibility criteria	Strategy-monitoring criteria
Cytokine release	Hyper-immune activation leading to activation of the innate immune system is only a theoretical safety concern, as there is no *in vitro* and *in vivo* evidence of cytokine release associated with LAG-3+ and T cell depletion mechanism, in the presence or absence of pre-existing ADA.	**Initial cohorts (1-5) will exclude subjects with pre-existing ADA (Exclusion criteria #8)**	Study sites will include facilities and expertise for emergency care/resuscitation, including access to hospital and ICU. Monitoring for clinical symptoms associated with cytokine release such as fever, nausea, chills, hypotension, tachycardia, asthenia, headache, rash, tongue and throat swelling, and dyspnea. Standard safety haematology and clinical chemistry assessments to include CRP will be performed. In addition limited cytokine analysis will be performed within 24 hours if any clinical signs suggest cytokine release syndrome (See Section 6.3.7)
Type III Hypersensitivity (Immune complex deposition in kidney, liver, skin)	**Reactions due to immune complexes formed from pre-existing ADA and GSK2831781 are a theoretical risk. Risk is assessed as low as pre-existing ADAs are predominantly of low titre.**	**Initial cohorts (1-5) will exclude subjects with pre-existing ADA (Exclusion criteria #8)**	**Targeted clinical monitoring will include physical examination, urinalysis to detect haematuria and proteinuria, and clnical chemistry to monitor renal and liver function.**

Section 6.3.4 Infusion-related Reactions and Hypersensitivity Reactions, 1st paragraph 1st sentence

ADDED TEXT

Subjects with a history of allergies or urticaria, allergic responses to foods, drugs, or insects may receive diphenhydramine and paracetamol (acetaminophen) prior to dosing at the discretion of the Principal Investigator **or as a result of emerging data**.

CHANGE 6

Change to apply population appropriate BMI inclusion criteria for subjects in Germany.

Section 4.2.1 Inclusion Criteria #2

REVISED TEXT

2. A body weight ≤120 kg and BMI within the range 19 – 32 kg/m2 (inclusive). For **healthy volunteer** subjects participating in Germany the BMI must be within the range of 19 – 30 kg/m2 (inclusive).

CHANGE 7

Change to allow assessments for clinical response in psoriasis subjects beyond Day121 if a response is still present

Section 6.1 Time and Events Table, Table 6 Screening and Follow-up

REVISED/ADDED TEXT

Protocol Activity	Screening[i]	Follow Up
	Up to 35 Days prior to Day 1	Week X[a]
Window		
Psoriatic Body Surface Area	X[f]	**X[k]**
Psoriatic Lesion Severity Score	X[f]	**X[k]**
Psoriasis Area Severity Index		**X[k]**

k Subjects with psoriasis may be assessed for BSA, PASI and for index lesion PLSS, if reduction from baseline is maintained at Day 121 (See Section 6.3.5.3)

Section 6.3.5 Immunosuppression, Infections and Malignancies

ADDED TEXT

6.5.3 Follow-up of subjects with psoriasis who exhibit clinical effect

Subjects who maintain a clinical response in BSA, PASI and or PLSS (of index lesion) at Day 121 compared to baseline may be assessed for clinical response at follow-up and if still maintained, at the final surveillance visit.

CHANGE 8

Change to allow flexibility of assays used for exploratory assessment of ex vivo stimulation.

Section 6.1 Time and Events Table , Table 6, Table 7, Table 8, Table 9,

REVISED TEXT

Replace Ex Vivo Antigen Stimulation Test

WITH

Ex Vivo Antigen/**Cytokine** Stimulation Test

Section 6.8.6 *Ex vivo* Antigen Stimulation

REVISED TEXT

6.8.6 Ex vivo Antigen/Cytokine Stimulation

Studies may be initiated, dependent on feasibility, to assess antigen specific ~~or~~ polyclonally **or cytokine** activated T cell response in *ex vivo* blood. Amongst other assays to measure antigen specific T cell responses, an IFNγ T cell ELISpot may be used to monitor antigen-specific immune responses to the challenge antigens, as well to Tetanus toxoid or other antigens as an internal/safety control.

CHANGE 9

To clarify extent of additional duration of screening for vaccinated subjects

Section 6.1 Time and Events Table, Table 6 Screening and Follow-up, footnote i

ADDED TEXT

i. Screening can be longer**, up to a maximum of 42 days** if vaccinations are required prior to dosing.

CHANGE 10

To clarify measurement of Body Surface Area

Section 6.4.1 Body Surface Area (BSA), 2nd paragraph

REVISED TEXT

The BSA will be estimated by the ~~number of patients' palm areas affected (the patients palm and thumb together), assuming that one "handprint" reflects approoximately 1% of~~ **'palm' method whereby the palm to the proximal interphalangeal (PIP) joints, including the thumb, of the patient represents 1% of the total** BSA**)** (~~Ramsey~~Christensen *et al*, ~~1991~~**2006**).

Section 11 References

ADDED TEXT

Christensen TE, Callis KP, Papenfuss J, et al. Observations of Psoriasis in the Absence of Therapeutic Intervention Identifies Two Unappreciated Morphologic Variants, Thin-Plaque and Thick-Plaque Psoriasis, and their Associated Phenotypes. *J Invest Derm,* 2006;126:2397-2401.

DELETED TEXT

~~Ramsay B, Lawrence CM. Measurement of involved surface area in patien ts with psoriasis. *Br J Dermatol*. 1991 Jun;124(6): 565-70.~~

CHANGE 11

To add flexibility to clinical specimen potentially used for transcriptomics

Section 6.8.1 LAG-3+ cells in DTH challenge site skin biopsies (Part A), 4th paragraph 2nd sentence

ADDED TEXT

These sections may also be analysed for histology including but not limited to the number of perivascular infiltrates **and mRNA transcriptome analysis for novel biomarkers (see Section 6.8.9 and SPM)**.

AMENDMENT 6

Summary of Amendment Changes with Rationale

This amendment has been introduced to meet country specific regulatory and ethics requirements.

This includes update of the exclusion criteria to include aspartate aminotransferase and/or gamma glutamyltransferase outside of normal range at screening and/or at baseline and amendment of text for malignancy history. Specific sections of the protocol have also been updated to provide greater clarity regarding the composition of the Dose Escalation Committee and to provide a clearer explanation of the decision making by the DEC.

List of Specific Changes

CHANGE 1

Change to provide clearer explanation of dose escalation activities by the DEC.

Section 3.2 Study Design Detail, 4th paragraph

REVISED TEXT

Based on ~~DEC review~~ **the criteria which are defined in Section 5.4, 'Planned Dose Adjustments', Section 5.7 'Dose Adjustment/Stopping Pharmacokinetic Criteria' and the DEC Charter, the DEC may recommend that,** doses and intervals between dose~~s~~ **levels** ~~may be~~ **are** changed **within these limits** based on any of the following emergent data: safety and tolerability, PK, clinical measures and PD (~~See Section 5.4).~~

CHANGE 2

Reference to protocol Section 3.2 added to text.

Section 3.4 Risk Management, 2nd paragraph, 5th line

REVISED TEXT

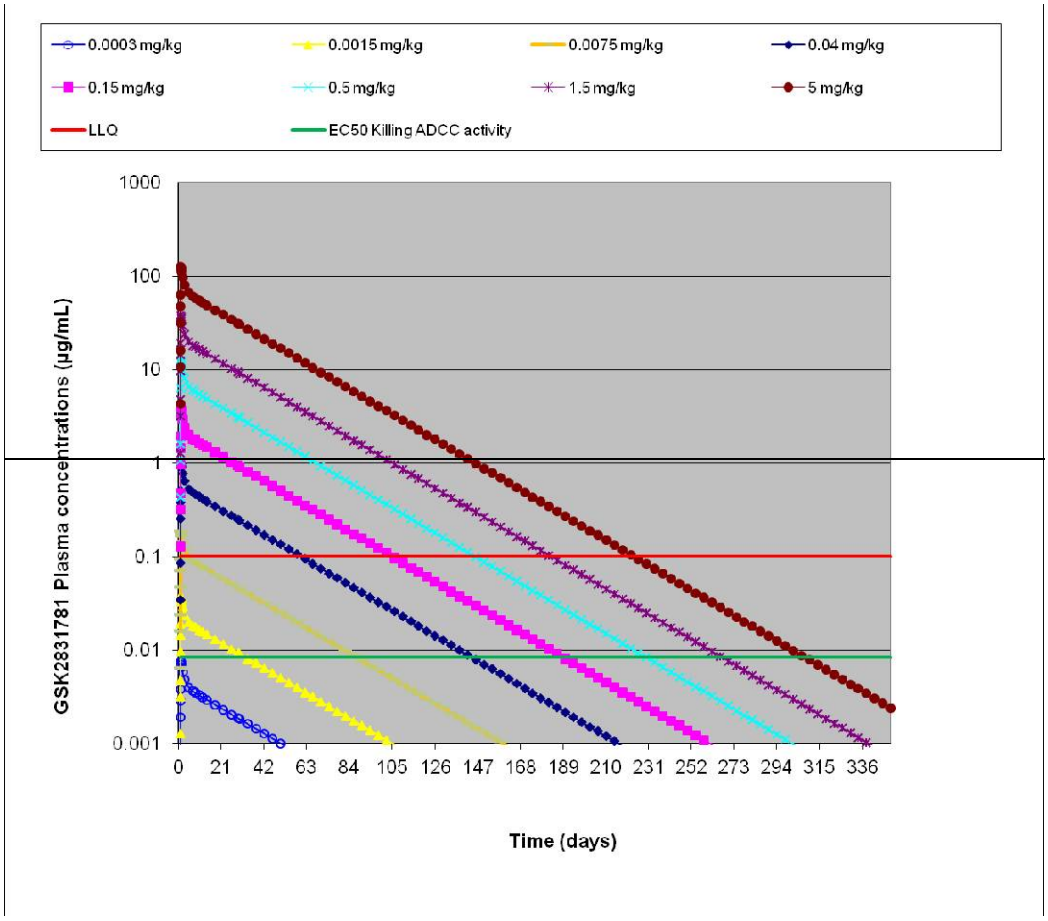
After the GSK medical monitor and investigator have reviewed the safety data up to 48 hours, the remaining subjects (where appropriate) from that cohort will be dosed **(see Section 3.2)**.

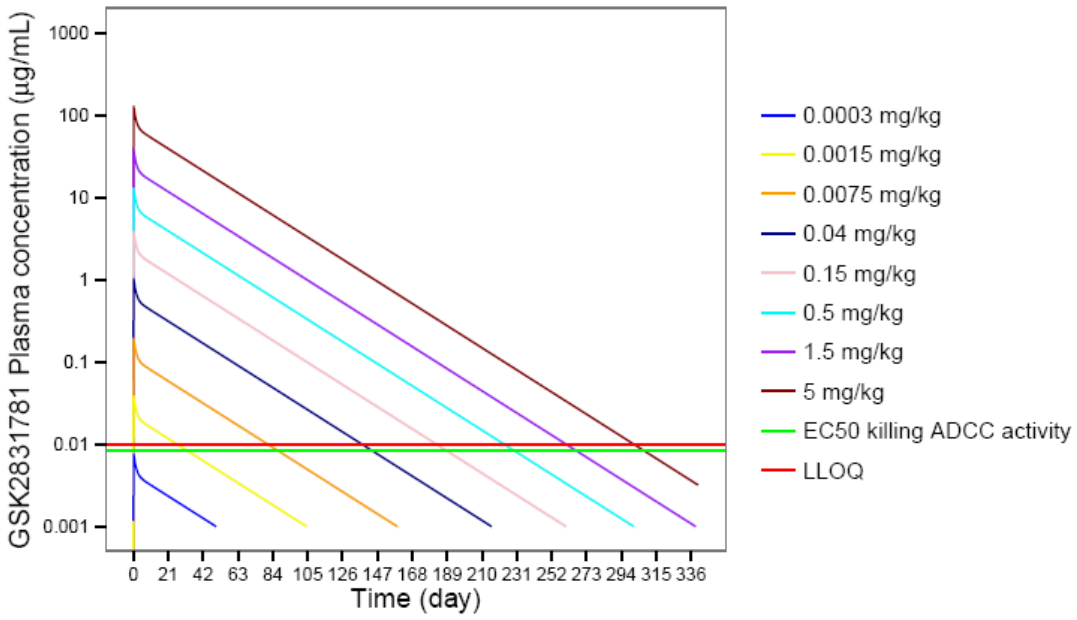
CHANGE 3

LLQ stated in Figure 1 was based on original planned technology but assay subsequently required different technology which was more sensitive (100ng/ml rather than 10 ng/ml). Figure 1 has been updated with correct LLQ.

Section 3.3.2.1 Human PK Prediction, Figure 1

REVISED SCHEMATIC





CHANGE 4

Updated Hepatotoxicity Section of the Risk Table to reflect changes made to Exclusion Criteria 10.

Section 3.4, Table 5

REVISED TEXT

Hepatotoxicity	Minimal to mild Kupffer cell activation at doses >30mg/kg in primates.	Only subjects with liver chemistry results within the limits specified in the inclusion **and exclusion** criteria will be included (Inclusion #10; **Exclusion #10**)	Standard GSK liver stopping applied for dosing new subjects, and monitoring guidance (See Section 5.5 and Section 5.6.1)

CHANGE 5

Modification of exclusion criteria to remove exception for subjects with malignancy and to include aspartate aminotransferase and gamma glutamyltransferase outside of normal range at screening and/or baseline.

Section 4.2.2 Exclusion Criteria

REVISED TEXT

9. History of malignancy~~, except for basal cell or squamous cell carcinoma, or *in situ* cervical carcinoma that has been fully treated and shows no evidence of recurrence.~~

10. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). **Subjects with an aspartate aminotransferase and/or gamma glutamyltransferase level above the upper limit of normal at screening and/or baseline will be excluded.**

CHANGE 6

Modification of text to give further detail on the membership of the Dose Escalation Committee and to provide more explicit information on the decision making of the DEC.

Section 5.4 Planned Dose Adjustments, 2nd paragraph 1st sentence

REVISED TEXT

Safety/tolerability data monitoring and the decision to proceed to the next dose level of GSK2831781 will be made by the DEC, consisting of the Principal Investigators (or appropriate designees), GSK Medical Monitor, GSK Study Team Leader (either Clinical Investigator Lead [CIL] and/or Operations and Science Lead [OSL]), GSK CPMS

representative, a GSK GCSP representative, and GSK Statistician **and an independent GSK expert on FTIH studies. The DEC may also call on *ad hoc* internal/external members with specific expertise**.

Section 5.4 Planned Dose Adjustments, 3rd paragraph 3rd sentence and 4th paragraph 3rd sentence

REVISED TEXT

Outcomes of DEC review ~~could~~ include escalation to the next dose, stopping the escalation,

Section 5.4 Planned Dose Adjustments, after 4th paragraph

ADDED TEXT

Apart from stopping of the dose escalation, alterations to the planned dose levels and intervals between dose levels will be limited to the following. Other changes will require a substantial amendment:

- **Reduction in the dose increment to the next dose level (based on higher exposure than predicted and/or safety data of clinical significance).**
- **Introduction of an additional dose level cohort between the current and next planned dose level (based on higher exposure than predicted and/or safety data of clinical significance).**

CHANGE 7

Reference to protocol Section 5.4 added to text.

Section 9.3.1 Interim Analysis, 4th paragraph, 5th line

REVISED TEXT

PK data will provide supporting evidence for each dose modification decision. Importantly, if the emerging PK data is significantly different from the predicted values, adjustment may have to be made to the planned doses **(see Section 5.4)**.

CHANGE 8

Reference to current IB updated in Section 1.2.1 GSK2831781, Section 4.2 Eligibility Criteria and References.

REVISED TEXT

~~2013N175515_00~~ **2013N175515_01**

AMENDMENT 5

Summary of Amendment Changes with Rationale

This amendment is to replace 2 Healthy Volunteer cohorts undergoing DTH challenge with those without DTH challenge, in order to reduce complexity of study and improve operational feasibility.

The opportunity has been taken to make some other changes to correct text that was not logistically possible, or required clarification, add flexibility to timing of vaccination, and remove limitation in PK assessment due to an improved assay. Additional text has also been added to the eligibility criteria in order to meet country specific ethics requirements.

List of Specific Changes

CHANGE 1

Change to indicate change in study design - that the 2 initial DTH cohorts have been replaced by no DTH cohorts, including resulting change in subject numbers.

Synopsis, 2nd paragraph, 2nd and 3rd sentences

REVISED TEXT

Part A of the study will be a single dose escalation in healthy volunteers. The first ~~2~~**4** cohorts will be given an intravenous (IV) dose of GSK2831781 or placebo over approximately 2 hours on Day 1. The ~~latter~~ **last** healthy volunteer cohort~~s~~ will receive a skin challenge of 2 Tuberculin Unit (TU) or 10TU Purified Protein Derivative (PPD) on Day 1.

Section 1.1 Study Rationale, 1st paragraph, 1st ,2nd 4th, 5th sentences

REVISED TEXT

This study is the first administration of GSK2831781 in humans and will evaluate in two parts the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of single intravenous (IV) doses of GSK2831781 administered to healthy volunteers **(Part A), including a cohort of those** previously vaccinated with Bacillus Calmette Guérin (BCG) (Part A delayed type hypersensitivity [DTH] cohort~~s~~) and patients with plaque psoriasis (Part B). Single dose escalation will allow for the identification of any immediate dose-limiting toxicities. Investigation of pharmacology in healthy subjects in **the** Part A **DTH cohort** will **confirm whether the selected dose is** ~~aim to select doses~~ likely to result in pharmacodynamic effects in immune-inflammatory diseases associated with the target Lymphocyte Activation Gene 3+ (LAG-3+) T cells, which are then tested in Part B. As there are very low levels of LAG-3+ T cells in blood it is necessary to monitor LAG-3+ cells at the site of antigen challenge or the disease site. The use of a DTH in healthy subjects in Part A allows investigations into the impact of GSK2831781 on immunological endpoints after a controlled challenge. The switch to patients with psoriasis in Part B, ~~once a pharmacological effect has been seen, or~~ at a

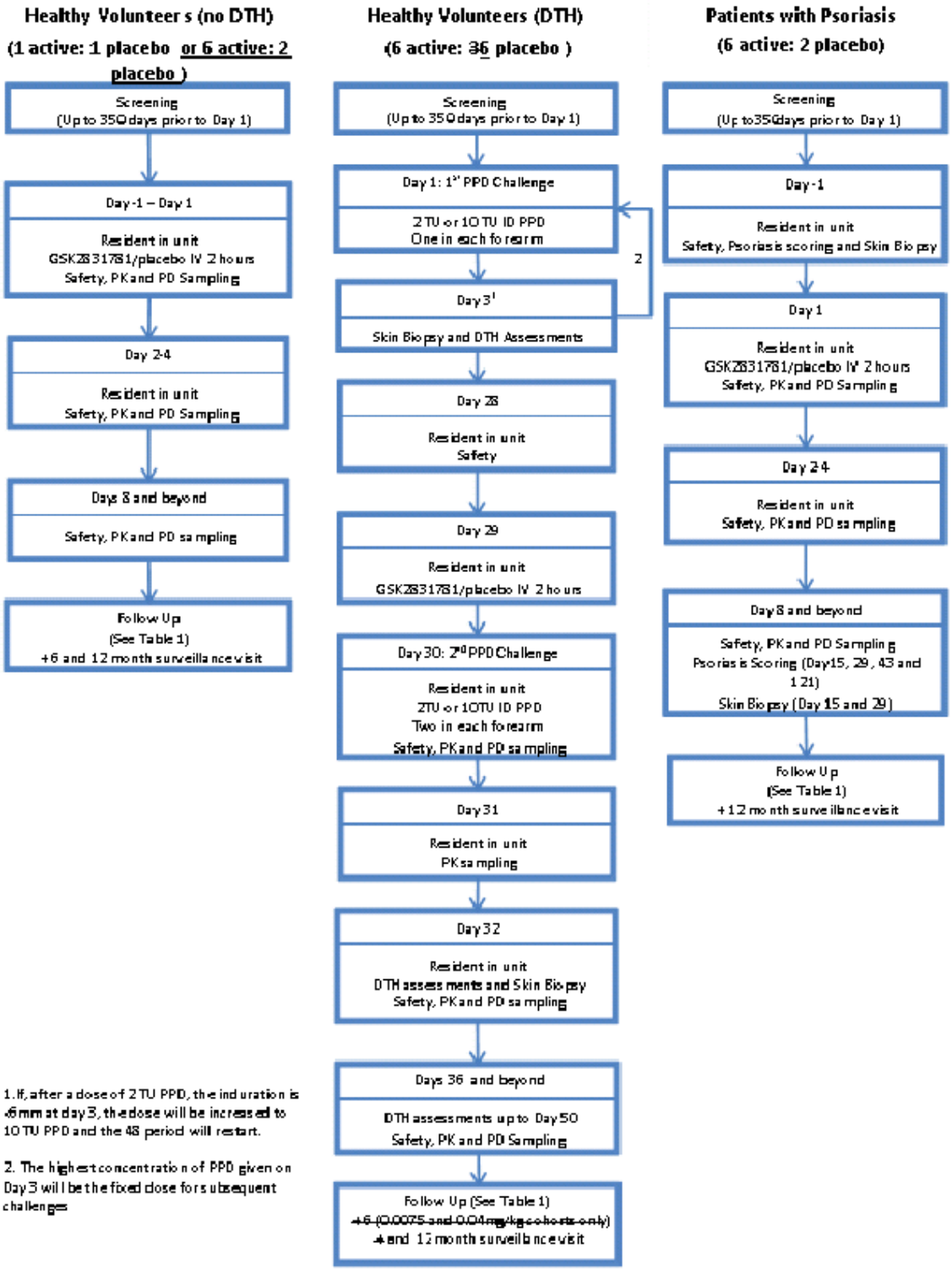
dose by which effects would be expected, then allows investigations of higher doses in a chronic disease setting. Measuring the pharmacology of GSK2831781 using the depletion of LAG-3+ T cells in skin biopsies from Tuberculin Purified Protein Derivative (PPD) skin challenge and lesional skin biopsies from patients with psoriasis, is an important component of the study and **for the latter** may enable an understanding of the dose response relationship, which will be important for decision making and the design of future studies in immuno-inflammatory diseases, including psoriasis.

CHANGE 2

Changes made to reflect the updated study design and increased screening period from 30 to 35 days.

Section 3.1 Study Schematic

REVISED GRAPHIC



CHANGE 3

Change to indicate change in study design - that the 2 initial DTH cohorts have been replaced by no DTH cohorts, including resulting change in subject numbers.

Section 3.1.2 Study Design Summary, Table 1

REVISED TEXT

Planned Doses	**Number of subjects (active:placebo)**	**Safety Follow-up period to progress to next subjects/cohorts**	**PPD DTH Challenge if Healthy volunteer/ Biopsy if patient**	**Follow-up and end of exclusion of systemic immunosuppressives**
0.0075mg/kg	**6:~~3~~2**	**1:1 wait 48 hours post-dose** **5:~~2~~1 wait 28 days post-dose**	**No DTH**	**Day ~~11~~385 ± 2 days** **(84 days post-dosing)**
0.04mg/kg				**Day ~~175~~147 ± 3 days** **(146 days post-dosing)**
0.15mg/kg	**6:6**	**1:1 wait 48 hours post-dose** **5:~~25~~ wait 28 days post-dose**	**DTH**	**Day 219 ± 7 days** **(190 days post-dosing)**
Note: Cohort~~s~~ with a DTH start**s** dosing on Day 29 Maximum dose for healthy volunteers may change based on emerging exposure ~~or earlier reduction in DTH response~~(See Section 3.2.1)				

CHANGE 4

Change to indicate change in study design - that the 2 initial DTH cohorts have been replaced by no DTH cohorts.

Section 3.2 Study Design Detail, 3rd paragraph, 2nd sentence

REVISED TEXT

Healthy volunteers will be dosed up to a maximum dose of 0.15mg/kg (unless criteria in Section 3.2.1 are met) ~~or until a reduction in DTH response occurs (whichever is sooner).~~

CHANGE 5

Change made to reflect the increased screening period from 30 to 35 days.

Section 3.2 Study Design Detail, PART A, Healthy volunteers without DTH, Healthy volunteers with DTH and PART B, Psoriasis patients, 3rd paragraph

REVISED TEXT

Subjects will attend screening up to ~~30~~ **35** days before dosing

CHANGE 6

Change to indicate change in study design - that the 2 initial DTH cohorts have been replaced by no DTH cohorts, including resulting change in subject numbers.

Section 3.2 Study Design Detail, PART A, Healthy volunteers without DTH

REVISED TEXT

In cohorts 1 and 2, one active and one placebo subject will be recruited ~~in each cohort~~**.**

For cohorts 3 and 4, one active and one placebo subject will be recruited initially. After the GSK medical monitor and Investigator have reviewed the safety data up to 48 hours post dose, an additional 5 active and 1 placebo subjects will be dosed (no more than 2 subjects per day with dosing separated by at least 1 hour).

After the DEC have reviewed the safety data up to 28 **days on all subjects within the cohort** along with the available PK data, a dose escalation may occur to the next planned dose. If safety findings are noted in the active subjects **in cohorts with 2 subjects**, the cohort may be expanded to a maximum cohort size of 6:3 (active:placebo) or the escalation stopped (See Section 5.5).

CHANGE 7

Change to indicate change in study design - that the 2 initial DTH cohorts have been replaced by no DTH cohorts, including resulting change in subject numbers.

Section 3.2 Study Design Detail, PART A, Healthy volunteers with DTH, 1st paragraph

REVISED TEXT

One active and one placebo subject will be recruited initially ~~in each cohort~~. After the GSK medical monitor and investigator have reviewed the safety data up to 48 hours post dose, an additional 5 active and ~~2~~**5** placebo subjects will be dosed (no more than 2 subjects per day with dosing separated by at least 1 hour). Once data up to 28 days post dose has been collected for all subjects within the cohort, the DEC will review the safety data along with the available PK data, the DTH clinical response data and available PD data, before ~~proceeding to the next dose level or~~ switching to patients with plaque psoriasis.

CHANGE 8

Change to indicate change in study design

Section 3.2 Study Design Detail, PART A, Healthy volunteers with DTH, 8th paragraph, 1st sentence

DELETED TEXT

~~All subjects in the 0.0075 and the 0.04mg/kg cohorts will attend a surveillance visit at 6 months and 12 months.~~

CHANGE 9

Change to indicate change in study design.

Section 3.2.1 Healthy Volunteer to Patient Switching, 1st, 2nd paragraph 1st and 2nd sentences

DELETED TEXT/REVISED TEXT

~~The switch from healthy volunteers to patients with psoriasis will occur when clear reduction of DTH response is found on review by the DEC. Reduction of DTH response leading to a decision to switch dosing to psoriasis patients will be defined as at least 3 out of 6 subjects on active treatment within a cohort showing an induration response on post dosing PPD re-challenge less than or equal to their baseline induration response. Switching to psoriasis patients may also occur if a strong trend in inhibition is seen, as will be documented in the DEC Guidance/Charter document. If there is no reduction detectable by 0.15mg/kg the switch will occur at this dose. This will ensure that healthy volunteers do not require more than approximately 6 months lifestyle restrictions that is required until GSK2831781 plasma concentrations become on average below the *in vitro* EC50 for LAG-3+ T cells depletion (See Section 3.3.2).~~

~~If a dose switch occurs earlier than 0.15mg/kg, extra cohorts would be added at the lower doses for psoriasis patients so that the starting dose is the same as the last dose used in healthy volunteers.~~ When the ~~decision to~~ switch to psoriasis patients is made, no further dosing of healthy volunteers will occur.

CHANGE 10

Change to indicate change in study design.

Section 3.3.1 Design Rationale, 1st paragraph

REVISED TEXT

This study has been designed to be a 2-part study. Firstly, **in Part A,** a single ascending dose escalation will enrol healthy volunteers ~~previously vaccinated with BCG (Part A DTH cohorts only)~~ and then Part B will ~~initiate and~~ enrol patients with psoriasis.

Section 3.3.1 Design Rationale, 2nd paragraph 2nd sentence

The assessment of GSK2831781 pharmacology in healthy subjects is challenging due to the low numbers of LAG-3+ T cells in the blood of healthy volunteers which makes the

monitoring of the depletion of this cell population technically difficult. To circumvent this issue, **the last cohort of** Part A of the study will employ a DTH model of a PPD intradermal injection, in healthy volunteers previously vaccinated with BCG to induce a DTH skin reaction and an increase of LAG-3+ T cells in the skin.

Section 3.3.1 Design Rationale, 5th paragraph 1st sentence

Proof of pharmacology and mechanism will be tested in healthy subjects ~~up to a dose demonstrating reduction of DTH response, or~~ up to 0.15mg/kg (to limit duration of exposure above the *in vitro* EC50 ADCC killing activity) before switching to psoriasis patients for further evaluation of pharmacology and mechanism (see Section 3.3.2.3 for dose rationale).

CHANGE 11

Increase in sensitivity of PK assay has made sentence redundant.

Section 3.3.2.1 Human PK Prediction, 1st paragraph, 7th sentence

DELETED TEXT

~~Of note, with the current expected limit of quantification of the bioanalytical assay of 100 ng/mL, plasma concentrations are not anticipated to be measurable at the 3 first doses proposed (0.0003, 0.0015 and 0.0075 mg/kg).]~~

CHANGE 12

Text revised to reflect updated study design.

Section 3.3.2.3 Assessment of GSK2831781 pharmacology in healthy volunteers, 2nd paragraph

REVISED TEXT

To assess the pharmacology of GSK2831781 in healthy volunteers and confirm the findings in the baboon study conducted with the parent molecule IMP731 where a depletion of peripheral LAG-3 expressing T cells was associated with an inhibition of a DTH response (Poirier *et al*, 2011), a DTH challenge will be conducted at the ~~0.0075, 0.04 and~~ 0.15 mg/kg proposed dose~~s or until a pharmacological effect has been seen (see Section 5.4 Planned Dose Adjustments).~~

Section 3.3.2.3 Assessment of GSK2831781 pharmacology in healthy volunteers, 5th paragraph 1st and 2nd sentences

~~However, reduction of the DTH response could occur at a lower or higher dose. Therefore, the decisions to switch to psoriasis patients will be based on demonstration of reduction of the DTH response but with~~ **There will be** a maximum dose for healthy subjects of 0.15mg/kg (dose could be altered dependent on emerging PK data and/or PD data), to limit the duration of exposure above the in vitro EC50 ADCC killing activity

(where there are lifestyle and medication restrictions), to no more than approximately 6 months (See Section 3.2.1 and Section 5.4 Planned Dose Adjustments)

CHANGE 13

Vaccine changed to M-M-RVAXPRO as Priorix SPC has the 6 week requirement between MMR and PPD.

Section 3.4 Risk Management, Table 5 Summary of Key Issues, Their Impact and Strategy to Mitigate Risk – Vaccination section

REVISED TEXT

As per Boostrix-IPV and/or **M-M-RVAXPRO** ~~Priorix~~ or equivalent SPC.

CHANGE 14

Subject numbers updated to reflect updated study design.

Section 4.1 Number of Subjects, 1st paragraph

REVISED TEXT

Approximately ~~63~~ **64** subjects will be enrolled to complete dosing and critical assessments. The subject numbers will be split to approximately ~~31~~ **32** healthy volunteers and 32 patients with psoriasis.

CHANGE 15

Text updated to reflect updated study design and addition of anti-Hepatitis B core antibody testing to hepatitis B exclusion criteria to support new sponsor guidance for first time in human studies of immunosuppressive drugs. Text also added to meet country specific ethics requirements.

Section 4.2.1 Inclusion Criteria and Section 4.2.2 Exclusion Criteria

Amend all instances of 'Part A DTH cohorts' to 'Part A DTH cohort' and 'Part A (only cohorts with DTH challenge)' to 'Part A (only cohort with DTH challenge)

ADDED TEXT

4.2.1 Inclusion Criteria

2. A body weight ≤120 kg and BMI within the range 19 – 32 kg/m2 (inclusive). **For subjects participating in Germany the BMI must be within the range of 19 – 30 kg/m2 (inclusive).**

12. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form**, and has provided written informed consent.**

4.2.2 Exclusion Criteria

13. A positive pre-study Hepatitis B surface antigen **or Hepatitis B core antibody,** or positive Hepatitis C antibody result within 3 months of screening.

31. Vulnerable subjects (e.g. person kept in detention).

32. Subjects who are not able to understand and communicate in the native language of the country where the study is conducted.

33. Subjects who work for the Sponsor or CRO.

CHANGE 16

Table and text updated to reflect updated study design.

Section 5.3 Treatment Assignment, Regimen table rows 4-6

REVISED TEXT

Regimen	Description	Ratio (Active:Placebo)
C	0.0075mg/kg GSK2831781 IV single dose	~~2~~**3**:1
D	0.04mg/kg GSK2831781 IV single dose	~~2~~**3**:1
E	0.15mg/kg GSK2831781 IV single dose	~~2~~**1**:1 for HV 3:1 for Psoriasis patients

CHANGE 17

Text modified to reflect updated study design.

Section 5.4 Planned Dose Adjustments, 3rd paragraph, 1st sentence

REVISED TEXT

For healthy volunteer cohorts, once safety data up to 28 days post-dose has been collected in all subjects for that cohort, the DEC will review the safety/tolerability data (including trends in neutrophil counts), the available PK data and for **the** DTH cohort~~s~~, the clinical DTH response (induration diameter), before proceeding to the next dose level (See Section 3.2.1).

CHANGE 18

Text added to determine cause of clinical symptoms if required so as not to assume clinical symptoms are due to viral reactivation.

Section 5.6.5 Febrile Monitoring Criteria, 2nd sentence

REVISED TEXT

If the subject demonstrates any clinical symptoms consistent with viral reactivation e.g. fever, a blood sample will be taken and analysed for viral reactivation **and/or other appropriate medical investigations as suggested by the clinical context.**

CHANGE 19

Text modified to reflect updated study design.

Section 5.10.1 PPD 2TU and 10TU Dose, 1st paragraph, 3rd paragraph 1st sentence

REVISED TEXT

In Part A Healthy volunteers DTH cohort~~s~~ only

In **the** Part A DTH cohort~~s~~, on Day 1, 0.1ml of PPD 2 TU (0.04 µg/0.1ml) will be injected intradermally into the volar aspect of the left forearm and the volar aspect of the right forearm.

CHANGE 20

Text added to provide additional clarity regarding immunisations.

Section 5.14 Concomitant Medications and Non-Drug Therapies, 2nd sentence

REVISED TEXT

In those who are likely to require immunisation in the period up to the follow-up visit **for non-study reasons**, such as subjects requiring vaccinations or boosters for their professional activity, the administration of any required vaccination/booster should be given at least 4 weeks prior to Day 1.

CHANGE 21

Time and Events tables and footnotes revised to reflect updated study design.

All Time and Events Tables, ECG Footnote

Triplicate. Only required if screening ECG not within 3~~0~~**5** days of Day 1.

Section 6.1 Time and Events Table 7 (Day 8-121) and Footnotes

Out Patient Visits										
Day 8										
168 hour post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25[a]	Day 29[k]	Day 43	Day 57[l]	Day 85	Day 121
-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+2d	-/+2d	-/+2d	-/+3d
X		X		X		X	X	X	X	X
X	X	X	X	X	X	X	X	X	X	X
X		X		X		X	X	X	X	X
X		X		X		X	X	X	X	X
X						X			X	
X		X				X		X	X	X
X		X				X		X	X	X
X		X				X	X	X	X	X
X		X				X	X	X	X	X
X										

j. Triplicate. Only required if screening ECG not within 3~~0~~**5** days of Day 1.

k. **Cohort 0.0015mg/kg last out patient visit will be on Day 29.**

l. **Cohort 0.0075mg/kg last out patient visit will be on Day 57.**

Section 6.1 Time and Events Table 8 Footnotes

a. ~~Cohort 0.0075mg/kg last out patient visit will be on Day 85~~ **Triplicate. Only required if screening ECG not within 35 days of Day 1.**

o. ~~Triplicate. Only required if screening ECG not within 35 days of Day 1.~~

Section 6.1 Time and Events Table 10 Footnotes

a. When PK is taken in the healthy volunteer DTH cohort~~s~~ all PK times are relative to the start of the infusion on Day 29.

CHANGE 22

Text added to determine cause of clinical-symptoms if required so as not to assume clinical symptoms are due to viral reactivation.

Section 6.3.5 Immunosupression, Infection and Malignancies, final sentence

REVISED TEXT

If the subject demonstrates any clinical symptoms consistent with viral reactivation e.g. fever, then another sample would be taken and this and the baseline sample sent for analysis **and/or other appropriate medical investigations as suggested by the clinical context.**

CHANGE 23

Addition of anti-Hepatitis B core antibody testing to hepatitis B exclusion criteria to support new sponsor guidance for first time in human studies of immunosuppressive drugs.

Section 6.3.7 Clinical Laboratory Assessments, Other screening Tests, 2nd row

REVISED TEXT

Hepatitis B (HBsAg**, HBcAb**)

CHANGE 24

Add flexibility to allow timing of vaccination by extending default maximum screening period and specifying M-M-RVAXPRO vaccine for MMR.

Section 6.3.8 Vaccination

REVISED TEXT

Subjects who have no history of vaccination for diphtheria, pertussis, and tetanus may consent to receive a booster of an appropriate licensed combined vaccine. **at least 2 weeks prior to dosing** (If a suitable serology test is available to confirm vaccination status then this may be used prior to vaccinating.).

Subjects who have no history of vaccination for measles, mumps and rubella may ~~have a serology sample taken to assess levels of antibodies and if necessary may consent to receive a booster of an appropriate licensed combined vaccine.~~ consent to receive a booster of an appropriate licensed combined vaccine **(M-M-RVAXPRO or similar) at least 4 weeks prior to dosing which will be given after serology results are available to assess levels of antibodies**.

It has been reported that live attenuated measles, mumps, and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity (PPD challenge). Therefore, for this study, vaccination using M-M-RVAXPRO (or similar) should be administered a minimum of 28 days (4 weeks) before the first PPD challenge (based on advice in SPC). When a serology sample to assess MMR vaccination status is taken, results must be obtained and interpreted prior to administering MMR vaccination. If required, MMR vaccination will be administered at a separate visit during the screening period.

CHANGE 25

Subject numbers revised to reflect updated study design.

Section 9.2.1 Sample Size Assumptions, 2nd paragraph

REVISED TEXT

It is anticipated that sufficient number of healthy volunteers and patients will be enrolled in the study so that data are obtained from approximately ~~31~~ **32** healthy subjects (20 on active, ~~11~~ **12** on placebo) and approximately 32 psoriasis patients (24 on active, 8 on placebo).

CHANGE 26

Add additional interim analysis after healthy volunteer DTH cohort.

Section 9.3.1 Interim Analysis

REVISED TEXT

Dependant on the dose cohorts reached in the escalation, a formal interim analyses may be performed after the last subject **in the Healthy Volunteer group has completed their 4 week post dose assessment visit, and also after the last subject in the Psoriasis group** has completed the final PK assessment visit, to inform internal development decisions. **If required, an additional interim analysis for internal development decisions may also be performed after the last subject in the Psoriasis group has completed their 6 week post dose assessment visit.**

CHANGE 27

To confirm final analysis of Part A will be reported when after all subjects in Part A have completed their follow-up visit.

Section 9.3.2 Final Analyses

ADDED TEXT

Final analysis of Part A will be reported when after all subjects in Part A have completed their follow-up visit. Final analysis for all endpoints will be reported when all subjects in all groups have completed their 12 month surveillance visit.

CHANGE 28

Text revised to meet country specific ethics requirements.

Section 10.2 Regulatory and Ethical Considerations, Including the Informed Consent Process, 3rd paragraph

REVISED TEXT

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the **1996 (Germany) and** 2008 **(UK)** Declaration of Helsinki.

AMENDMENT 4

Summary of Amendment Changes with Rationale

To reinstate eligibility criteria regarding vaccinations at MHRA request, and to enable this, to add potential to vaccinate during screening and potential to use serology.

List of Specific Changes

CHANGE 1

Re-instated text due to inclusion #8 being re-instated.

Section 3.4 Risk Management, Table 5, 3rd row

ADDED TEXT

Impact eligibility criteria column

Subjects will need to be vaccinated against infectious agents (Inclusion #8).

CHANGE 2

Potential risk information added relating to vaccinations.

Section 3.4 Risk Management, Table 5

ADDED TEXT

Vaccination	**As per Boostrix-IPV and/or Priorix or equivalent SPC.**	**Subjects who are ineligible due to lack of history of vaccinations for diphtheria, tetanus, pertussis, measles, mumps or rubella, who consent to vaccination may only be vaccinated in accordance with the restrictions for these vaccines in the SPC. If such subjects are unable to be vaccinated, they will be ineligible for the study.**	**As per Boostrix-IPV and/or Priorix or equivalent SPC.**

CHANGE 3

Re-instated criteria as per MHRA request with slight amendment to wording for clarity.

Section 4.2.1 Inclusion criteria

8. <u>Subjects with a history of vaccination for Tetanus, diphtheria, measles, pertussis, mumps and rubella.</u>

CHANGE 4

Addition of serology testing and vaccinations if required to support inclusion criteria #8.

Section 6.1 Time and Events Table, Table 6

Protocol Activity	Screening[h]	Follow Up	Surveillance Visit	
	Up to 30 Days prior to Day 1	Week X[a]	6 months[b]	12 months
Window			-/+14d	-/+14d
<u>Serology to confirm vaccination status (if required)</u>	<u>X[i]</u>			
<u>Vaccination for MMR and/or DPT (only if required)</u>	<u>X[i]</u>			

h. <u>Screening can be longer if vaccinations are required prior to dosing.</u>
i. <u>See Section 6.3.8 for more details.</u>

CHANGE 5

Addition of ECG at Day -1 or Day 1 to reconfirm eligibility if screening was greater than 30 days prior to Day 1. Also extended concomitant medications review to include Day -1 for the same reason in Table 7 and Table 9.

Section 6.1 Time and Events Table, Table 7

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits						
		Day 1						Day 2	Day 3	Day 4	Day 8						
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 hour post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25[a]	Day 29
Window											**-/+1d**	**-/+1d**	**-/+1d**	**-/+1d**	**-/+1d**	**-/+1d**	**-/+1d**
12 - Lead ECG	**X**[i]	X	◄----------► [b]			X				X							
Concomitant Medications	◄----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------►

j. Triplicate. Only required if screening ECG not within 30 days of Day 1.

Section 6.1 Time and Events Table, Table 8

Protocol Activity	1st Challenge		In Clinic Period										Out Patient Visits										
			Day 28	Day 29 (Day 1)						Day 30 (Day 2 post-dose)	Day 31 (Day 3 post-dose)	Day 32 (Day 4 post-dose)											
	Day 1	Day 3	Day 28	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hours post-infusion start	72 hour post-infusion start	Day 36 (Day 8 post-dose)	Day 39 (Day 11 post-dose)	Day 43 (Day 15 post-dose)	Day 46 (Day 18 post-dose)	Day 50 (Day 22 post-dose)	Day 53 (Day 25 post-dose)	Day 57 (Day 29 post-dose)	Day 71 (Day 43 post-dose)	Day 85 (Day 57 post-dose)[a]	Day 113 (Day 85 post-dose)	Day 149 (Day 121 post-dose)
Window			-/+3d										-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+2d	-/+2d	-/+2d	-/+3d
12 - Lead ECG	X[o]			X	◄----------► [b]			X				X											

o. Triplicate. Only required if screening ECG not within 30 days of Day 1.

Section 6.1 Time and Events Table, Table 9

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits										
		Day 1						Day 2	Day 3	Day 4	Day 8										
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 43	Day 57	Day 85	Day 121
Window											-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+2d	-/+2d	-/+2d	-/+3d
12 - Lead ECG	X[k]	X	◄----------► [a]			X				X											
Concomitant Medications	◄----------►																				

k. Triplicate. Only required if screening ECG not within 30 days of Day 1.

CHANGE 6

Addition of serology testing if required to support inclusion criteria #8

Section 6.3.7 Clinical Laboratory assessments

ADDED TEXT

Other screening tests
Serology to confirm vaccination status (if required)

CHANGE 7

Addition of details regarding serology testing andvaccinations to support inclusion criteria #8.

Section 6.3.8 Vaccination

Subjects who have no history of vaccination for diphtheria, pertussis, and tetanus may consent to receive a booster of an appropriate licensed combined vaccine. (If a suitable serology test is available to confirm vaccination status then this may be used prior to vaccinating.)

Subjects who have no history of vaccination for measles, mumps and rubella may have a serology sample taken to assess levels of antibodies and if necessary may consent to receive a booster of an appropriate licensed combined vaccine.

For further details refer to the SPM.

CHANGE 8

Replaced template guidance text with investigational product ID.

Section 12.2 Pharmacogenetic research

Replaced [insert the name of the study treatment] with **GSK2831781** throughout section.

AMENDMENT 3

Summary of Amendment Changes with Rationale

This amendment is to remove the inclusion criteria for history of vaccination for tetanus, diphtheria, measles, pertussis, mumps and rubella, following a comprehensive assessment of the relevance of this criterion based on the mode of action, the risk assessment, existing clinical precedence and feasibility. In addition, it is to remove the exclusion of subjects from high risk areas for tuberculosis, as the use of the Quantiferon test for latent and active TB makes this redundant.

The opportunity has been taken to make some other changes to correct text that was not logistically possible, or required clarification.

List of Specific Changes

CHANGE 1

Change made for operational reasons to enable samples to arrive at lab for testing following occurrence of clinical signs.

Section 3.4 Risk Management, Table 5, 2nd row

REVISED TEXT

Strategy-monitoring criteria column, 4th paragraph

In addition limited cytokine analysis will be performed within 24 hours ~~of dosing~~ if any clinical signs suggest cytokine release syndrome (See Section 6.3.7).

Section 6.3.7 Clinical Laboratory Assessments 4th paragraph

REVISED TEXT

Cytokines for safety assessment may include but are not limited to IL-6, TNFα, IL-8, IL-1b. Analysis will be performed within 24 hours ~~of dosing~~ **if** any clinical signs suggest cytokine release syndrome.

CHANGE 2

Change made following review of risks. Review of other T cell agents targeting specific T cells subsets, as well as pre-clinical experiments did not support the need for these specific vaccinations as an inclusion criteria to mitigate risk of infections. Additional guidance for subjects who may need vaccinations for other reasons, to be reviewed and vaccinated prior to study.

Section 3.4 Risk Management, Table 5, 3rd row

DELETED TEXT

Impact eligibility criteria column, 4th paragraph

~~Subjects will need to be vaccinated against standard infectious agents (Inclusion #8).~~

Section 4.2.1 Inclusion Criteria, #8

DELETED TEXT

~~9. Subjects with a history of current vaccination for Tetanus, diphtheria, measles, pertussis, mumps and rubella.~~

Section 5.14 Concomitant Medications and Non-Drug Therapies

ADDED TEXT

It is recommended that a subject's vaccination record and the need for immunisation prior to Day 1 should be carefully investigated in all subjects prior to entering the study. In those who are likely to require immunisation in the period up to the follow up visit, such as subjects requiring vaccinations or boosters for their professional activity, the administration of any required vaccination/booster should be given at least 4 weeks prior to Day 1.

CHANGE 3

As Quantiferon testing is part of the criteria and can be used for both latent and active detection of tuberculosis, exclusion text based on prior location is redundant.

Section 4.2.2 Exclusion Criteria, #2

REVISED TEXT

10. Subjects ~~from a high risk area of the world for tuberculosis or~~ **who** have history of tuberculosis or have close family members with confirmed MTB infection or **who are** positive at screening by Quantiferon testing.

CHANGE 4

Correction to status of pharmacist, to ensure consistency.

Section 5.10 Preparation/Handling/Storage/Accountability, 2nd paragraph

Study treatment must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study treatment. Only authorized site staff may supply or administer study treatment. An un-blinded pharmacist will perform the dilutions and preparation of the IV bags for active and placebo subjects. The **un-**blinded pharmacist must ensure that the blind is maintained.

CHANGE 5

Change made to ensure consistent terminology for timing of live vaccine restrictions through protocol.

Section 5.14.2.2 Part A and B

REVISED TEXT

Live, attenuated or recombinant vaccine(s) within ~~one month~~ **4 weeks** of Day 1 and until completion of the follow up visit.

CHANGE 6

Clarification of type of ECG used during infusion, compared to at other times, and addition of action on finding of abnormalities.

Section 6.1 Time and Events Table, Table 7 (footnote b), Table 8 (footnote b), Table 9 (footnote a)

REVISED TEXT

Continuous **2-lead ECG** during infusion. Only significant abnormalities during this time will be databased.

Section 6.3.3 Electrocardiogram (ECG), 3rd bullet

REVISED TEXT

- **2-lead ECG** will be measured continuously during the IV infusion (0-2 hours). Only abnormalities during this time will be databased. **If abnormalities are detected a 12-lead ECG will be obtained.**

AMENDMENT 2

Summary of Amendment Changes with Rationale

This amendment is to include a test at screening to only allow pre-existing ADA-subjects to be included in Parts A and B of the study. This will minimise the potential for diluting/confounding a signal of pharmacological or clinical response.

The opportunity has been taken to make some other changes to correct inconsistencies and clarifications for exploratory assays.

List of Specific Changes

CHANGE 1

Repetitive paragraph removed and remaining paragraph reworded to combine healthy volunteer and psoriasis patient measures.

Synopsis, 2nd paragraph, last sentence

DELETED TEXT

~~Safety, delayed type hypersensitivity (DTH) measures, pharmacokinetic (PK) and pharmacodynamic (PD) data will be reviewed, after each cohort, by the dose escalation committee (DEC) before dose escalation occurs.~~

Synopsis, 4th paragraph

REVISED TEXT

Safety, ~~delayed type hypersensitivity (DTH)~~ **clinical response** measures, pharmacokinetic (PK) and pharmacodynamic (PD) data will be reviewed, after each cohort, by the dose escalation committee (DEC) before dose escalation occurs.

ADDED TEXT

All dosing will be carried out in healthy volunteers and patients with psoriasis who do not have pre-existing antibodies to GSK2831781.

CHANGE 2

Paragraph added to provide background on pre-existing ADA findings in pre-clinical investigations.

Section 1.2.1 Brief Background, GSK2831781

ADDED TEXT

Pre-existing anti-drug antibodies (ADA) that bind GSK2831781 have been noted in approximately 10 - 32% and 6 - 45% of sera from healthy and psoriatic human subjects respectively. The relevance of pre-existing ADAs for biotherapeutics in general is poorly understood, but they may have an effect on pharmacological and clinical parameters (Xue *et al*, 2013).

CHANGE 3

Addition of exploratory endpoint relating to the functional activity of GSK2831781 to bind LAG-3+.

Section 2 Objectives and Endpoints

ADDED TEXT

To evaluate the effect of a single IV dose of GSK2831781 in healthy volunteers and psoriasis patients on pharmacodynamic biomarkers.	• Proof of pharmacology biomarker endpoints may include, but not limited to, the following as data permit: • LAG-3 expression on different blood immune cell populations including T cells • Transcriptomic profiling to assess mRNA levels in peripheral blood • Quantification of LAG-3 mRNA in whole blood • **Functional activity of GSK2831781 to bind to LAG-3+ cells and induce Fcγ3a receptor signalling** • Antigen specific T cell response • Inflammatory cytokine levels • Free and GSK2831781 bound sLAG-3 concentrations • NK cell CD16 receptor occupancy in whole blood • NK cell activation marker expression in whole blood

CHANGE 4

Additional text added to clarify that only subjects that do not have pre-existing ADAs will be included in the study. Also, added time window between the first DTH challenge and the second DTH challenge to allow flexibility for the site.

Section 3.2 Study Design Detail, 1st paragraph, 2nd sentence

ADDED TEXT

In Parts A and B of the study subjects will be screened for pre-existing ADA status and only subjects who do not have pre-existing ADAs will be randomised.

REVISED TEXT

Healthy Volunteers with DTH

Day 28 to Day 32 - After a period of at least 28 days **(-/+ 3 days)** from the first challenge, subjects will return to the unit and will remain resident in the unit from Day 28 **(-/+ 3 days)** until at least 72 hours after dosing.

CHANGE 5

Rationale added regarding the inclusion of ADA- subjects only.

Section 3.3.1 Design Rationale, 9th paragraph

ADDED TEXT

Due to the presence of pre-existing ADA in a variable percentage in sera from both healthy and psoriatic human subjects, the initial investigation of GSK2831781 will be carried out in ADA negative subjects in Part A and Part B of the study to minimise the potential for diluting/confounding a signal of pharmacological or clinical response.

CHANGE 6

Change made to rectify an inconsistency in the protocol regarding the time when a vaccine may be given prior to the study start.

Section 3.4 Risk Management, Table 5, 3rd row

REVISED TEXT

Strategy-monitoring criteria column, 4th paragraph

Close monitoring of subjects for infections to follow-up visit with targeted surveillance to 12 months.

Subjects will not be allowed to receive live (attenuated) vaccine within the 4 weeks prior to ~~dosing~~ **Day 1** or during the study until the end of follow-up.

CHANGE 7

Change made to rectify an inconsistency in the protocol regarding the time when a vaccine may be given prior to the study start. Addition of exclusion criteria for ADA+ subjects. Also, clarified that #20 and #21 are only required for subjects receiving the DTH challenge.

Section 4.2.2 Exclusion Criteria, #1

REVISED TEXT

11. Received live, attenuated or recombinant vaccine(s) within 4 weeks of ~~screening (Part A) and within 4 weeks of dosing (Part B)~~ **Day 1** or plan to receive a vaccination during the study until follow-up.

Section 4.2.2 Exclusion Criteria, #8

ADDED TEXT

j. Subjects who test positive for pre-existing ADA to GSK2831781 at screening.

Section 4.2.2 Exclusion Criteria, #20 and 21

REVISED TEXT

20. **Part A (only cohorts with DTH challenge) only:** Use of nicotine patches on the arm at screening that would interfere with the injection sites.
21. **Part A (only cohorts with DTH challenge) only:** Subjects participating, within seven days of screening, in recreational sun-bathing, or the use of a sun-bed, on the area of the skin from the wrist to the shoulder (inclusive).

CHANGE 8

Amended text to allow screen failure data to be collected to meet the CONSORT requirements.

Section 4.4 Screen and Baseline Failures

DELETED TEXT

~~Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to GSK.~~

ADDED TEXT

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including, but

not limited to, Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

CHANGE 9

Change made to rectify an inconsistency in the protocol regarding the time when a vaccine may be given prior to the study start.

Section 5.14.2.2 Prohibited Medications and Non-Drug Therapies, Part A and B

REVISED TEXT

Live, attenuated or recombinant vaccine(s) within one month of ~~screening~~ **Day 1** and until completion of the follow up visit.

CHANGE 10

Blood volume increased to allow for extra blood tests due to pre-existing ADA screening and any repeated tests required. As the study takes place over a long duration this is not perceived to be a safety risk.

Section 6 Study Assessments and Procedures

REVISED TEXT

No more than ~~500~~ **600** mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

CHANGE 11

Inclusion of a sample for pre-existing ADA testing.

Section 6.1 Time and Events Table, Table 6

REVISED TEXT

Protocol Activity	Screening	Follow Up	Surveillance Visit	
	Up to 30 Days prior to Day 1	Week X[a]	6 months[b]	12 months
Immunogenicity Sample	**X**	X		

CHANGE 12

Inclusion of *in vitro* LAG-3+ activity blood test. Also added footnote to confirm when weight should be measured to calculate dose required.

Section 6.1 Time and Events Table, Table 7

ADDED TEXT

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits						
		Day 1						Day 2	Day 3	Day 4	Day 8						
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 hour post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25[a]	Day 29
In vitro LAG-3+ activity		**X**		**X**							**X**						

ADDED TEXT

i. To calculate the correct dose, weight must be measured on Day -1 or Day 1 pre-dose.

CHANGE 13

Inclusion of *in vitro* LAG-3+ activity blood test and time window on Day 28. Also added footnote to confirm when weight should be measured to calculate dose required.

Section 6.1 Time and Events Table, Table 8

ADDED TEXT

Protocol Activity	1st Challenge		In Clinic Period										Out Patient Visits										
			Day 28	Day 29 (Day 1)						Day 30 (Day 2 post-dose)	Day 31 (Day 3 post-dose)	Day 32 (Day 4 post-dose)											
	Day 1	Day 3	Day 28	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hours post-infusion start	72 hour post-infusion start	Day 36 (Day 8 post-dose)	Day 39 (Day 11 post-dose)	Day 43 (Day 15 post-dose)	Day 46 (Day 18 post-dose)	Day 50 (Day 22 post-dose)	Day 53 (Day 25 post-dose)	Day 57 (Day 29 post-dose)	Day 71 (Day 43 post-dose)	Day 85 (Day 57 post-dose)[a]	Day 113 (Day 85 post-dose)	Day 149 (Day 121 post-dose)
Window			-/+3d										-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+1d	-/+2d	-/+2d	-/+2d	-/+3d
In vitro LAG-3+ activity				X		X							X										

ADDED TEXT

n. To calculate the correct dose, weight must be measured on Day 28 or Day 29 pre-dose.

CHANGE 14

Inclusion of *in vitro* LAG-3+ activity blood test. Also added footnote to confirm when weight should be measured to calculate dose required.

Section 6.1 Time and Events Table, Table 9

ADDED TEXT

Protocol Activity	Base-line	In Clinic Period									Out Patient Visits										
		Day 1						Day 2	Day 3	Day 4	Day 8										
	Day -1	Pre-dose	0 hour	2 hour post-infusion start	4 hour post-infusion start	6 hour post-infusion start	12 hour post-infusion start	24 hour post-infusion start	48 hour post-infusion start	72 hour post-infusion start	168 post-infusion start	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 43	Day 57	Day 85	Day 121
In vitro LAG-3+ activity		X		X							X										

ADDED TEXT

j. To calculate the correct dose, weight must be measured on Day -1 or Day 1 pre-dose.

CHANGE 15

Included a blood test for serum tryptase if a suspected acute hypersensitivity reaction occurs.

Section 6.3.4 Infusion-related Reactions and Hypersensitivity Reactions, 2nd paragraph

ADDED TEXT

In the event of a suspected acute hypersensitivity reaction a blood sample should be taken between 30minutes – 3 hours of the event for serum tryptase analysis.

CHANGE 16

Added further information regarding the ADA testing.

Section 6.7.1 Immunogenicity, Blood Sample Collection

ADDED TEXT

In Parts A and B, only subjects with a negative pre-existing ADA status at screening will be included.

Section 6.7.1 Immunogenicity, Sample Analysis

REVISED TEXT

~~Samples will be analyzed for the presence of anti-GSK2831781 antibodies using a validated immunoelectrochemiluminescent (ECL) assays. The assay involves screening, confirmation and titration steps (tiered-testing approach).~~ **Immunogenicity assays will be performed by Clinical Immunology, GSK. ADAs to GSK2831781 will be detected using a validated bridging electrochemiluminescent (ECL) immunoassay. This assay will be used both to prospectively define subjects' pre-existing ADA status and to evaluate post-dose ADA responses. The bioanalytical cut points of screening and confirmation for a positive antibody response will be determined statistically during ADA assay validation from drug-naive human serum samples. Samples will be directly tested in confirmatory ADA assay to define subjects' pre-existing ADA status for subject screening if required. An ADA assay involving screening, confirmation and titration steps (tiered-testing approach) will be adopted for study samples.** Confirmed positive samples will be titrated to obtain the titre of the anti-GSK2831781 antibodies. ~~Further antibody characterization may be performed, if needed. Results will be reported at the end of the study.~~ **Samples testing positive for anti-GSK2831781 antibodies may be further characterized for the presence of GSK2831781 neutralising activity (NAb) using a validated ADCC reporter gene assay, if needed.** Details on sample preparation, storage and analysis will be given in the SPM.

CHANGE 17

Added section relating to the *in vitro* LAG-3+ activity assay.

Section 6.8.7 In Vitro LAG-3+ activity

ADDED TEXT

The functional activity of GSK2831781 to bind to LAG-3+ cells and induce Fc gamma receptor 3A signalling may be assessed using the Fc gamma 3A reporter cell assay

CHANGE 18

Changed volume of blood required for PGx due to change in guidelines.

Section 12.2 Pharmacogenetic Research, Study Assessments and Procedures, 2nd paragraph

REVISED TEXT

In addition to any blood samples taken for the clinical study, a whole blood sample (~~10~~**6**ml) will be collected for the PGx research using a tube containing EDTA.

AMENDMENT 1

Summary of Amendment Changes with Rationale

This amendment is to address the queries raised by the MHRA.

The opportunity has been taken to make some minor administrative changes.

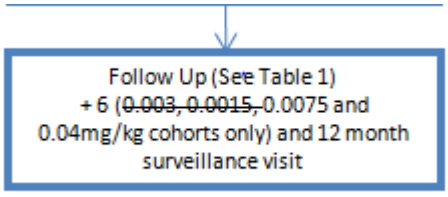
List of Specific Changes

CHANGE 1

Incorrect doses removed from Follow-up box.

Section 3.1 Study Schematic, Healthy Volunteers (DTH) schematic

REVISED TEXT



CHANGE 2

Change made to address comment from MHRA.

Table 1 Dose escalation/Cohort Structure and Safety review periods, 8th row.

REVISED TEXT

Planned Doses	**Number of subjects (active:placebo)**	**Safety Follow-up period to progress to next subjects/cohorts**	**PPD DTH Challenge if Healthy volunteer/ Biopsy if patient**	**Follow-up and end of exclusion of systemic immunosuppressives**
Healthy Volunteers				
0.0003mg/kg	1:1	1:1 wait 28 days post-dose	No DTH	Day 29 ± 1 day (28 days post-dosing)
0.0015mg/kg				Day 43 ± 1 day (42 days post-dosing)
0.0075mg/kg	6:3	1:1 wait 48 hours post-dose 5:2 wait 28 days post-dose	DTH	Day 113 ± 2 days (84 days post-dosing)
0.04mg/kg				Day 175 ± 3 days (146 days post-dosing)
0.15mg/kg				Day 219 ± 7 days (190 days post-dosing)
Note: Cohorts with a DTH start dosing on Day 29 **Maximum dose for healthy volunteers may change based on emerging exposure or earlier reduction in DTH response (See Section 3.2.1)**				

CHANGE 3

Allowance of a phone call to replace the 12 month visit has been removed as per MHRA request. Clarification of why additional 6 month surveillance visit for 0.15mg/kg cohort is not required, as per MHRA request. Removal of incorrect doses from text in 'Healthy volunteers with DTH' paragraph.

Section 3.2 Study Design Detail

REVISED TEXT

Healthy volunteers without DTH

All subjects will attend a surveillance visit at 6 and 12 months ~~(a telephone call is permitted for the 12 month visit if required)~~.

REVISED TEXT

Healthy volunteers with DTH

All subjects in the ~~0.003, 0.0015,~~ 0.0075 and the 0.04mg/kg cohorts will attend a surveillance visit at 6 months and 12 months ~~(a telephone call is permitted for the 12 month visit if required)~~. As the follow-up visit is at approximately 6 months **(190 days post-dose, as per Table 1),** subjects in the 0.15mg/kg cohort **do not require an additional post-dose surveillance visit at 6 months and** will only attend a surveillance visit at 12 months ~~(a telephone call is permitted for the 12 month visit if required)~~.

CHANGE 4

Change made to address comment from MHRA.

Section 3.2.1 Healthy Volunteer to Patient Switching, 2nd paragraph

REVISED TEXT

If a dose switch occurs earlier than 0.15mg/kg, extra cohorts would be added at the lower doses for psoriasis patients so that the starting dose is the same as the last dose used in healthy volunteers. **When the decision to switch to psoriasis patients is made, no further dosing of healthy volunteers will occur.** If the understanding of EC50 for LAG-3+ T cells depletion change and/or emerging PK profiles differs markedly from prediction, the maximum dose for healthy volunteers may also change. **If GSK2831781 exposure is substantially less than predicted the maximum dose into healthy subjects would be increased to a dose predicted by the emerging pharmacokinetic data to provide a similar exposure as currently predicted at 0.15mg/kg (i.e. a target AUC of ~1800µg*h/mL (See Table 2).** If a dose switch then occurs later, psoriasis cohorts would start at the last dose used in healthy volunteers. Details of dose adjustment can be found in Section 5.4.

CHANGE 5

Change made for clarity as per MHRA request.

Section 3.3.1 Design Rationale, 5th paragraph, 2nd sentence

REVISED TEXT

This dose of 0.15 mg/kg might be altered if emerging PK profiles differ markedly from predictions **(See Section 3.2.1)**.

CHANGE 6

Change made for clarity as per MHRA request.

Section 3.3.2.3 Assessment of GSK2831781 pharmacology in healthy volunteers, 5th paragraph

REVISED TEXT

However, reduction of the DTH response could occur at a lower or higher dose. Therefore, the decisions to switch to psoriasis patients will be based on demonstration of reduction of the DTH response but with a maximum dose for healthy subjects of 0.15mg/kg (dose could be altered dependent on emerging PK data and/or PD data), to limit the duration of exposure above the *in vitro* EC50 ADCC killing activity (where there are lifestyle and medication restrictions), to no more than approximately 6 months (**See Section 3.2.1 and** Section 5.4 Planned Dose Adjustments).

CHANGE 7

Change made for clarity as per MHRA request.

Section 5.4 Planned Dose Adjustments, 3rd paragraph, last sentence

REVISED TEXT

If emerging PK data departs from prediction, outcomes may also include continuing dose escalation in healthy volunteers beyond the maximum of 0.15mg/kg up to a maximum duration of exposure above EC50 of approximately 6 months, if there are no other safety/tolerability findings or reduction of DTH response **(See Section 3.2.1)**.

CHANGE 8

Change made to address comment from MHRA.

Section 5.5 Dose Adjustment/Stopping/Monitoring Criteria, 1st and 2nd paragraphs

REVISED TEXT

If one or more subject experiences an Serious Adverse Event (SAE) that can be reasonably attributed to GSK2831781, the dose escalation will be ~~temporarily~~ halted and no further subject will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the DEC, (which must include the GSK medical monitor), relevant GSK personnel, and with the Ethics Committee and Regulatory

Agency will then take place ~~prior to any resumption of dosing~~. **If following the safety review a decision is made to restart dose escalation, this may be allowed after approval of a substantial amendment.**

If two or more subjects experience a severe or significant non-serious AE that can be reasonably attributed to GSK2831781, the dose escalation will be ~~temporarily~~ halted and no further subject will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the DEC (which must include the GSK medical monitor), relevant GSK personnel, and with the Ethics Committee and Regulatory Agency will then take place ~~prior to any resumption of dosing~~. **If following the safety review a decision is made to restart dose escalation, this may be allowed after approval of a substantial amendment.**

CHANGE 9

Change made to address comment from MHRA.

Section 5.5 Dose Adjustment/Stopping/Monitoring Criteria

REVISED TEXT

22. Neutropenia (the following must be confirmed by repeat samples):

- **If one subject experiences neutrophil count < 1.5 x 109/L for >7 days for the first 28 days for the first 2 healthy volunteer cohorts.**
- If one or more subjects experiences neutrophil count <0.5 x 10^9/L for >7 days

CHANGE 10

Allowance of a phone call to replace the 12 month visit has been removed as per MHRA request.

Section 6.1 Time and Events Table, Table 6 Footnote c.

DELETED TEXT

~~c. A telephone call is permitted for healthy volunteers only, if required.~~

CHANGE 11

Correction to demographic parameters being collected.

Section 6.2 Demographic/Medical History Assessments, 1st paragraph

REVISED TEXT

The following demographic parameters will be captured: ~~date~~ **year** of birth, gender, race and ethnicity.

CHANGE 12

Removal of viral testing parameters from screening list for consistency with Time and Events table. These tests are taken at baseline and are reflected in the baseline tests list.

Section 6.3.7 Clinical Laboratory Assessments, Other screening tests, 6th row

REVISED TEXT

Other screening tests
HIV
Hepatitis B (HBsAg)
Hepatitis C (Hep C antibody)
FSH and estradiol (as needed in women of non-child bearing potential only)
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).
~~CMV, EBV, HSV, VZV~~
Thyroid Function Test
Quantiferon test