Protocol Amendment

Study ID: 215253

Official Title of Study: A Phase Ib, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study of the Clinical Effect, Safety and Tolerability of a Single Intravenous Infusion of GSK1070806 in Moderate to Severe Atopic Dermatitis Patients

NCT ID: NCT04975438

Date of Document: 06-Jun-2022

TITLE PAGES

Protocol Title: A Phase Ib, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study of the Clinical Effect, Safety and Tolerability of a Single Intravenous Infusion of GSK1070806 in Moderate to Severe Atopic Dermatitis Patients.

Protocol Number: 215253/Amendment 2

Compound Number or Name: GSK1070806

Brief Title:

Clinical Effect, Safety and Tolerability of GSK1070806 in Atopic Dermatitis.

Study Phase: Phase Ib:

Sponsor Name and Legal Registered Address:

Nicolas Wisniacki VP, Head of Discovery Medicine

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information will be provided separately

Manufacturer: GSK

Regulatory Agency Identifying Number(s):

IND: 156168

Approval Date: 06 Jun 2022

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 2	06 Jun 2022	TMF-14679521
Amendment 1	25-FEB-2022	TMF-14357132
Original Protocol	20-JUN-2021	TMF-13833595

Amendment 2 06 Jun 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 2:

To permit (following consultation with the Medical Monitor), the screening of potential participants whose occasional recreational use of marijuana or medical use of marijuana will not likely impact the study.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 5.2: Exclusion Criteria (No. 30)	**Substance abuse:** **ORIGINAL:** Active substance abuse or a history of substance abuse within 6 months prior to the initial Screening visit. **REVISED:** Active substance abuse or a history of substance abuse (in the opinion of the Principal Investigator) within 6 months prior to the initial Screening visit. Note that *documented* medical use of marijuana or occasional recreational use of marijuana may be permitted subject to a priori agreement with the Medical Monitor.	When either the use of medical marijuana or the occasional recreational use of marijuana would be judged to not confound safety, efficacy or study compliance, then subject to a prior agreement with the Medical Monitor, such potential participants may progress to the Initial Screening Visit.

Section # and Name	Description of Change	Brief Rationale
Section 5.1: Inclusion Criteria (No. 13)	**Sequential numbering:** Inclusion criteria No. 15 amended to Inclusion Criteria No. 13	Erroneous numbering

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase Ib, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study of the Clinical Effect, Safety and Tolerability of a Single Intravenous Infusion of GSK1070806 in Moderate to Severe Atopic Dermatitis Patients.

Brief Title: Clinical Effect, Safety and Tolerability of GSK1070806 in Atopic Dermatitis.

Rationale: Interleukin-18 (IL-18) is a pleiotropic cytokine with potential to amplify pathways important in Atopic Dermatitis (AtD) and for which increased IL-18 levels correlate with disease severity. GSK1070806 is a potent anti-IL-18 monoclonal antibody that is being developed for the treatment of AtD.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To compare the clinical effect of a single intravenous (IV) infusion of 2 mg/kg GSK1070806 *versus* placebo in moderate to severe Atopic Dermatitis in the Biologic Naïve (BN) population (Group 1).	Percent change from baseline (PCFB) in the Eczema Area and Severity Index (EASI) at Week 12.
Secondary	
To further compare the clinical effect (GSK1070806 *versus* placebo) in the BN population (Group 1).	• Change from baseline (CFB) in the EASI at Week 12. • EASI 50/75/90 defined as ≥ 50/75/90% reduction in the EASI from Baseline at Week 12. • Investigator Global Assessment (IGA) score of 0 or 1 at Week 12.
To estimate the clinical effect of GSK1070806 in the dupilumab inadequate responder (Dupi-IR) population (Group 2).	• PCFB in the EASI at Week 12.
To assess safety and tolerability (GSK1070806 *versus* placebo) in the combined AtD population (Groups 1 and 2).	• Incidence of serious adverse events (SAEs) and adverse events (AEs). • Incidence of clinically important findings in: o vital signs o electrocardiogram o laboratory: haematology, clinical chemistry and urinalysis.

Objectives	Endpoints
To assess anti-drug antibody (ADA) formation in the AtD population (Groups 1 and 2 combined)	Incidence of ADAs.

Overall Design:

A multi-centre, 12-week, randomized, double-blind, parallel-group, placebo-controlled study of GSK1070806 to investigate efficacy and safety in moderate-to-severe AtD participants.

Brief Summary:

The study will assess the impact of GSK1070806 in two groups of patients with moderate-to-severe AtD:

- Group 1: Patients naïve to biologic treatment (and who have failed topical therapies).
- Group 2: Patients who have not adequately responded (or have been intolerant) to dupilumab (Dupixent).

All participants must wash out topical therapies (corticosteroids, calcineurin inhibitors, phosphodiesterase (PDEIV) inhibitors) for at least 7 days prior to dosing on Day 1.

All participants are required to undergo Coronavirus strain 19 (COVID-19) testing prior to dosing and at the End of Study.

Changes in the clinical signs of AtD as well as changes in disease biomarkers in blood and in skin (*via* serial biopsies and tape stripping) are to be assessed as well as patient reported outcomes (itch, sleep disturbance, fatigue), pharmacokinetics and anti-drug antibodies.

The primary completion is at Week (Wk) 12 and the End of Study Visit is at Wk 24.

Nine outpatient visits are scheduled: Screening (1), Treatment Period (6), Follow-Up Period (2). Skin biopsies and tape strips will be collected on Day 1 (prior to dosing), Wks 4 and 12.

Number of Participants:

Approximately 64 patients are expected to be screened to achieve approximately 48 randomly assigned participants.

Intervention Groups and Duration:

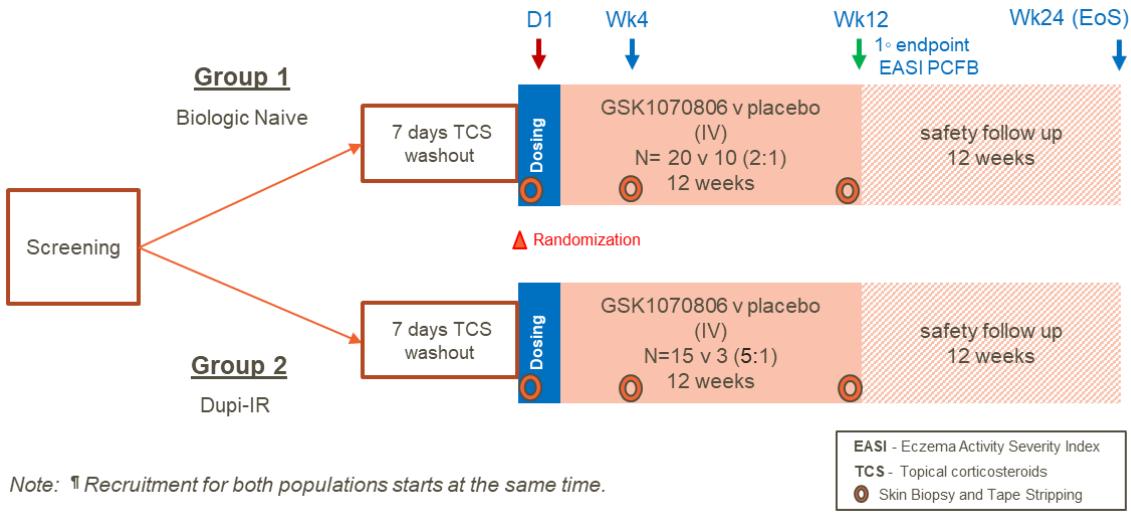
A single 2 mg/kg one-hour IV infusion of either GSK1070806 or placebo is to be administered as follows:

- Group 1: N = 30. 20 participants will receive GSK1070806, 10 will receive placebo.
- Group 2: N = 18. 15 participants will receive GSK1070806, 3 will receive placebo.

The study duration for an individual participant is not expected to exceed 28 weeks (Screening 4 is weeks; Treatment Period is 12 weeks; Follow-Up Period is 12 weeks).

Data Monitoring/ Other Committee: An internal safety review team will review blinded safety data. A data review committee may conduct an interim analysis(es) on unblinded data.

1.2. Schema



Note: ¶ Recruitment for both populations starts at the same time.

1.3. Schedule of Activities (SoA)

1.3.1. Screening Period

PROCEDURE	SCREENING PERIOD Up to Day -28	NOTES: **Please also refer to Appendix 2.** Screening may be performed across one or more visits if needed.
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Demography	X	
Physical Examination (Full)	X	
Height and Weight	X	
Medical/medication/drug/alcohol history	X	
Alcohol Screen	X	As per standard local practice.
Urine Drug Screen	X	
HIV, Hepatitis B and C.	X	
COVID-19 (SARS-CoV-2) Test	X	***EITHER*** a documented (Regulatory Approved) negative test within two days of Initial Screen ***OR*** test performed at Initial Screen
TB Screening (QuantiFERON)	X	
Pregnancy Test (serum, WOCBP) *or* FSH/Oestradiol (serum, WONCBP)	X	WOCBP must have confirmed menstruation within 28 days of anticipated dosing on Day 1 and continue to return a negative pregnancy test up to and including prior to dosing on Day 1.
12-lead ECG	Triplicate	
Vital Signs	X	
Haematology, Clinical Chemistry	X	See Appendix 2.
Urinalysis	X	See Appendix 2.
Clinical Assessments (Screening EASI, IGA)	X	Inc Criterium No. 1
Identify target lesion	X	
STOP TCS /TCI /topical PDEIVi	Day -7 onwards	Inc. Crit. No. 9 - Participant must STOP Topicals at Day -7
START application of bland emollient	Day -7 onwards	
PP-NRS (itch)	Day -7 onwards	Record daily
CCI [redacted]	Day -7 onwards	Record daily
SAE assessment	X	From signing the Informed Consent Form

1.3.2. Treatment / Follow-Up Period

PROCEDURE	TREATMENT Period						Follow-Up		Unscheduled Visit	Early withdraw	NOTES: a) Primary Endpoint = Day 85 (Wk 12). b) End of Study = Day 169 (Wk 24)
End of WEEK	1	2	4	8	[a]12	16	[b]24				Visit Windows: Days 8 to 29 (±1), Days 57 to 113 (±2), Day 169 (±3).
DAY	1	8	15	29	57	85	113	169			
Discharge from clinical unit	X										Discharge not sooner than 2 hours post-end of infusion.
Inclusion/Exclusion Criteria	X [1]										1) Re-check clinical status before dosing on Day 1.
Alcohol Screen	X										Method per standard local practice (*e.g. urine alcohol due to COVID*)
Physical Examination (Full [1] / Brief)	(X) [1]	X	X	X	X	X	X	X[1]	X	X[1]	1) Full.
12-lead ECG	(X) [1]					X		X	X	X	1) *Triplicate Readings.* On Day 1: pre-dose, then 30 and 60 mins *post- start* of infusion.
Vital Signs	(X) [1]	X	X	X	X	X	X	X	X	X	1) Dosing Day 1: pre-dose, 30 mins, 1, 1.5 and 2 hrs *post- end* of infusion.
Pregnancy Test	(X)			X	X	X	X	X		X	High sensitivity urine pregnancy test (or serum testing if required by local regulations)
Haematology, Clinical Chemistry	(X)	X	X	X	X	X	X	X	X	X	See Appendix 2.
Urinalysis	(X)			X		X		X	X	X	See Appendix 2.
COVID-19 (SARS-CoV-2)	(X[1])	<----------X[2]---------->						X	X[3]	X	1) NEGATIVE RESULT *must* be obtained prior to dosing. 2) Ad hoc test in case of symptoms. 3) If necessary (at investigator's discretion).
EASI	(X)		X	X	X	X	X	X	X	X	
IGA	(X)		X	X	X	X	X	X	X	X	
PP-NRS (itch)	<----------Daily---------->								X	X	Weekly: end of Wks 1, 2, 3, 4.
CCI Sleep Disturbance 8b	(X)	Weekly			Bi-weekly				X	X	Bi-Weekly: every two weeks, starting at the end of Wk 6.
FACIT-Fatigue (13 items)	(X)	Weekly			Bi-weekly				X	X	
CCI [redacted]	<----------Daily---------->								X	X	
DLQI: Dermatology Life Quality Index	(X)	Weekly			Bi-weekly				X	X	
Randomization & DOSING (IV inf.)	X										
Skin Biopsy (Lesion and Non-Lesional)	(X)[1]			X		X					1) Non-Lesional Biopsy obtained only on Day 1. RNAseq and IHC (Section 8.7.4)
Skin Tapestripping	(X)			X		X					RNAseq and Proteomics (Section 8.7.5)
Pharmacokinetics (PK)	(X)[1]	X	X	X	X	X	X	X	X	X	1) Day 1 PK samples: prior to infusion, *immediately* at the end of infusion and then 2 hours *post* -end of infusion. TE assessment is comprised of at least, but not limited to, Total IL-18. (Section 8.7.1.)
Target Engagement (TE)	(X)	X	X	X	X	X	X	X	X	X	
Serum Biomarkers (incl proteomics)	(X)			X		X		X	X	X[1]	1) If withdrawal occurs earlier than Day 85. (Section 8.7.2.)
Whole Blood: RNA Sequencing	(X)			X		X					PAX gene tubes - (Section 8.7.3.)
Immunogenicity	(X)			X	X	X		X	X	X	(Section 8.8.)
PGx	X										PGx *is optional* (Section 8.6.)
SAE and AE	<---------->								X	X	SAEs recorded throughout. AEs recorded from start of IV infusion.
Concomitant Medications	<---------->								X	X	
Note: On Day 1, all activities and blood samples are to be acquired *prior to dosing* , unless stated otherwise.											
Note: (X) brackets denote the Baseline Assessment.											

2. INTRODUCTION

GSK1070806 is a potent anti-interleukin-18 (IL-18) monoclonal antibody that is being developed for the treatment of Atopic Dermatitis (AtD) [see Investigator Brochure (IB), [GSK Document Number WM2009/00047/07].

2.1. Study Rationale

Atopic Dermatitis

Atopic dermatitis is a chronic relapsing inflammatory skin disease characterized by eczematous lesions and intense pruritus [Weidinger, 2016, Simpson, 2016a], and is associated with skin barrier dysfunction and immune dysregulation. Intense pruritus results in sleep deprivation, signs of anxiety and depression, impaired quality of life and reduced productivity [reviewed Yosipovitch, 2019].

AtD is a heterogeneous disease with primary T-helper cell (T_H)2/T_H22-skewing and variable T_H1/T_H17 contribution [Glickman, 2020]. Changes in the transcriptional profile of AtD have been observed with a number of experimental / approved therapies that have also shown clinical efficacy including cyclosporin [Khattri, 2014], topical corticosteroids [Brunner, 2016], Janus kinase inhibitors [Pavel, 2019], phosphodiesterase 4 inhibitor [Bissonnette, 2019] dupilumab [Beck, 2014], ustekinumab [Khattri, 2017] and fezakinumab [Brunner, 2019]. The AtD skin proteome shows an inflammatory and vascular-endothelial signature (even in non-lesional skin), emphasizing the need for early treatment [Pavel, 2019].

Prevalence and Economic Burden

Population-based estimates place adult prevalence between 2.1 - 4.4% across countries [Barbarot, 2018]. Severity is consistent worldwide with mild, moderate and severe at ~60%, ~29%, and 11%, respectively [Fuxench, 2019].

In the United States (U.S.) three recent studies report that AtD occurs in approximately 7-8% adults [Silverberg, 2015, Barbarot, 2018, Sacottte, 2018, Fuxench, 2019].

From a 2004 study investigating the burden of skin disease in the United States, it was estimated that total annual burden of AtD (direct, indirect and costs due to quality of life) was $4.2 billion, equating to approximately $5.4 billion in 2016 [Adamson, 2017].

Treatment(s) and Unmet Medical Need

Dupilumab (Dupixent, see Summary of Product Characteristics, 2021] is a fully human monoclonal antibody directed against the IL-4 receptor α subunit and is licenced for use in moderate-severe AtD when topical prescription therapies have failed. Clinical trials of dupilumab in adults and adolescent populations with moderate to severe AtD have demonstrated significant improvement in clinical outcomes: for example, in two pivotal studies, SOLO 1 and SOLO 2, a 75% improvement in the eczema activity severity index, (EASI-75) was achieved in approximately 50% patients (*versus* placebo, 15%) with approximately 37% patients achieving an investigator global assessment (IGA) score of 0/1 (clear/nearly clear skin), as compared to placebo (10% IGA 0/1). Other important measures including itch, quality of life and symptoms of anxiety and depression also

showed meaningful clinical improvement [Beck, 2014; Thaci, 2015; Simpson, 2016b; Blauvelt, 2017; de Bruin-Weller, 2018; Cork, 2020; Simpson, 2020a].

Although it was recently reported that the Investigator Global Assessment (IGA) 0/1 end point significantly *under* estimated dupilumab's treatment effects [Silverberg, 2019], the post-hoc analyses using other validated clinical endpoints suggest that there still remains an unmet medical need. Therefore, alternative therapies continue to be explored for patients who must discontinue dupilumab (or any other therapy) due to limited or slow-onset efficacy or adverse reactions. Indeed, there exists an opportunity to explore a broader approach and for which relatively infrequent dosing may also be possible, such as an anti-IL-18 mAb (GSK1070806).

2.2. Background

Rationale for a potential role of IL-18 in Atopic Dermatitis

Interleukin-18 (IL-18) is a pleiotropic cytokine which acts as a modulator of the innate and adaptive immune response in a context dependent manner with potential to amplify pathways important in AtD [Saikiran, 2013, Lee, 2015]. Increased IL-18 levels were observed in the skin and plasma of patients with AtD and correlated with disease severity [Inoue, 2011]. In preclinical models, overexpression of IL-18 induces skin inflammation, while neutralisation of IL-18 can prevent development of an AtD-like phenotype suggesting that IL-18 may have potential in clinical disease [Antonopoulos, 2008; Röse, 2012; Plitz, 2003; Kawase, 2003; Ricardo-Gonzalez, 2018; Chen, 2020; Konishi, 2002; Terada, 2006]. Polymorphisms in the IL-18 gene locus are associated with higher circulating IL-18 levels and increased incidence of AtD. Collectively, these data suggest that IL-18 may play a key role in the pathophysiology of AtD which warrants clinical evaluation.

GSK1070806 and prior clinical studies

GSK1070806 is a highly potent anti-IL-18 monoclonal immunoglobulin G1 (IgG1) antibody which was previously explored in a first time in human (FTIH) and in exploratory studies in Type 2 Diabetes and Delayed Graft Function following renal transplantation [Mistry, 2014; McKie, 2016;Wlodek, 2021]. One additional early phase clinical study was also conducted in Crohn's Disease but results have not yet been reported [see IB "Previous Human Experience" and Appendix "Tabulated List of Clinical Studies" for details, GSK Document Number WM2009/00047/07].

Study 215253 in Atopic Dermatitis:

This translational medicine study (215253) will test the impact of GSK1070806 in two groups of patients with moderate-severe AtD. Group 1 participants are those who have failed topical therapies and remain naïve to both biologic therapies (e.g. dupilumab) and to inhibitors of the Janus kinase pathway (JAKi); the biologic naïve (BN) population. The primary efficacy endpoint of Group 1 is percent change from baseline in the eczema area and severity index (PCFB EASI [Hanifin, 2001]) at Wk 12.

Given that the range of biological processes impacted by IL-18 is considerably broader than those impacted by IL-4/IL-13, there is the potential that GSK1070806 may provide

improved benefit compared to dupilumab in some patients. Therefore, the study will address efficacy in patients whose disease was not previously controlled by dupilumab ("dupilumab inadequate responder" Dupi-IR population, Group 2).

CCI

[redacted]

2.3. Benefit : Risk Assessment

The study benefit : risk assessment is based upon considerations of the mechanism of action of blocking IL-18 (a modulator of the immune response), data from the one month cynomolgus monkey toxicology study and on prior clinical experience following single (up to 10 mg/kg GSK1070806) and two doses (5 mg/kg) of GSK1070806, see IB, [GSK Document Number WM2009/00047/07].

More detailed information about the potential benefits and risks of GSK1070806 may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) GSK1070806		
Increased susceptibility to infection	IL-18 plays a role in host defence against microbial pathogens. Therefore, there is a theoretical risk that blocking of IL-18 signalling by GSK1070806 may increase a patient's susceptibility to bacterial and viral infections. Cynomolgus monkeys can be asymptomatic carriers of *Shigella flexneri*. Clinical signs of *Shigella flexneri* were first noted in a monkey administered vehicle control (0 mg/kg) and later in monkeys who received GSK1070806 at doses (3, 30 and 300mg/kg) in the 4-week repeat dose study. With the exception of 1 female in the top (300mg/kg) dose group, all animals responded to intramuscular antibiotic (Baytril) treatment prior to necropsy. In clinical studies, there was no apparent increase noted in infections, immune system disorders, or haematologic abnormalities in human participants dosed up to 10mg/kg.	Appropriate exclusion criteria are included in the protocol (Section 5.2) to exclude patients with high risk of acute, recurrent and chronic infections Appropriate stopping criteria are included in the protocol (Section 7.1.1) with reviews of SAEs and severe AEs should they occur.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion related and immune mediated side effects.	No intravenous infusion-related or injection site reactions were noted in the monkey IV 4-week repeat dose study and in human clinical studies.	Participants will be monitored closely in a clinical unit for clinical signs of infusion-related and immune-mediated side effects for 2 hours post-end of IV infusion. Patients will be informed of the potential for and symptoms of a late drug infusion reaction and on what to do (and this will also be detailed in the informed consent form [ICF]). Training for delegated staff on how to manage / available facilities will have been performed and documented.
Immunogenicity	No anti-drug antibodies (ADAs) were detected following 4 weekly administrations at doses up to 300 mg/kg/week, or following the 8-week treatment free period, in cynomolgus monkeys. To date, 3 human participants had confirmed ADAs post dosing (1mg/kg), with relatively low titres. In 2 of 3 participants the ADA titre were transient (positive at one time point) and were therefore not considered to be of major clinical significance. The third participant	Monitoring of ADAs is included in the protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	had confirmed low titre ADA from Day 14 to Day 213 post dose, but these did not result in any clinical sequelae. To date, there is no evidence that ADAs affected the safety or pharmacokinetic profile of GSK1070806.	
Effects on blood pressure	There was no apparent change in blood pressure in a single 300 mg/kg dose non-clinical safety pharmacology study and a 4-week toxicology study in monkeys (300 mg/kg administered weekly for 4 weeks). In the FTIH clinical study (A18110040), no apparent change was observed in any mean value for any vital sign parameters (systolic and diastolic blood pressure, heart or respiration rate and body temperature) following administration of placebo or GSK1070806 at any dose level. Following administration of 3 mg/kg in obese participants, there was one AE report of transient elevated heart rate and blood pressure values associated with an episode of supraventricular tachycardia that was noted on Holter monitoring. The investigator considered this AE to be unrelated to GSK1070806	Vital signs are routinely monitored in the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In Study A18116378 AEs of hypertension were reported in Type 2 Diabetic Mellitus patients following GSK1070806 administration (2/13 (15%) participants at 0.25 mg/kg; 3/12 (25%) participants at 5 mg/kg), but not placebo. A detailed review of blood pressure did not suggest an overall trend, although there were some individuals with variations in blood pressure.	
Effects on pregnancy	A reproductive toxicology study has not been conducted. GSK1070806 is not considered genotoxic. Elevated levels of IL-18 in placentas of blood samples from women with preeclampsia have been observed. Non-clinical modelling suggested that the likely transferable drug concentration for sperm to female via the vaginal tract is negligible.	Women who are pregnant, lactating or are planning on becoming pregnant during the study are excluded. (please refer to Section 5.2 for male and female contraception). WOCBP require the use of highly effective contraceptive methods and are to be monitored for pregnancy and withdrawn from selected study procedures in case of pregnancy (excepting continued safety monitoring)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Skin biopsy	Complications of skin biopsy are uncommon but may include bleeding, infection, and scarring.	Biopsies are to be performed under a local anaesthetic to reduce any discomfort. The small risk of infection after biopsy will be minimised by cleaning of the site before biopsy and the addition of a steri-strip/suture if required (or similar). Participants are instructed to visually inspect skin biopsy sites and are informed on the signs of inflammation/infection to watch for and to contact the investigator with any concerns.
Skin tape stripping	Repeated tape stripping may cause mild discomfort.	Participants are to be instructed to apply a bland emollient (if appropriate) following the procedure.
Risk associated with attending an investigative site during the Coronavirus strain 19 (COVID-19) Pandemic	The current COVID-19 (Severe acute respiratory syndrome-Coronavirus-2 [SARS-CoV-2]) pandemic may pose a challenge to the integrity of the trial, protection of participants′ rights, safety and wellbeing and the safety of clinical trial staff. Therefore, risk mitigation strategies have been introduced and will be evaluated on an ongoing basis per each country. The	**Participant Selection:** If it is deemed appropriate at a local level, participants will be counselled regarding the importance of infection control measures such as hand washing, reducing inter-personal contacts as much as possible and of potential COVID 19 symptoms. Site trial staff in direct contact and/or within 1 m distance of study participants will receive additional

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	study will be halted if the dynamics of the SARSCoV-2 outbreak change in such a way that the safety of the trial participants and clinical trial staff or integrity of the data collected cannot be guaranteed.	protection *via* the use of Personal Protective Equipment (PPE) and disinfectants. **Participant monitoring:** If it is deemed appropriate at a local level, prospective AtD participants will be contacted by sites to check on COVID-19-related symptoms prior to being pre-screened (SARSCoV-2 test) and prior to consenting. Consented participants may also be contacted (if it is deemed appropriate at a local level) prior to each scheduled visit. Participants will be screened prior to dosing on Day 1 and tested at the End of Study Visit (or at early withdrawal) as per protocol (see Section 1.3). **Protection of Trial Integrity:** Adherence to the protocol and investigative site procedures will go towards protecting the integrity of the data collected during this clinical trial, as well as the participants' data protection rights. **COVID-19 Contingency Plan:** Any participant presenting with COVID-19-related symptoms (**2**) and having a positive

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		SARS-CoV-2 test (**3**) may continue in the study (or may be temporarily suspended during recovery) if the investigator judges this to be possible (e.g. if the participant is able to adhere to local management guidance). If a participant needs to be excluded from (further) participation in the trial s/he will receive follow-up medical attention as per local procedure.

2.3.2. Benefit Assessment

AtD participants may experience benefit in improved symptoms and clinical presentation following a single administered dose of GSK1070806. By enrolling in this study, participants will be contributing to the process of developing a new medicine to address the unmet need for patients intolerant or unresponsive to currently available treatments.

2.3.3. Overall Benefit: Risk Conclusion

There remains an unmet medical need for effective treatment of AtD in patients who inadequately responded to topical SoC.

Considering the measures taken to minimise the potential risks of GSK1070806, the potential for clinical benefit outweighs the potential risks of testing GSK1070806 in study participants.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To compare the clinical effect of a single intravenous (IV) infusion of 2 mg/kg of GSK1070806 *versus* placebo in moderate to severe Atopic Dermatitis in the Biologic Naïve (BN) population (Group 1).	Percent change from baseline (PCFB) in the Eczema Area and Severity Index (EASI) at Week 12 (Section 8.1.1).
Secondary	
To further compare the clinical effect (GSK1070806 *versus* placebo) in the BN population (Group 1).	• Change from Baseline (CFB) in the EASI at Week 12. • EASI 50/75/90 defined as ≥ 50/75/90% reduction in the EASI from Baseline at Week 12. • Investigator Global Assessment (IGA) score of 0 or 1 at Week 12.
To estimate the clinical effect of GSK1070806 in the dupilumab inadequate responder (Dupi-IR) population (Group 2).	• PCFB in the EASI at Week 12.
To assess safety and tolerability (GSK1070806 *versus* placebo) in the combined AtD population (Groups 1 and 2).	• Incidence of serious adverse events (SAEs) and adverse events (AEs). • Incidence of clinically important [(1)] findings in:

Objectives	Endpoints
	○ vital signs ○ electrocardiogram ○ laboratory: haematology, clinical chemistry and urinalysis. (Section 8.3)
To assess anti-drug antibody (ADA) formation in the combined AtD population (Groups 1 and 2)	Incidence of ADAs (Section 8.8)
CCI [redacted]	

Objectives	Endpoints

1) Absolute or change in important clinical findings are defined in the statistical analysis plan (SAP) for each relevant safety endpoint.

4. STUDY DESIGN

4.1. Overall Design

This is a multi-centre, 12-week, randomized, double-blind, parallel group, placebo-controlled study of GSK1070806 administered as a single 2 mg/kg IV and will investigate the efficacy and safety in moderate-severe AtD participants. See the Study Schematic (Section 1.2) and the Schedule of Activities (Section 1.3).

Study Populations and Randomisation

Group 1 - BN: for whom disease was not adequately controlled by topical treatments. Approximately 40 BN patients may need to be consented for screening to provide 30 randomized. Thirty BN participants will receive GSK1070806 or placebo in a 2:1 ratio (20 and 10 participants, respectively).

Group 2 - Dupi-IRs: patients whose disease was not adequately controlled following at least 16 weeks of dupilumab treatment (please refer to inclusion and exclusion criteria) or who could not tolerate dupilumab. Approximately 24 Dupi-IR patients may need to be consented for screening to provide 18 randomized. Eighteen Dupi-IR participants will receive GSK1070806 or placebo in a 5:1 ratio (15 and 3 participants, respectively).

Primary Efficacy Endpoint

The primary efficacy endpoint is percent change from baseline in the eczema area and severity index (PCFB EASI [Hanifin, 2001]) at Wk 12 in participants of Group 1.

Study Duration

Groups 1 and 2 will be conducted in parallel.

The overall study duration for an individual participant is not expected to exceed 28 weeks (Screening is 4 weeks; Treatment Period is 12 weeks; Follow-Up Period is 12 weeks).

The End of Study (Wk 24, Day 169) allows for continued safety monitoring beyond the Wk 12 primary endpoint in this new disease population (AtD), for which GSK1070806 has not yet been tested.

Treatment and Follow-Up Periods Screening Period

- The Screening Period is 28 days.
- All participants must stop using topical treatments (corticosteroids, calcineurin inhibitors or Phosphodiesterase 4 [PDEIV] inhibitors) for at least 7 days (starting on Day -7) prior to dosing on Day 1.
- Participants should apply bland topical emollient at least once from at least Day -7 (until at least Wk 12).
- Participants must record itch (PP-NRS) and fatigue (brief fatigue inventory, CCI item 3) daily starting on Day -7 (see SoA Section 1.3).

Following the end of the single intravenous infusion of study treatment, participants are to be monitored for at least a two-hour period before discharge from the clinical unit.

The Treatment and Follow-Up Periods are both 12 weeks in duration. The participant will be instructed to make contact with the site at any time in case of any concern. Participants who withdraw from the study must be encouraged to complete the assessments listed for the Withdrawal Visit.

Safety Review Team (SRT)

In line with routine pharmacovigilance, an internal GSK safety review team (SRT, see Section 10.1.5) will have oversight of any emerging safety data related to GSK1070806 and will review *blinded* safety data at appropriate intervals.

Statistical Analyses

- The primary analysis will be performed when all participants in Group 1 have reached Wk 12 (or have withdrawn from the study prior to Wk 12).
- Interim analyses may be performed in Groups 1 and 2, and will be overseen by a Data Review Committee (DRC, Section 10.1.5):
    - Group 1: One unblinded efficacy interim analysis may be performed when approximately 50% participants in Group 1 have completed Wk 12 (or have withdrawn prior to Wk 12, see Section 9.5.2). The study may be terminated following the interim analysis. Additional unblinded interim analyses may be performed to support internal decisions and will have no impact on the conduct of the study.
    - Group 2: One unblinded efficacy interim analysis may be performed when approximately 30 participants in Group 1 have been randomized (Section 9.5.2). Group 2 recruitment may be terminated following the interim analysis. Additional unblinded interim analyses may be performed to support internal decisions and will have no impact on the conduct of the study.
- An end of study analysis will be performed when the last participant last visit (LPLV) has been achieved.

4.2. Scientific Rationale for Study Design

Randomized, double-blind, placebo-controlled design

GSK1070806 is an experimental drug which has not previously been studied in the AtD population. The inclusion of a placebo arm in Groups 1 and 2 will ensure blinding of any attribution of treatment to potential safety signals whilst also providing control data for the comparison of efficacy and biomarkers.

Rationale for Two Study Populations

Participants are to be grouped on the basis of their prior treatment: *either* Group 1 - biologic naïve (BN) and having failed topical therapies, *or* Group 2 - whether having specifically demonstrated an inadequate response to dupilumab (Dupi-IR).

- Group 1: Participants with moderate to severe AtD who have not responded adequately to topical treatments (after 4 weeks treatment with either TCS or TCI within the last 6 months) may usually, at this stage, be considered for an approved therapy (if available) e.g. Dupixent, or JAKis, or be considered for clinical trials.

  Potential BN participants must not have ever been treated for AtD with either dupilumab, other experimental biological treatments, or JAKi(s), owing to the potential for an overlapping mechanism of action with GSK1070806

  Studying GSK1070806 in the BN population will enable evaluation of preliminary efficacy in moderate-severe AtD and will allow indirect comparison with historical data.

- Group 2: Although approximately 50% AtD patients receiving dupilumab (Dupixent, an anti-interleukin-4 receptor [IL-4R] mAb) achieve EASI75, there remains a significant unmet need. Since the range of biological processes impacted by IL-18 is broader than those impacted by IL-4/IL-13, there is the potential that GSK1070806 may provide benefit to those patients who were not adequately controlled by dupilumab. Therefore, it is of particular interest to additionally select/include a small group of Dupi-IRs to broaden the investigation.

Given the putative difference in efficacy between the two study populations (as a consequence of prior treatment with dupilumab), the clinical endpoints for these populations are to be analysed separately (see Section 9).

Washout of prior therapy during Screening.

All participants must meet all clinical criteria at the point of randomization (for subsequent dosing on Day 1) following at least a 7-day washout of TCS (starting from Day -7).

Duration of Treatment / Follow-Up Period

The duration of the Treatment Period is 12 weeks (see both this Section 4.2 “Efficacy Endpoints” and Justification for Dose: Section 4.3).

The duration of the Follow-Up Period is based upon the observed half-life of GSK1070806 in healthy volunteers, which was 31 days at 1mg/kg and 38 days at 3mg/kg [Investigator's Brochure: GSK Document Number WM2009/00047/07]. Following patients for 24 weeks after administration of GSK1070806 allows safety monitoring to continue for approximately 5 half-lives in this new disease population (see Justification for Dose, Section 4.3).

Randomization Ratio

Group 1 (BN): participants will be randomized in a 2:1 ratio to increase the overall chance of participants receiving GSK1070806 over placebo. To supplement the number of participants in the placebo arm, historical data were used and a robust meta-analytic predictive (MAP) prior was constructed with an effective sample size of 14 participants (expected local-information-ratio [ELIR] method [Neuenschwander, 2020]).

Group 2 (Dupi-IR): participants will be randomized in a 5:1 ratio. The clinical effect in this group will not be compared against placebo (see Section 9) but a small placebo arm has been included to maintain the study blind.

Efficacy Endpoints

The primary endpoint is PCFB in the EASI at Wk 12 in the BN population (Group 1).

EASI (see Section 8.1.1) is a precedented composite clinical endpoint for use in early clinical trials of moderate to severe AtD [Hanifin, 2001]. The magnitude of efficacy (measured as PCFB and CFB EASI) observed as clinically meaningful was evident by 12 weeks after administration of both marketed products (Crisaborole [Bissonnette, 2019], Dupixent [Beck, 2014] and of Phase II/III experimental drugs, Upadacitinib [Guttman-Yassky, 2020] and Abrocitinib [Simpson, 2020b] and will allow for indirect comparison to other therapies.

Similarly, the IGA response is an established Food and Drug Administration (FDA) regulatory endpoint. Clinical scores will be measured throughout to ensure preliminary assessment of the onset, extent and duration of clinical response.

Patient Reported Outcomes (PROs)

Nearly two-thirds (62·9%) of moderate to severe AtD patients report itching for at least 12 h each day, with 60·5% of patients rating their itch as either severe or unbearable (Simpson, 2016c). Reducing the itch–scratch cycle is an important treatment goal and forms a key aspect of reducing overall disease severity. The PP-NRS is a recognized clinical instrument for itch in AtD (reviewed Yosipovitch, 2019). Three additional PRO instruments have been introduced to collect qualitative and meaningful data on sleep disturbance [CCI] Sleep Disturbance, Lei, 2020) and [CCI] [Tennant, 2019] and [CCI] [Mendoza, 1999]). The dermatology life quality index (DLQI) covers the impact of AtD on general aspects of daily living [Finlay, 1994], see details in Section 8.2.

CCI

[redacted]

CCI [redacted]

4.2.1. Participant Input into Design

Feedback on study design obtained during interview with one patient based in US held on 22-04-021. Based on the patient feedback from the interview, the number of biopsies was decreased from 5 to 4.

4.3. Justification for Dose

A single 2 mg/kg dose GSK1070806 administered via intravenous infusion is proposed for Study 215253.

The predicted exposures of GSK1070806 (Cmax and AUC; 0.05 mg/mL and 27.2 mg.h/mL, respectively) after a single dose of 2 mg/kg are 376 and 65 fold below the NOAEL thresholds (Cmax and weekly AUC; 18.8 mg/mL and 1775 mg.h/mL, respectively) from the 1 month cynomolgus monkey study (4 weekly 300 mg/kg doses).

The safety, tolerability and PK of GSK1070806 have been evaluated in humans after administration of a single escalating dose (dose level ranging from 0.008 mg/kg up to 10 mg/kg) and after two doses administered 28 days apart (dose levels studied: 0.25 mg/kg or 5 mg/kg). In all clinical studies to date, GSK1070806 was well tolerated over at least 210 days (see Investigator Brochure [GSK Document Number WM2009/00047/07]).

A mechanistic PKPD model based on both preclinical affinity data and the observed clinical PK and PD data suggests that a single 2 mg/kg dose GSK1070806 administered via intravenous infusion is anticipated to provide >90% reduction in plasma free IL-18 levels in at least 90% of participants for at least 12 weeks: this extent and duration of inhibition is judged to be sufficient to provide a robust assessment of the potential of GSK1070806 to treat AtD.

GSK1070806 has a terminal half-life ranging from 31 to 38 days after single dose administration of 1 or 3 mg/kg. Therefore, it is expected that after a single dose of 2 mg/kg, drug levels at the End of Study (Day 169) will be reduced 32-fold (2^5) as compared to the C_{Max} at the end of infusion. Although the concentration of GSK1070806 at Day 169 is predicted to be >10,000 fold below the NOAEL threshold, the extended pharmacodynamic effect observed in previous studies suggest that circulating GSK1070806 at this time may still retain some pharmacological activity. However, in previous clinical studies, GSK1070806 was well tolerated over at least 210 days after dosing when compared to placebo at doses up to 10mg/kg, so safety monitoring for a 24-week period in this study is appropriate.

4.4. End of Study Definition

The End of Study is defined as the date of the last visit of the last participant according to the Schedule of Activities.

A participant is considered to have completed the study if he/she has completed the last scheduled procedure shown in the Schedule of Activities.

5. STUDY POPULATION

Inclusion Criteria Numbers 4 and 5 and Exclusion Criterion Number 21 distinguish the two study populations.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
1. Moderate to severe atopic dermatitis (confirmed by a dermatologist) according to the Hannifin and Rajka criteria or Eichenfield revised criteria [Eichenfield, 2014; Hanifin, 1980]. 2. Onset of AtD symptoms occurring at least 6 months prior to Screening, with stable disease for at least 1 month prior to Screening. 3. The participant should meet the following criteria at the initial Screen and immediately prior to trial drug infusion on Day 1 (Baseline): a. EASI ≥16 b. IGA score ≥3. 4. Group 1 - Biologic Naïve: Topical First Line Treatment: Documented recent history (within 6 months before Screening) of: a. ***either*** an inadequate response (IR) to out-patient treatment with *at least one* topical treatment (intermittent TCS, TCI), topical PDEIV inhibitor (Crisaborole). b. ***or*** that topical treatments were otherwise not recommended. 5. Group 2 – Dupi-IRs: Documented history of an inadequate response (IR) to dupilumab: a. **either** following at least 16 weeks of treatment according to the Investigator's judgement b. ***or*** intolerant to dupilumab owing to adverse events. 6. Willing to discontinue topical corticosteroids, topical calcineurin inhibitors or topical PDEIV inhibitors from at least 7 days (starting Day -7) prior to trial drug infusion on Day 1.

7. Stable use of topical emollient e.g. use of an additive-free, bland emollient for at least 7 days (starting Day -7) prior to dosing on Day 1 and be willing to continue a stable regimen for at least 12 weeks after dosing). 8. Willing to contribute three serial 4.5 mm punch biopsies of lesional skin and a set of tape strips at Baseline, Wk 4 and Wk 12. Willing to contribute one 4.5 mm punch biopsy of non-lesional skin at Baseline. 9. If receiving concomitant medications for any reason, the participant should try to stay on a stable regimen throughout the entire study.
AGE
10. Between 18 and 75 years of age inclusive, at the time of signing the informed consent.

WEIGHT
11. Body mass index (BMI) within the range 18 - 39.9 kg/m^2 (inclusive).

SEX and CONTRACEPTIVE/BARRIER REQUIREMENTS
12. Sex and Contraceptive /Barrier requirements for males and females a. Male Participants: Male participants are eligible to participate. b. Female Participants: • A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies: o Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4, Contraception and Barrier Guidance. OR o Is a woman of childbearing potential WOCBP and using an acceptable contraceptive method as described in Section 10.4 during the study period. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention. • A WOCBP must have a negative highly sensitive serum pregnancy test result (as required by local regulations) at the initial Screening visit and a negative urine pregnancy test result immediately prior to dosing on Day 1: see Section 8.3.5 Pregnancy Testing.

- [If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.]

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

INFORMED CONSENT
13. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Medical Conditions
1. **Skin Morbidity:** other than atopic dermatitis, the presence of a significant skin morbidity that will influence the Investigator's ability to assess the severity of the disease (e.g. psoriasis, confirmed or suspected cutaneous T-cell lymphoma, autoimmune bullous disease, fixed drug reaction and Stevens Johnson Syndrome).
2. **Major Diseases/Conditions:** Participants with any uncontrolled medical conditions, other than Atopic Dermatitis, that in the opinion of the investigator puts the participant at unacceptable risk or will likely interfere with study assessments or data integrity. Other medical conditions should be stable at the time of screening and be expected to remain stable for the duration of the study.
3. **Malignancy:** solid or hematological malignancy or a history of malignancy (in the past 5 years), *except for treated/cured* basal cell or squamous cell *in situ* skin carcinomas, cervical intraepithelial neoplasia (CIN) or carcinoma *in situ* of the cervix.
4. **Infection:** • An acute infection within 2 weeks of dosing on Day 1. • history of, or currently being treated for, a clinically significant recurrent or chronic infection/s (except very minor localised infections, for example tinea pedis). • hospitalized for treatment of infection (anti-bacterials, anti-virals, anti-fungals or anti-parasitic agents) within 30 days of dosing on Day 1.
5. Known **varicella, herpes zoster**, or other severe viral infection within 6 weeks of anticipated dosing on Day 1. Or history of recurrent herpes reactivation in the past 2 years.
6. **COVID-19 (SARS CoV-2):** • Has had COVID-19 infection within 4 weeks of the initial Screening visit.

- Positive test obtained at initial Screening.
- Signs and symptoms suggestive of COVID-19 (i.e. fever, cough, etc) within 14 days of initial Screening.
- Known COVID-19-positive contacts within 14 days of initial Screening, at any time during the Screening Period, or within 14 days of dosing on Day 1.

7. **Tuberculosis (TB):** Evidence of active or latent TB as documented by medical history, examination, and TB testing with a positive QuantiFERON test at initial Screening visit.
   NOTE: In cases where the QuantiFERON test is *indeterminate*, the participant may have the test repeated once, but they will not be eligible for the study unless the second test is negative. In cases where the QuantiFERON test is positive, the participant should be followed up as per standard of care.
8. **Drug Allergy or hypersensitivity:** history of clinically significant multiple or severe drug allergies or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A (IgA) dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
9. **Sensitivity** to any of the study interventions, or components/excipients thereof, in the opinion of the Principal Investigator (or following consultation with the GSK Medical Monitor), contraindicates participation in the study.
10. **Hepatic**: current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
    a. Alanine transaminase (ALT) >2x upper limit of normal (ULN).
    b. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
11. **Cardiology** assessment/co-morbidity defined as: corrected Q (QTc) >450 msec (480 msec for those with Bundle Branch Block). Either QTcb (Bazett) or QTcf (Fridericia), machine or manual overread, may be used. The QT correction formula used to determine exclusion and discontinuation should be the same throughout the trial. The QTc should be based on a single value (derived from the average of triplicate readings) of ECG obtained over a brief recording period.
12. A participant with either a **clinical abnormality or a laboratory parameter(s)** outside of the reference range (or both) that is not specifically listed in the inclusion or exclusion criteria may only be included if the Investigator, in consultation with the GSK Medical Monitor, agrees and documents that the finding is unlikely to introduce additional risk factors that will not interfere with the study procedures or interpretation.

PRIOR / CONCOMITANT THERAPY

Any patients that are receiving medication(s) detailed in this Section will *not* be eligible for randomisation into the trial.

13. **Surgery:** major surgery (as per investigator's judgement) within 3 months prior to dosing on Day 1.

14. **Phototherapy:** treatment with phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]), within 4 weeks of dosing on Day 1. 15. **Sun/tanning:** prolonged sun exposure or use of tanning booths (which may confound interpretation of study data) within 2 weeks before Initial Screening. 16. **Bleach bath:** three or more bleach baths during any week within 4 weeks of the initial Screening visit. 17. **Medical Devices:** treatment of AtD with a medical device (eg, Atopiclair, MimyX, Epicerum, Cerave, etc) within 1 week of the initial Screening visit. 18. **Vaccines**: participant has received a live, attenuated or recombinant vaccine within 8 weeks of anticipated dosing (Day 1), or will require vaccination within 24 weeks following dosing. Note that, the recombinant adenovirus vector vaccines against COVID-19 (both human and non-human primate in type) are permitted (refer to the study reference manual, SRM). 19. **Systemic corticosteroids**: treatment within 30 days of dosing on Day 1. Note that, intra-articular steroids are permitted. 20. **Topical corticosteroids:** treatment within 7 days of dosing on Day 1. 21. **Biologic agents:** treatment with biologic agents (investigational and marketed monoclonal antibodies) within 12 weeks or 5 pharmacokinetic half-lives (whichever is longer) prior dosing on Day 1. 22. **JAK inhibitors:** treatment with JAK inhibitors (e.g. baricitinib, upadacitinib) within 4 weeks or 5 half-lives (whichever is longer) prior to dosing on Day 1. 23. **Other systemic treatments**: mycophenolate mofetil, azathioprine, methotrexate, or calcineurin inhibitors within 4 weeks of Screening.
Prior / Concurrent Clinical Study Experience
24. **Blood / product loss**: participation in this study would result in loss of blood or blood products in excess of 500 mL within 3 months. 25. **Investigational drug:** use of any investigational drug within 30 days prior to the initial Screening visit, or 5 pharmacokinetic half-lives, or twice the duration of the biological effect (if known), whichever is longer.
Diagnostic assessments
26. **Hepatitis B**: patients will be excluded with **any** evidence of acute or chronic infection, or if interpretation of their results is unclear at the initial Screening visit.This includes: a. Hepatitis B surface antigen (HbsAg) + b. Anti-hepatitis B core (HBc) + Note that, it is permissible to enrol patients who are anti-HBs+, ***only*** when this is attributable to vaccination and there is ***no*** history of previous infection.

Note that, if the serology test results remain unclear, a confirmatory hepatitis B (HB) deoxyribonucleic acid (DNA) + test may be performed. 27. **Hepatitis C**: patients will be excluded if there is *any* evidence of past or current hepatitis C infection at the initial Screening visit (hepatitis C antibody [quantitative immunoassay, qIA], hepatitis C radio immunoblot assay [RIBA or PCR]). NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease may be enrolled, *only if* a confirmatory negative Hepatitis C RNA (PCR) test is obtained. 28. **HIV:** Positive human immunodeficiency virus (HIV) antibody test (obtained at the initial Screening visit) or known to have a historically positive HIV test.
Other Exclusions
29. **Alcohol:** Regular alcohol consumption within 6 months prior to the initial Screening visit defined as an average weekly intake of >14 units for males and >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits. 30. **Substance abuse:** Active substance abuse or a history of substance abuse (in the opinion of the Principal Investigator) within 6 months prior to the initial Screening visit. Note that *documented* medical use of marijuana or occasional recreational use of marijuana may be permitted subject to a priori agreement with the Medical Monitor. 31. **Compliance:** is unlikely to comply with scheduled study visits based on investigator judgment; has a history of a psychiatric disorder or condition that may compromise communication with the investigator.

5.3. Lifestyle Considerations

5.3.1. COVID-19 related restrictions

Participants will be required to adhere to the measures and procedures outlined locally at each of the investigative sites to reduce the risk of COVID-19 infections among trial participants and clinical site staff.

5.3.2. Meals and Dietary Restrictions

Not appropriate

5.3.3. Caffeine, Alcohol, and Tobacco

- There are no restrictions on ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate).
- Participants must abstain from alcohol for 24 hours before all scheduled visits.
- Participants who use tobacco products will be instructed that smoking will not be permitted while they are in the clinical unit.

5.3.4. Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

5.4.1. Re-screening

Participants who do not meet the eligibility criteria for this study may be rescreened once. Re-screened participants should be assigned a new participant number.

5.4.2. Re-testing of Clinical Laboratory Values during Screening

If a participant fails any of the laboratory criteria (e.g. variability around the threshold limit of a normal value, or spurious result), the test may be repeated once within the screening period. If the participant fails the laboratory criteria for a second time they will be considered a screen failure.

If a blood sample needs to be repeated due to sample handling problems, breakage or sample integrity, this is not considered a re-testing. Further details regarding the procedure for re-testing may be found in the SRM.

5.5. Criteria for Temporarily Delaying

Not applicable

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

ARM Name	Active	Placebo
Intervention Name	GSK1070806 Injection, 100 mg/mL	0.9% sodium chloride injection
Dosage Form	Solution for infusion	Solution for infusion
Unit Dose Strength(s)	100 mg/mL with 100 mg (1 mL) withdrawable per vial.	Variable volume
Dosage Level(s)	2 mg/kg - once (Groups 1 and 2)	The appropriate volume of 0.9% sodium chloride injection will be infused (IV) in the same manner as the corresponding active cohort
Route of Administration	IV infusion (Groups 1 and 2)	IV infusion (Groups 1 and 2)
Dosing Instructions	1 hour IV infusion. Dilute into 100 mL sterile IV infusion bag 0.9% Sodium Chloride (for details, see Pharmacy Manual)	1 hour IV infusion.
Manufacturer/ Source of Procurement	Provided centrally by the Sponsor	Provided locally by the trial site
Packaging and Labelling	Study Intervention will be provided in vials. Each vial will be labelled as required per country requirement.	N/A

6.2. Preparation/Handling/Storage/Accountability

For the required dose, the IP will be diluted in 0.9% sodium chloride injection and administered through IV infusion. Description of the methods and materials required for preparation and handling of GSK1070806 dosing solutions are detailed in the Pharmacy Manual.

Study treatment must be dispensed or administered according to procedures described herein and in the SRM and Pharmacy Manual.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records)

Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. 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 GSK study contact.

Precaution will be taken to avoid direct contact with the study intervention. 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. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinded study with unblinded site pharmacist who is dispensing intervention	All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS): RAMOS-NG. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. Participants will be randomized in a 2:1 ratio (Group 1 Biologic Naïve versus placebo) or 5:1 ratio (Group 2 Dupi-IR) to receive study intervention. Investigators will remain blind to each participant's assigned study intervention. In order to maintain the blind, an otherwise uninvolved 3rd party will be responsible for the dispensing of study intervention and will endeavour to ensure that there are no differences in the preparation time following randomization. Unblinded monitors, and in the event of a Quality Assurance audit, the auditor(s) will be permitted access to un-blinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

A participant may continue in the study if that participant's intervention assignment is unblinded.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant 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 participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.3.1. Controlled Early Access to Unblinded PK and PKPD Data

Designated independent representative(s) may be unblinded for performing population PK and PKPD dataset preparation and draft PK and PKPD model development at one or more time points throughout the trial using scrambled (random reassignment of subject identification numbers) PK and PKPD unblinded datasets.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention 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 intervention 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 intervention.

6.5. Dose Modification

Not applicable

6.6. Continued Access to Study Intervention after the End of the Study

Not applicable

6.7. Treatment of Overdose

For this study, any dose of GSK1070806 greater than 2 mg/kg will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

- Contact the Medical Monitor immediately to discuss details (actual dose administered) and next steps.
- Monitor the participant for any AE/SAE and clinical laboratory parameters for 24 weeks (until End of Study) following dosing.
- Document the quantity of the excess dose in the case report form (CRF).

6.8. Concomitant Therapy

The Medical Monitor should be contacted if there are any questions regarding prior, concomitant (including rescue) or non-permitted therapies.

Documenting therapies: Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest (topical therapies for AtD) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

6.8.1. Permitted Concomitant Therapies

Patients are to be instructed to apply topical non-medicated emollient at least once daily from Day -7 until at least Day 85.

The following concomitant therapies are permitted under the conditions described.

- Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day at any time during the study.
- Oral anti-histamines (at the approved dose) at any time during the study.
- Intra-articular steroids (at the approved dose) at any time during the study.
- COVID-19 vaccines: see SRM for updated list of vaccines permitted per each country.
- Other concomitant medication may be considered on a case-by-case basis by the investigator (and in consultation with the Medical Monitor if required).

6.8.2. Prohibited Medications

Medications prohibited between Screening and Wk 12 are as follows owing to their potential to confound safety (and efficacy) assessments.

- Topical corticosteroids, topical calcineurin inhibitors, topical PDE4 inhibitors
- Oral immunosuppressants
- IV corticosteroids or biological immunosuppressants
- Phototherapy

If a participant requires a prohibited medication to address an urgent clinical need (e.g. extremely active disease, see Section 7.1.4) this should be recorded as a protocol deviation. The protocol deviation may affect the evaluability of the participant and should be discussed with the Medical Monitor in advance, if possible.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The study stopping criteria are based upon the mechanism of action of blocking IL-18 (a modulator of the immune response), the one month cynomolgus monkey toxicology study finding(s) and on prior clinical experience following single (up to 10 mg/kg GSK1070806) and two doses (up to 5 mg/kg) GSK1070806, see IB, [GSK Document Number WM2009/00047/07].

7.1. Discontinuation of Study Intervention

As this is a single dose study, discontinuation of study intervention is not applicable. This section describes additional monitoring or participant management that should be implemented if specific safety-related criteria are fulfilled. Unless otherwise specified, participants experiencing any of these criteria should continue in the study.

7.1.1. Adverse Event Criteria

- A participant develops a serious or severe opportunistic or atypical infection.
- The participant experiences a serious or severe adverse reaction following study investigational product administration, meeting Grade 3 or 4 of the Common Terminology Criteria for Adverse Events (CTCAE) criteria, irrespective of causality.

Full CTCAE descriptions and grades can be found in the accompanying SRM or the U.S Department of Health and Human Services, CTCAE, Version 5.0 (2017).

Study assessments may be missed if it is determined by the investigator that it is not in the best interests of the participant to attend scheduled study visits prior to resolution of the adverse event. Once resolved, participants should complete remaining study assessments according to the SoA

7.1.2. Liver Chemistry Criteria

Since participants will receive a single dose of study medication, there are no liver specific stopping criteria as such and the participant may continue in the study according to the SoA. In the event of liver parameters deviating from the thresholds described in Section 10.6, follow the instructions in that section.

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

fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

7.1.3. QTc Criteria

The same QT correction formula (either Bazett's formula [QTcB] or Fridericia's formula [QTcF]) must be used for all QTc data being collected for each individual participant to determine eligibility for the study. This formula must not be changed or substituted once the participant has been enrolled.

If an abnormal (prolonged) QTc is observed post-dose, obtain 2 more ECGs over a brief period, and then use the averaged QTc value of the triplicate ECGs to determine whether the participant meets these criteria:

- QTc >500 msec OR uncorrected QT >600 msec.
- Change from baseline of QTc >60 msec.

The Investigator should assess the participant for clinical consequences and potential causes (including concomitant medications and electrolytes). Appropriate follow-up should be determined by the Investigator according to their assessment and in some cases might include referral to an emergency facility or cardiology for further evaluation.

The investigator or qualified designee will determine if the participant may continue in the study according to the SoA, and if any change in participant management is needed.

The review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4. Other Criteria

- Prohibited Medications: If the participant initiates *and continues* a prohibited medication (see Section 6.8.2) owing to a *considerable* worsening of AtD, s/he must be withdrawn from the study. Considerable worsening of AtD is defined as an increase in EASI of ≥25% from Baseline at 2 consecutive visits between Wks 4 and 12, according to the clinical judgement of the investigator.
- Surgery: the participant requires surgery prior to Wk 12.
- Pregnancy: the participant should be withdrawn from the study.

7.1.5. Study Safety Stopping Criteria

Blinded AEs, SAEs, laboratory abnormalities, ECG abnormalities, and changes in vital signs occurring across all randomised participants will be regularly reviewed by the SRT to ensure appropriate participant safety.

The study may be paused or terminated if there are emergent safety findings that require further investigation or invalidate the positive benefit-risk assessment. Any changes to the study due to safety reasons will be promptly communicated to the appropriate Regulatory Authorities. The study may re-start only following approval of a substantial amendment by the regulatory agencies as well as the local ethics committees.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study 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 compliance reasons.
- Since participants will receive a single dose of study medication on Day 1, withdrawal following dosing will constitute declining to participate in study activities. Participants should be encouraged to remain in the study and complete the planned visits and assessments for the purposes of continued safety monitoring, if possible.
- The Investigator must determine the primary reason for early withdrawal. Withdrawal due to an AE (according to the definition of an adverse event) should be distinguished from withdrawal due to an insufficient efficacy response.
- In the event of an early withdrawal participants should be encouraged to complete at least the Early Withdrawal visit as soon as feasible. Participants should be encouraged to complete any/all remaining scheduled visits for the purposes of safety monitoring including the End of Study Visit (approximately 24 weeks after dosing) to mitigate safety risks associated with administration of a long-acting, novel immunosuppressive. The investigator should aim to follow up participants until all AEs and SAEs have resolved.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant may continue in the study.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Safety/Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

8.1.1. Eczema Area and Severity Index (EASI)

EASI [Hanifin, 2001] is an internationally used classification of atopic dermatitis severity and is recommended for use by Harmonising Outcome Measures for Eczema, an international group for standardizing clinical trial outcomes in atopic dermatitis.

EASI is an investigator-assessed measure that is used to assess the extent (area) and severity of atopic dermatitis. The range of the scale is 0-72, with a higher score indicating greater severity.

Please refer to the SRM for details on scoring the EASI.

8.1.2. Investigator Global Assessment (IGA)

Investigator's Global Assessment (IGA) for Atopic Dermatitis is a measure of overall disease severity at the time of assessment and is the established FDA regulatory endpoint. It is measured on the following scale:

0: Clear (No inflammatory signs of atopic dermatitis)

1: Almost Clear (Just perceptible erythema and just perceptible papulation/infiltration)

2: Mild Disease (Mild erythema and mild papulation/infiltration)

3: Moderate Disease (Moderate erythema and moderate papulation/infiltration)

4: Severe Disease (Severe erythema and severe papulation/infiltration with or without oozing/crusting).

Please refer to the SRM for details on scoring the IGA.

8.2. Patient Reported Outcomes (PROs)

Refer to Section 1.3 for the scheduling of PROs.

8.2.1. Peak Pruritis Numerical Rating Scale (PP-NRS)

Pruritus (itch) is a patient reported measure (in the past 24 hours) of itch intensity assessing worst itch using an 11-point scale (from 0 to 10), with 0 being no itch and 10 being the worst imaginable itch [Yosipovitch, 2019].

Participants complete the assessment once daily at approximately the same time each day, and are asked the following question in their local language: "On a scale of 0 to 10, with 0 being [redacted] and 10 being [redacted] how would you rate your itch at the worst moment during the previous 24 hours?"

8.2.2. Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item questionnaire [Finlay, 1994] that asks participants to evaluate the degree that their skin disease has affected their quality of life in the last week in the following 6 aspects:

- symptoms and feelings,
- daily activities,
- leisure,
- work or school activities,
- personal relationships and
- treatment related feelings.

Participants answer the 10 questions on a scale from 0 [redacted] to 3 [redacted]

The DLQI is calculated by summing the scores of the 10 questions, ranging from 0 to 30 with higher scores indicating more impaired quality of life. A score of 0 or 1 means that the disease has no effect at all.

Participants will be required to record their DLQI scores weekly up to Wk 4 and then bi-weekly for the remainder of the study (refer to Section 1.3, SoA).

CCI

[redacted]

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. The participant will be encouraged to contact the site at all times in case of any adverse event.

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (baseline only) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Temperature, pulse rate, and blood pressure are to be assessed.
- Blood pressure and pulse measurements are to be assessed in semi-supine position with a completely automated device. Manual techniques are only appropriate if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

  Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.

8.3.3. Electrocardiograms

- Triplicate or Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QTc intervals. Refer to Section 7.1.3 for QTc criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 24 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If clinically significant/any values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory tests, as defined in Section 8.3, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during study intervention period.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3.

The definitions of unsolicited and solicited adverse events can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of study intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will

review and then file it along with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until time period for reporting pregnancies should align with the time period for post-intervention contraception determined in Section 5.1.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. 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 participant who becomes pregnant during the study will be withdrawn from the study.

8.4.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3 and all deaths, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

CCI

[redacted]

8.6. Genetics and/or Pharmacogenomics

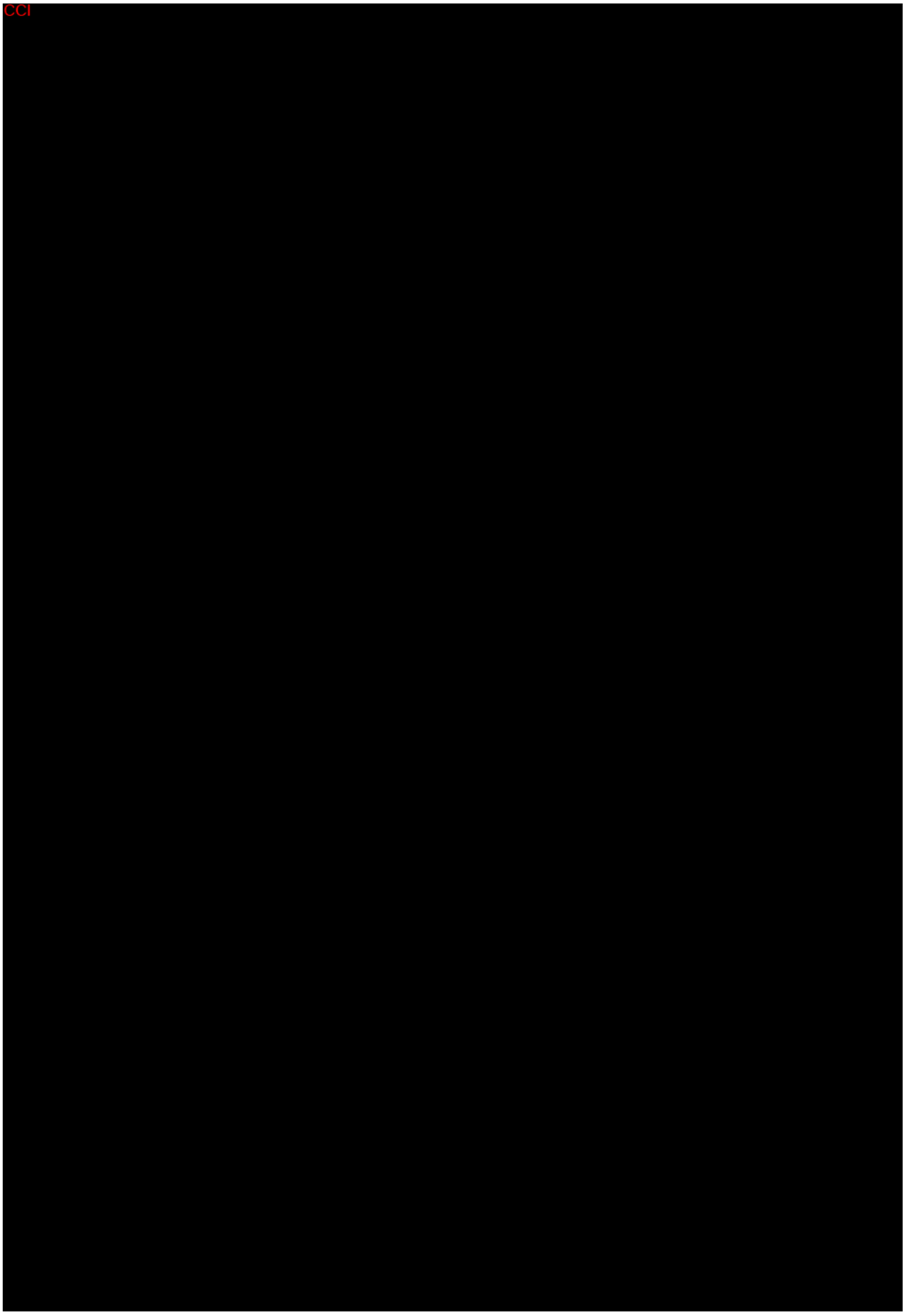
A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

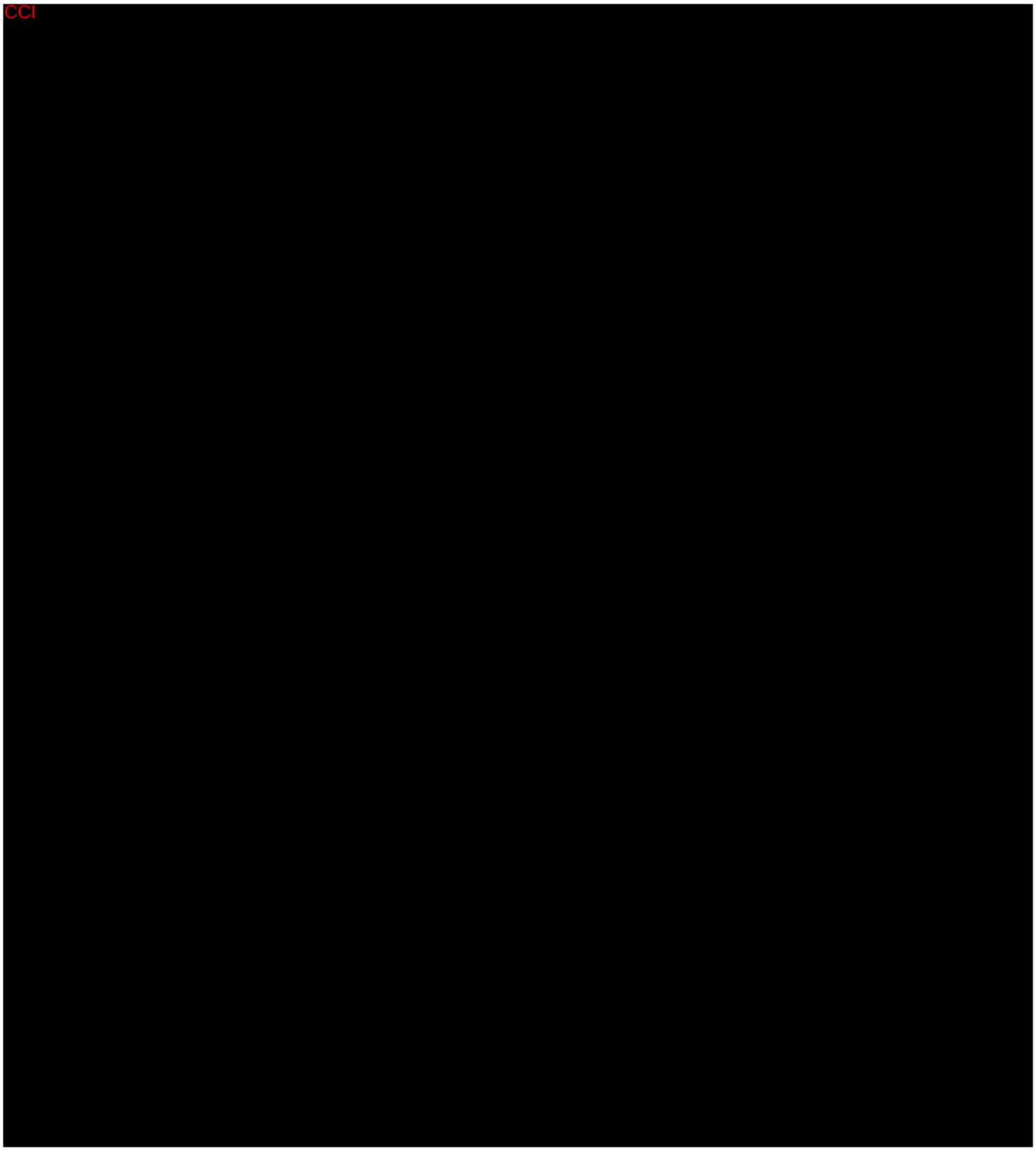
See Section 10.5. Genetics and Pharmacogenomics for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

CCI

[redacted]


CCI

CCI



8.8. Immunogenicity Assessments

Antibodies to GSK1070806 will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples are to be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to GSK1070806 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to GSK1070806 and/or further characterize the immunogenicity of GSK1070806.

The detection and characterization of antibodies to GSK1070806 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to study intervention will also be evaluated for GSK1070806 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to GSK1070806.

8.9. Health Economics

Health economic parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There are no formal hypotheses to be tested.

9.2. Sample Size Determination

Approximately 64 patients may need to be screened to obtain 48 randomized participants (approximately 30 and 18 participants in Groups 1 and 2, respectively).

Participants who have withdrawn from the study, may be replaced at the discretion of the sponsor.

The sample sizes for Groups 1 and 2 are selected to support preliminary assessment of the clinical effect, based on PCFB in the EASI for Groups 1 and 2.

Operating characteristics of some criteria of interest for the both groups of the study have been calculated and presented below.

Group 1:

Based on 30 participants (20 administered GSK1070806 and 10 administered placebo), the probability of different criteria of interest are given in the table below.

A Bayesian linear regression was used, assuming that the PCFB in the EASI follows a Normal distribution. The priors were as follows:

- Placebo arm: a robust meta-analytic predictive (MAP) prior was constructed based on placebo PCFB in the EASI reported in recent clinical trials in AtD. The resulting mixture prior has 28.5% weight on a Normal (-31.56, SD=5.67), 21.5% weight on a Normal (-31.21, SD=11.00) and 50% weight on a Normal (-30, SD = 50), with an effective sample size of 14 participants (expected local-information-ratio (ELIR) method (Neuenschwander, 2020)) assuming a between-participant SD = 50.
- GSK1070806 arm: a vague Normal prior was used, with mean = -30 and SD = 50, corresponding to an effective sample size (ELIR method) of 1 participant assuming a between-participant SD = 50.

Operating characteristics are provided below. A true PCFB in the EASI of -30% in the placebo arm was assumed, based on recent clinical trials in AtD. Various true PCFBs in the EASI for the GSK1070806 arm at Wk 12 were assumed, giving various true treatment differences. A between-participant SD of 50% was assumed for both GSK1070806 and Placebo arms.

Criteria	**True treatment difference**			
	-40%	**-25%**	**-15%**	**0%**
Observing a >75% posterior probability that the true difference from placebo is <-15%	82.6%	43.9%	18.4%	2.5%
Observing a >75% posterior probability that the true difference from placebo is <-7.5%	92.8%	66.6%	37.7%	7.8%
Observing a >97.5% posterior probability that the true difference from placebo is < 0%	68.8%	30.3%	10.9%	1.0%

Group 2:

There are no planned statistical analyses comparing GSK1070806 *versus* placebo. The analysis will be conducted on PCFB in the EASI in the GSK1070806 arm.

Based on 15 participants on GSK1070806, the operating characteristics are given below.

A vague Normal prior was used, with mean = 0 and SD = 1×10^6, corresponding to an effective sample size (ELIR method) of 0 participant assuming a between-participant SD=50.

Criteria	**True PCFB in the EASI in GSK1070806**			
	-70%	**-55%**	**-45%**	**-30%**
Observing a >50% posterior probability that the true PCFB in EASI is <-45%	97.4%	78.1%	50.0%	12.3%
Observing a >50% posterior probability that the true PCFB in EASI is <-37.5%	99.4%	91.2%	71.9%	28.1%
Observing a >50% posterior probability that the true PCFB in EASI is <-30%	99.9%	97.4%	87.7%	50.0%

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Screened	All participants who signed the ICF and are screened for eligibility.
Enrolled	All participants in the Screened analysis set who entered the study.
Randomized	All participants in the Enrolled analysis set who are randomly assigned to study intervention in the study.
Safety	All participants in the Randomized analysis set who received the study intervention. Participants will be analyzed according to the intervention they actually received.
PK	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable values will be considered as non-missing values). Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

The SAP will be finalized prior to unblinding of the study and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

9.4.1.1. Bayesian inference

The main statistical analyses will be carried out in the Bayesian framework. Weakly informative priors may be used. In that case, a sensitivity analysis using vague priors will also be carried out.

The following summaries of the posterior distribution will be reported: posterior median, 95% equal tailed credible interval, posterior probabilities of the true treatment effect being greater/lower than pre-specified thresholds.

9.4.1.2. Baseline definition

The baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

If baseline data is missing, no derivation will be performed, and baseline will be set to missing.

9.4.1.3. Statistical methods

The following statistical models will be used for the main analysis of the primary and secondary endpoints:

- Bayesian repeated measures model for longitudinal continuous endpoints.
- Bayesian logistic regression for binary endpoints at Wk 12.

When needed, the underlying assumptions of the models will be assessed visually.

Covariates such as baseline value may be added and will be stated in the SAP.

9.4.1.4. Site pooling

Data from all participating sites will be pooled prior to analysis. It is anticipated that participant accrual will be spread thinly across sites and summaries of data by site would unlikely be informative and will not, therefore, be provided.

9.4.2. Primary Endpoint(s)

The primary endpoint is the PCFB in the EASI at Wk 12 in Group 1. The population-level summary is the treatment difference (GSK1070806 – placebo) in PCFB in the EASI scores at Wk 12.

The analysis will be based on the Safety analysis set. Participants will be analysed according to the treatment they received.

A Bayesian repeated measures model will be used, including study treatment, visit, study treatment-by-visit interactions, baseline EASI value, baseline-by-visit interactions and subject-level repeated measures.

Priors defined in Section 9.2 will be used for the analyses. For the MAP prior, details of the included studies will be documented in the SAP. An inverse Wishart prior will be used for the within-subject unstructured covariance. Other options may be investigated to determine an appropriate covariance structure in case of issues.

A Bayesian repeated measures analysis will be conducted under the missing-at-random assumption.

Further details on any sensitivity estimators used to assess the primary objective will be provided in the SAP.

9.4.3. Secondary Endpoint(s)

9.4.3.1. Safety Endpoints

No formal statistical testing will be performed on safety data.

All safety evaluations will be based on the Safety analysis set and will be reported for group 1 and 2 together.

Clinical interpretation will be based upon review and displays of adverse events, laboratory values and vital signs. The principal consideration in this evaluation will be the

investigator-reported relationships of adverse events or the clinical important findings in laboratory tests to study treatment (refer to the SAP).

The immunogenicity of GSK1070806 will be based on the PK analysis set and characterized with summary statistics of incidence, i.e. the number of participants with anti-drug antibodies by treatment over time.

9.4.3.2. Efficacy Endpoints

The secondary endpoints in Group 1 are:

- CFB in the EASI at Wk 12. The population-level summary is the treatment difference (GSK1070806 – Placebo) in CFB in the EASI at Wk 12. A Bayesian repeated measures model will be used.
- EASI 50/75/90 defined as ≥ 50/75/90% reduction in the EASI from Baseline at Wk 12. The population-level summary is the treatment difference (GSK1070806 – Placebo) in proportion of participants achieving EASI 50/75/90% reduction from baseline at Wk 12. A Bayesian logistic regression analysis will be used.
- IGA score of 0 or 1 at Wk 12. The population-level summary is the treatment difference (GSK1070806 – Placebo) in proportion of participants achieving IGA score 0 or 1 at Wk 12. A Bayesian logistic regression analysis will be used.

The secondary endpoint in Group 2 is:

- PCFB in the EASI at Wk 12. The population-level summary is the mean PCFB in the EASI in GSK1070806 arm at Wk 12. A Bayesian repeated measures model will be used.

The analyses of the secondary endpoints will be based on the Safety analysis set. Details of the analyses for these endpoints will be documented in the SAP.

CCI

9.5. Interim Analysis

9.5.1. Routine pharmacovigilance

In line with routine pharmacovigilance, the internal GSK107086 SRT will review blinded safety data at appropriate intervals during the study. Data reviewed will include but not necessarily be limited to clinical laboratory parameters, vital signs and adverse events. The GSK107086 SRT will include members of the study team.

9.5.2. Planned Unblinded Interim Analyses

Interim analyses for Groups 1 and 2 may be carried out and will be conducted by a DRC, (see Section 10.1.5). The composition and conduct of the DRC are described in the DRC Charter.

All interim analyses will be based on unblinded data and outputs will be prepared by the sponsor study statistics and programming team and the clinical pharmacology modelling and simulation team (as required). The randomisation schedules and unblinded datasets will be stored on internal restricted drives. The GSK study team, with the exception of the statistics and programming and also Clinical Pharmacology and Modelling Simulation (CPMS) teams, will not have access to an unblinded copy of the randomisation schedule during the course of the trial.

Interim Analyses for Group 1:

Group 1 unblinded individual data and data aggregated by treatment group may be reviewed when approximatively 50% participants in Group 1 have completed Wk 12 (or have withdrawn prior to Wk 12). A potential outcome of the interim analysis might be to stop the study (Group 1 and Group 2).

Additional Group 1 unblinded individual data and data aggregated by treatment group may be reviewed during the conduct of the study. The purpose will be only for internal decisions and will have no impact on the study conduct. Recruitment will continue while the interim analyses are being conducted, except in the case of a safety concern.

Interim Analysis for Group 2:

Group 2 unblinded individual data and data aggregated by treatment group may be reviewed when approximatively 30 participants in Group 1 have been randomized, although it could be done earlier. The potential outcome of this interim analysis is to stop recruitment to Group 2. Additional reviews of Group 2 unblinded data by treatment group may be carried out during the conduct of the study. The purpose will be only for internal decisions and will have no impact on the study conduct. Recruitment will continue while the interim analysis is being conducted, except in the case of a safety concern.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB,, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable),), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK1070806 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have GSK1070806 approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Safety Review Team (SRT): Participant safety will be continuously monitored by an internal SRT, which includes safety signal detection at any time during the study. Blinded data will be reviewed. The SRT will include a subset of the 215253 study team and will operate to a charter.

Data Review Committee (DRC): The study will utilise a DRC to conduct the Interim Analyses described in Section 9.5. Full details of the decisions to be made, membership of the committee and how study integrity will be maintained will be documented in the DRC Charter. Details of the DRC Charter (and statistical analysis plan, SAP) will outline the decision-making criteria. The DRC membership will be comprised of a predefined subset of project team members and senior GSK stakeholders to ensure that persons with the appropriate expertise and knowledge conduct and interpret interim reviews of data. No one external to the DRC will see unblinded study data. No study personnel with direct contact with sites or site staff will be involved in the DRC. Further details of how the DRC will ensure data integrity and appropriate quality control of data prior to decision making are also included.

The DRC will also conduct any unplanned interim analyses that become necessary during the study. These analyses will be documented through an amendment of the DRC charter and, if necessary, a protocol amendment.

10.1.6. Dissemination of Clinical Study Data

- 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 all investigators who participated in the study with a summary of the study results and will inform the investigators what treatment their patients' received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF completion guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the Quality Tolerance Limits Report to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Pharmacology Study Report (CPSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the SRM.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) %Reticulocytes Absolute reticulocyte count	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Hematocrit			
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein and albumin.
		Corrected calcium	Alkaline phosphatase[2]	

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, nitrite, leukocyte esterase, by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)3
Other Screening Tests	• Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) • Alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antigen antibody and hepatitis C virus antibody) • QuantiFERON-TB Gold / QuantiFERON-TB Gold PLUS • COVID-19.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.2 and Section 10.6. All events of ALT ≥5 × upper limit of normal (ULN) or ALT ≥3 x ULN for 4 weeks and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Serum testing at the initial screening visit and at baseline (pre-dosing). Local urine testing at other timepoints.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. 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 study intervention.

Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant/participant's parent(s)/legally acting representative (LAR)(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants/ participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/ parental /LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by participant/participant's parent(s)/LAR(s) will be collected during interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit. • Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

Events Meeting the AE Definition
• 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 intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant'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 participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which 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.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. 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 persistent or significant disability/incapacity • 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 with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorised medicinal product
g. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF 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 thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- 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) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant 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 submitted documents. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE 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 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, then the site can report this information on a paper SAE form (see next section) or to the contacts for SAE reporting by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the contacts for SAE reporting. • 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 or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the Study Reference Manual.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

2. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulationc
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulationc
  • oral
  • injectable

• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Notes: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK1070806 or atopic dermatitis and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK1070806 and/or atopic dermatitis. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK1070806 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK1070806 (or study interventions of this class) or atopic dermatitis continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments.

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Liver chemistry stopping criteria and required follow-up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin1, 2</td><td>ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR2</td><td>ALT ≥3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic3</td><td>ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE2
• Perform liver chemistry event follow-up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within Baseline (see MONITORING below)
• Do not restart/rechallenge participant with study intervention unless allowed per protocol and GSK Medical Governance approval is granted (see below).
• If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study intervention and continue participant in the study for any protocol specified follow-up assessments
<u>MONITORING:</u>
<u>For bilirubin or INR criteria:</u></td><td>• Viral hepatitis serology4
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, with timing to be guided by clinical pharmacokinetics representative on a case by case basis, after last dose5
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin ≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within Baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within 24-72 hours • Monitor participant weekly until liver chemistries resolve, stabilize or return to within Baseline	remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF pages.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A Immunoglobulin M (IgM) antibody; HbsAg and HBcAb; Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to pk blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.7. Appendix 7: Abbreviations and Trademarks

Abbreviations

µg/mL	Micrograms per millilitre
µg*day/mL	Micrograms day per millilitre
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AtD	Atopic dermatitis
AUC	Area Under the Curve
AUC(0-t)	Area under the plasma concentration time curve from zero to time t
AUC(0-∞)	Area under the plasma concentration time curve from zero to infinity
AUC(0-tau)	Area under the plasma concentration time curve overthe dosing interval
BCG	Bacillus Calmette-Guerin
BFI	Brief Fatigue Inventory (Item -3)
BL	Baseline
BMI	Body Mass Index
BN	Biologic Näive
BUN	Blood urea nitrogen
CFB	Change from baseline
CFR	Code of Federal Regulation
CI	Confidence Interval
CIN	Cervical intraepithelial neoplasia
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
Cmax	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus strain 19
CRF	Case Report Form
CPSR	Clinical pharmacology study report
CPMS	Clinical Pharmacology Modelling and Simulation
CV	Cardiovascular
DLQI	Dermatology Life Quality Index
DNA	De-oxyribonucleic acid
DRC	Data review committee
Dupi-IR	Dupilumab-Inadequate Responder
EASI	Eczema Activity and Severity Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELIR	Expected local-information-ratio

ePRO	Electronic Patient Reported Outcome
eDiary	Electronic diary
EoS	End of Study
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Agency
FPFV	First Participant First Visit
FTIH	First time in human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
GSVA	
h	Hours
HBsAg	Hepatitis B Surface Antigen positive
HBcAb	Hepatitis B core antibody
hCG	Human chorionic gonadotropin
HepC	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IGA	Investigator Global Assessment
IL-18	Interleukin-18
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive Web Recognition System
JAKi(s)	Janus Activated Kinase inhibitor(s)
Kdeg	Degradation rate
kg	Kilogram
kg/m^2	Kilograms per square meter
LAR	Legally Acting Representative
LLQ	Lower Limit of Quantification
LPLV	Last Participant Last Visit
mAb	Monoclonal Antibody
MABEL	Minimum Anticipated Biological Effect Level
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume

MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mg/day	Milligrams per day
mg/kg	Milligrams per kilogram
mg/kg/week	Milligrams per kilogram per week
MIA	Monosodium iodoacetate
min	Minutes
mL	Millilitre
mm	Millimetre
MM	Medical Monitor
MSDS	Material Safety Data Sheet
msec	Millisecond
NOAEL	No Observed Adverse Effect Level
NRS	Numerical Rating Scale
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDE4	Phosphodiesterase 4
pH	Potential Hydrogen
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PGx	Pharmacogenetics
PPE	Personal protective equipment
PP-NRS	Peak Pruritis – Numerical Rating Scale
PR	PR cardiac wave interval
PROMIS	Patient-Reported Outcomes Measurement Information System -Sleep Disturbance
PRO	Patient reported outcome
PTS	Platform Technology and Science
PUVA	Psoralen + ultraviolet A
qIA	Quantitative Immunoassay
QRS	QRS cardiac wave interval
QTc	Corrected QT
QTcB	Corrected QT using Bazett's formula
QTcF	Corrected QT using Fridericia's formula
QTL	Quality Tolerance Limit
RBC	Red Blood cell count
RIBA	Radio immunoblot assay
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome– Coronavirus-2
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SMG	Safety and Medical Governance
SoA	Schedule of Activities

SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reactions
T2DM	Type 2 Diabetes Mellitus
TB	*Mycobacterium tuberculosis*
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
TE	Target engagement
T_H	T helper (cell)
Tmax	Time to Cmax
t½	Apparent terminal phase half-life
ULN	Upper limit of normal
UVA1	Ultraviolet A1
UVB	Ultraviolet B
Vss	Volume of distribution
WBC	Whole Blood Count
Wk(s)	Week(s)
WONCBP	Women Of Non Childbearing Potential
WOCBP	Women Of Childbearing Potential
w/v	Weight by volume

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
RAMOS NG

Trademarks not owned by the GlaxoSmithKline group of companies
Atopiclair
Cerave
Dupixent
Epicerum
MedDRA
MimyX
PaxGene
QuantiFERON

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Summary of Previous Amendments

Amendment 1 25-Feb-2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 1:

To state that participants who have contracted COVID-19 during the study do not necessarily need to be immediately excluded.

In addition to the changes tabulated below, minor edits/corrections have also been made throughout to provide refinement and clarification.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1: Risk Assessment (Procedural Risk) - Risk associated with attending an investigative site during the Coronavirus strain 19 (COVID-19) Pandemic	Three changes: **Participant monitoring:** COVID test at Wk 12 (was removed to ensure consistency with the intent described in SoA). **COVID-19 Contingency Plan:** **ORIGINAL:** Any participant presenting with COVID-19-related symptoms and/or having a positive SARS-CoV-2 test will be excluded from (further) participation in the trial and will receive follow-up medical attention as per local procedure. **REVISED:** Any participant presenting with COVID-19-	(1) As per the Schedule of Activities: Participants need only have a mandated COVID test at Screening, prior to dosing (from Day -4 to Day 1), and at the End of Study Visit at Week 24 (or at early withdrawal). **(2)** A confirmed positive SARS-CoV-2 test is *also* required (as evidence of COVID-19 infection) *In addition* to initially presenting with COVID-19-related symptoms. **(3)** Given there have been changes to circumstance and management options since start of the COVID pandemic, participants who have presented with COVID-19 and have a

Section # and Name	Description of Change	Brief Rationale
	related symptoms **(2)** *and* having a positive SARS-CoV-2 test **(3)** may continue in the study (or may be temporarily suspended during recovery) if the investigator judges this to be possible (e.g. if the participant is able to adhere to local management guidance). If a participant needs to be excluded from (further) participation in the trial s/he will receive follow-up medical attention as per local procedure.	SARS-CoV-2 positive test, do not necessarily need to be immediately excluded from the study. The Investigator will judge whether the participant will be able to continue or not. There is a return to the emphasis of continued monitoring within-study. Note that Study 215253 administers only a single dose of this long-acting, novel immunosuppressive and so it is important to ensure continued safety monitoring (see Section 7.2).
Section 6.3.1. Controlled Early Access to Unblinded PK and PKPD Data	ADDED New Subsection 6.3.1. Controlled Early Access to Unblinded PK and PKPD Data Designated independent representative(s) may be unblinded for performing population PK and PKPD dataset preparation and draft PK and PKPD model development at one or more time points throughout the trial using scrambled (random reassignment of subject identification numbers) PK and PKPD unblinded datasets.	To allow controlled early access to unblinded PK and PKPD data
Section 9.4. Statistical Analyses	The SAP will be finalized prior to unblinding of the study ~~prior to first participant first visit (FPFV)~~	The SAP will be finalized before any unblinding of the study (this change neither compromises study conduct nor data integrity).

Section # and Name	Description of Change	Brief Rationale
Section 9.5.2. Planned Unblinded Interim Analysis	Added: Group 1 unblinded individual data and data aggregated by treatment group may be reviewed when approximatively 50% participants in Group 1 have been completed Wk 12 (or have withdrawn prior to Wk 12). Added: Group 2 unblinded individual data and data aggregated by treatment group…	To also enable unblinded individual data to be reviewed at the interim analysis. Study integrity will be maintained by using dummy participant IDs.

11. REFERENCES

Adamson AS. The Economics Burden of Atopic Dermatitis. Adv Exp Med Biol. 2017;1027:79-92.

Antonopoulos C, Marie Cumberbatch, John B. Mee, Rebecca J. Dearman, Xiao-Qing Wei, Foo Y. Liew, Ian Kimber and Richard W. Groves. IL-18 is a key proximal mediator of contact hypersensitivity and allergen-induced Langerhans cell migration in murine epidermis. Journal of Leucocyte Biology. 2008; 83:361-367.

Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy. 2018 Jun;73(6):1284-1293.

Beck LA, Thac¸i D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371(2):130-139.

Bissonnette R. Pavel A.B. Diaz A. Werth J.L. Zang C. Vranic I. et al. Crisaborole and atopic dermatitis skin biomarkers: an intrapatient randomized trial. J Allergy Clin Immunol. 2019 144: 1274-1289.

Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287-2303.

Brunner P.M. Khattri S. Garcet S. Finney R. Oliva M. Dutt R. et al. A mild topical steroid leads to progressive anti-inflammatory effects in the skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2016; 138: 169-178.

Brunner P.M. Pavel A.B. Khattri S. Leonard A. Malik K. Rose S. et al. Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab. J Allergy Clin Immunol. 2019; 143: 142-154.

Chen JL, Niu XL, Gao YL, Ma L, Gao XH, Chen HD and Qi RQ. IL-18 knockout alleviates atopic dermatitis-like skin lesions induced by MC903 in a mouse model. Int J Mol Med, 2020, 46: 880-888.

Cork MJ, Thac¸i D, Eichenfield L, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label and subsequent phase III open-label extension trial. Br J Dermatol. 2020;182(1):85-96.

de Bruin-Weller, M, Thac¸i D, Smith CH, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE´). Br J Dermatol. 2018;178(5):1083-1101.

Dupilumab: Summary of Product Characteristics. European Medicines Agency. Published 21 Jan 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent.

Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL. Guidelines of care for the management of atopic dermatitis. J Am Acad Dermatol. 2014 Feb; 70(2): 338–351.

Finlay AY and Khan GK. Dermatology Life Quality Index (DLQI) -a simple practical measure for routine clinical use. Clin Exp Dermatol 1994 May;19(3):210-6.

Fuxench ZCC, Block JK, Boguniewicz M, Boyle J, Fonacier L, Gelfand JM et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol Actions. 2019 Mar;139(3):583-590.

GlaxoSmithKline Document Number WM2009/00047/07: Investigator Brochure GSK1070806: Effective date: JUL 2021.

Glickman JW, Dubin C, Han J, Dahabreh D, Garcet S, Krueger JG et al. 2020. Comparing cutaneous molecular improvement with different treatments in atopic dermatitis patients. JACI April 1285 – 1288.

Guttman-Yassky E, Thac D, Pangan AL, Chih-ho Hong H, Papp KA, Reich K. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol 2020;145:877-84.

Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980; 60: 44-47.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol 2001;10:11-8.

He H, Bissonnette R, Wu J, Diaz A, Saint-Cyr Proulx E, Maari C, Jack C, et al. Tape strips detect distinct immune and barrier profiles in atopic dermatitis and psoriasis J Allergy Clin Immunol. 2021 Jan;147(1):199-212.

Inoue Y, Aihara M, Kirino M, , et al.. Interleukin-18 is elevated in the horny layer in patients with atopic dermatitis and is associated with Staphylococcus aureus colonization. Br J Dermatol. 2011;164(3):560-567.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

Kawase Y, Hoshino T, Yokota K, Kuzuhara, A,Kirii Y, Nishiwaki E et al. Exacerbated and prolonged allergic and non-allergic inflammatory cutaneous reaction in mice with targeted interleukin-18 expression in the skin; J Invest Dermatol, 2003 Sep;121(3):502-9.

Khattri S. Brunner P.M. Garcet S. Finney R. Cohen S.R. Oliva M. et al. Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. Exp Dermatol. 2017; 26: 28-35.

Khattri S. Shemer A. Rozenblit M. Dhingra N. Czarnowicki T. Finney R. et al. Cyclosporine in patients with atopic dermatitis modulates activated inflammatory pathways and reverses epidermal pathology. J Allergy Clin Immunol. 2014; 133: 1626-1634.

Konishi H, Tsutsui H, Murakami T, Yumikura-Futatsugi S, Yamanaka K-i, Tanaka M et al. IL-18 contributes to the spontaneous development of atopic dermatitis-like inflammatory skin lesion independently of IgE/stat6 under specific pathogen-free conditions. PNAS, 2002. 99 (17) 11340-11345.

Lee JH, Cho DH, Park HJ. IL-18 and Cutaneous Inflammatory Diseases; Int J Mol Sci. 2015 Dec 9;16(12):29357-69.

Lei DK, Yousaf M, Janmohamed SR, Vakharia PP, Chopra R, Sacotte R et al. Validation of Patient-Reported Outcomes Information System Sleep Disturbance and Sleep-Related Impairment in adults with atopic dermatitis. Br J Dermatol. 2020 Nov;183(5):875-882.

McKie EA, Reid JL, Mistry PC, DeWall SL, Abberley L, Ambery PD, Gil-Extremera B. 2016 A Study to Investigate the Efficacy and Safety of an Anti-Interleukin-18 Monoclonal Antibody in the Treatment of Type 2 Diabetes Mellitus. PLOS One.

Mendoza TR, Wang SX, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, Huber SL. The rapid assessment of fatigue severity in cancer patients. Use of the brief fatigue inventory. Cancer 1999; 85:1186–96.

Mistry P, Reid J, Pouliquen I et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single-dose anti-interleukin-18 mAb GSK1070806 in healthy and obese subjects. Int J Clin Pharmacol Ther . 2014 Oct;52(10):867-79.

Montan 2018. General Population Norms for the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale - ScienceDirect.

Neuenschwander B, Weber S, Schmidli H, O'Hagan A. Predictively consistent prior effective sample sizes. Biometrics. 2020 Jun; 76(2):578-587.

Pavel AB, Song T, Kim HJ, Del Duca E, Krueger JG, Dubin C. et al. Oral Janus kinase/SYK inhibition (ASN002) suppresses inflammation and improves epidermal barrier markers in patients with atopic dermatitis. J Allergy Clin Immunol. 2019; 144: 1011-1024.

Pavel AB, Zhou L, Diaz A, Ungar B, Dan J, He H et al. The proteomic skin profile of moderate-to-severe atopic dermatitis patients shows an inflammatory signature, J Am Acad Dermatol. 2020 Mar; 82(3):690-699.

Plitz T, Saint-Mézard P, Satho M, Herren S, Waltzinger C, de Carvalho Bittencourt M, Kosco-Vilbois MH and Chvatchko Y; IL-18 Binding Protein Protects Against Contact Hypersensitivity; J Immunol August 1, 2003, 171 (3) 1164-1171;

Ricardo-Gonzalez RR, Van Dyken SJ, Schneider C, Lee J, Nussbaum JC, Liang H-E et al. Tissue signals imprint ILC2 identity with anticipatory function. Nat Immunol. 2018 October; 19(10): 1093–1099.

Röse L, Schneider C, Stock C, Zollner TM and Döcke W-D. (2012), Extended DNFB-induced contact hypersensitivity models display characteristics of chronic inflammatory dermatoses. Experimental Dermatology, 21: 25-31.

Sacottte R and Silverberg JI. Epidemiology of adult atopic dermatitis: Clinics in Dermatology. 2018; 36: 595-605.

Saikiran KS, Hagglof T, Karlsson, MCI. IL-18 in inflammatory and autoimmune disease; Cell. Mol. Life Sci. (2013) 70:4795–4808.

Silverberg JI, Garg NI, Paller AS, et al. Sleep disturbances in adults with eczema are associated with impaired overall health: A US population-based study: J Invest Dermatol 2015; 135: 56-66.

Silverberg JI, Simpson EL, Ardeleanu M. Dupilumab provides important clinical benefits to patients with atopic dermatitis who do not achieve clear or almost clear skin according to the Investigator's Global Assessment: a pooled analysis of data from two phase III trials. Br J Dermatol. 2019;181:80-87.

Simpson EL, Bieber T, Eckert L et al Patient burden of moderate to severe atopic dermatitis (AD): insights from a phase 2b clinical trial of dupilumab in adults. J Am Acad Dermatol 2016a; 74:491–8.

Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016b; 375(24): 2335-2348.

Simpson EL, Gadkari A, Worm M, Soong W, Blauvelt A, Eckert L et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): a phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). J AmAcadDermatol. 2016c;75(3):506-515.

Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol. 2020a;156(1):44-56.

Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet. 2020(b) Jul 25;396(10246):255-266.

Tennant KF. The FACIT Fatigue Scale (Version 4) 2019. Hartford Institute for Geriatric Nursing (hign.org). Issue #30 of General Assessment Series.

Terada M, Tsutsui H, Imai Y, Yasuda K, Mizutani H, Yamanishi K, et al. Contribution of IL-18 to atopic-dermatitis-like skin inflammation induced by Staphylococcus aureus product in mice, PNAS, Jun 2006, 103 (23) 8816-8821.

Thaci D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet. 2015; 387(10013):40-52.

Thijs JL, Strickland I, Bruijnzeel-Koomen CAFM, Nierkens S, Giovannone B, Csomor E, et al. Moving toward endotypes in atopic dermatitis: Identification of patient clusters based on serum biomarker analysis J Allergy Clin Immunol 2017;140:730-7.

Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016; 387(10023):1109-1122.

Wlodek E, Kirkpatrick RB, Andrews S, Noble R, Schroyer R, Scott R. A pilot study evaluating GSK1070806 inhibition of interleukin-18 in renal transplant delayed graft function. PLOS One. March 8, 2021.

Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbé A, Nelson L. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019 Oct; 181(4): 761–769.

Signature Page for 215253 TMF-14679521 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 06-Jun-2022 10:36:19 GMT+0000

Signature Page for TMF-14679521 v1.0