CLINICAL STUDY PROTOCOL

Primary Study Intervention	GSK1070806
Other Study Intervention	Not Applicable
Study Identifier	219538
EU CT Number	2023-505414-15-00
Approval Date	07 Jun 2024
Title	A Phase 2b, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Dose Finding study to evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of GSK1070806 SC injection in Adult Participants with Moderate to Severe Atopic Dermatitis
Compound Number/Name	GSK1070806
Brief Title	A dose finding study to investigate the safety and effectiveness of GSK1070806 in adult participants with moderate to severe atopic dermatitis
Sponsor	GSK Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Deepak Assudani Sr. Director Clinical Lead Clinical Research (Immunology)

Medical monitor name and contact can be found in local study contact information document

Based on TMF-14732712 Protocol v3.0.

Protocol Amendment 1 Investigator Agreement

- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of and will comply with GCP and all applicable regulatory requirements.**
- **That I will comply with the terms of the clinical study site agreement.**
- **To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.**
- **To cooperate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.**

Study identifier	219538
EU CT number	2023-505414-15-00
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Investigator name	
Signature	
Date of signature (DD Month YYYY)	

Protocol Amendment Summary Of Changes Table

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	07 Jun 2024
Amendment 1 EU-1	05 February 2024
Amendment 1 KOR-1	05 January 2024
Original Protocol	03 August 2023

Type of Protocol Amendment	**Numbering**	**Type of changes**
Global	Amendment 1	Changes specific to all countries added to Original protocol (new change for Global)
EU-specific	Amendment 1 EU-1	Change specific to EU region added to Amendment 1 EU-1 (no new change for Global)
Country-specific	Amendment 1 KOR-1	Change specific to South Korea added to Amendment 1 KOR-1 (no new change for Global)

Amendment 1 (07 Jun 2024)

Overall rationale for the current Amendment:

This version harmonizes the changes made previously in EU and South Korea-specific Amendments into a single global protocol amendment 1, thereby realigning all the countries participating in the 219538 trial to a single global protocol. In addition, this protocol amendment updates the definition of biologic experience, refines the estimands, and adaptation to latest internal protocol template, minor clarifications, edits, and formatting changes are made throughout the protocol.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 1.1 Synopsis	Updated the section as per instructions in the latest template.	To harmonize the protocol with the latest protocol template.
Section 1.3 Schedule of Activities (Table 1)	Added clarification on eDiary requirements during screening activities.	To provide clarification on dispensation, training, and completion of eDiary.
Section 2.3.1 Risk assessment	Updated the immunogenicity data from completed clinical studies.	To provide latest immunogenicity information.
Section 2.3.1 Risk assessment; Section 5.2.3 Prior/Concurrent Clinical Study Experience	Added the exclusion criterion, "History of an allergic reaction or significant sensitivity to any constituents of the study drug (including excipients)"	As per EU CTR request, added this exclusion criterion for clarity.
Section 2.3.1 Risk assessment; Section 7.1 Discontinuation of study intervention	Included the terms 'exclusively', 'preferably' in the sentence referring to Withdrawal criteria related to serious or severe infection AEs	As per EU-CTR, for better clarity regarding one of the 'Withdrawal Criteria' related to serious or severe infection AEs
Section 3.1 Objectives and Endpoints Table 2	Updated the secondary endpoint of IGA. Updated exploratory endpoints.	To provide additional clarification and details relevant to the description of endpoints. Aligns with the accepted definition of IGA0/1 responders
Section 3.2 Estimands	Changed the handling strategy for use of rescue therapy in the estimands from hypothetical to composite.	To align the handling strategies for use of rescue therapy across all endpoints and simplify overall estimands framework.
Section 4.1 Overall design Section 4.2.1.1 Rationale for Study Populations Section 5.1 Inclusion criteria	Deleted "cost or loss of access" as one of criterion for stopping the biologic treatment.	To clarify that participants who have stopped biologic treatment due to cost or loss of access are not eligible to be enrolled in the study enabling enrolment to focus on biologic experienced participants who have failed due to an inadequate response or safety.
Section 5.2.2 Prior/Concomitant Therapy	Updated the list of prior therapy to include name and half-life of all the listed therapies.	To provide additional clarification and details to aid enrolment of biologic experienced participants.

Section # and title	Description of change	Brief rationale
Section 5.2.4 Diagnostic Assessments	Modified the sentence, “Participants with Gilbert’s syndrome can be included with total bilirubin >1.5xULN as long as direct bilirubin is ≤1.5xULN”	As per EU CTR, to clarify that the participants with Gilbert’s syndrome can be included in the study.
Section 6.1 Study interventions administered	Updated the table as per latest template.	To harmonize with the latest protocol template.
Section 6.4 Blinding	Provided information on blinding and reporting.	To provide clarity on blinding strategy to be followed after primary data reporting.
Section 6.9 Prior and concomitant therapy	Update the terminology from “enrollment” to “screening”.	To provide clarification that concomitant therapies are recorded from Day -28 i.e., screening.
Section 6.9.2 Prohibited Medications	Revised the section to provide clarification for the instructions on prohibited medications and specifically which medication are only prohibited to Week 16 and which are prohibited to Week 28.	Presentation updated for completeness of information and clarity.
Section 7.1 Discontinuation of study intervention	Added the discontinuation criteria of ‘withdrawal of informed consent’, and ‘lack of efficacy (as assessed by Investigator)	As per EU CTR, to ensure consistency across the document about the discontinuation criteria.
Section 7.1.1 Liver event stopping criteria	Updated the section to align with latest protocol template.	To harmonize the protocol with the latest protocol template.
Section 8.2.1.4 Scoring Atopic Dermatitis (SCORAD)	Updated the upper limit of SCORAD score from “100%” to “102%”.	To correct the upper limit as per feedback received.
Section 8.3.1 Physical examination	Updated the section to provide clarity and specificity regarding what should be assessed as part of a Full and Brief Physical Examination.	To align the presentation between protocol and CRF.
Section 8.3.2 Vital signs	Deleted the word ‘oral’ in relation to the assessment of temperature.	Updated for clarity around temperature assessment to give site flexibility.
Section 8.3.3 Electrocardiogram	Deleted “lung function testing”.	To clarify that lung function testing is not required for this study.

Section # and title	Description of change	Brief rationale
CCI [redacted]		
Section 9.3.1 General Considerations Section 9.3.2 Primary endpoint analysis Section 9.3.3 Secondary endpoint(s)/estimand(s) analyses	Updated the section to describe how the composite handling strategy for use of rescue therapy will be implemented.	To align with the changes made to the estimands in Section 3.2.
Section 10.1.4 Recruitment strategy	Additional information provided on recruitment strategy used during the study.	To provide further update on the recruitment strategy.
Section 10.7 Appendix 7 Country-specific requirements	Updated the section to include all country-specific requirements in a single appendix.	To comply with the local regulations of participating countries.
Global	Information added from latest protocol template.	To harmonize the protocol with the latest protocol template.
Global	Correction of grammar, formatting, or spelling	To correct minor errors

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AAD	American Academy of Dermatology
ACQ	Asthma control questionnaire
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AtD	Atopic dermatitis
AUC	Area under the ROC Curve
BFI	Brief Fatigue Inventory
BL	Baseline
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CFB	Change from baseline
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
D-E-R	Dose-Exposure-Response
DGF	Delayed Graft Function
DHT	Digital Health Technology
DLQI	Dermatology Life Quality Index
CCI	[redacted]
Dupi-IR	Dupilumab-Inadequate Responder
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
EoS	End-of-study

Abbreviation	Definition
ePRO	Electronic Patient Reported Outcomes
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
FDA	Food and Drug Administration, United States of America
FSFV	First subject first visit
FSH	Follicle stimulating hormone
FTiH	First-time in human
GCP	Good clinical practices
GI	Gastrointestinal
GSK	GlaxoSmithKline
HADS	Hospital Anxiety and Depression Scale
HBcAb	Hepatitis B core antibody
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICE	Intercurrent events
ICF	Informed consent form
ICH	International Council on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICSR	Individual case safety reports
IDRC	Internal data review committee
IEC	Independent ethics committee
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IL	Interleukin
IL-4Rα	Interleukin-4 receptor α
IMDH	Inosine-5'-monophosphate dehydrogenase Inhibitors

Abbreviation	Definition
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional review board
ISR	Injection site reaction
IV	Intravenous
IWRS	Interactive web response system
JAKi	Janus Activation Kinase inhibitors
KI	Kinase Inhibitors
KLH	Keyhole limpet hemocyanin
LAR	Legally acceptable representative
LSLV	Last Subject Last Visit
LTE	long-term extension
mAb	monoclonal antibody
MACE	Major adverse cardiovascular events
MAR	Missing at random
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MSDS	Material Safety Data Sheet
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	Non-investigational medicinal product
NOAEL	no-observed-adverse-effect level
NQ	Non-quantifiable
PCFB	Percent change from baseline
PCR	polymerase chain reaction
PD	Pharmacodynamic
PDE4	Phosphodiesterase-4
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

Abbreviation	Definition
CCI	
PI	Personal information
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PP	Per protocol
PP-NRS	Peak pruritus numerical rating scale
PRO	Patient reported outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
CCI	
QoL	Quality of life
QRS	Quartz Rate Sensor
QTc	Corrected QT interval
QTcF	QT interval according to Fridericia's formula
QTL	Quality tolerance limit
RAMOS NG	Registration and Medication Ordering System Next Generation
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCORAD	Scoring Atopic Dermatitis
SD	Standard deviation
SoA	Schedule of activities
SOC	System organ class
SP-NRS	Skin pain numerical rating scale
SRT	Safety Review Team
T2DM	Type 2 diabetes mellitus
TB	Tuberculosis
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TE	Target engagement
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
TMDD	Target-mediated drug disposition
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	United States of America
VAS	Visual analogic scale
WBC	White blood cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential
WPAI-AD	Work Productivity and Activity Impairment Questionnaire-Atopic Dermatitis

Term	Definition
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In a double-blind study, the participant, the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
eDiary	Electronically registered patient data and automated data entries on, for example, a handheld mobile device, tablet or computer.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.

Term	Definition
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal product	An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
Legally acceptable representative	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or LAR are used in some settings.
NIMP	A NIMP is a medicinal product that is not classified as an IMP in a study, but may be taken by participants during the study, e.g., concomitant or rescue/escape medication used for preventive, diagnostic, or therapeutic reasons or medication given to ensure that adequate medical care is provided for the participant during a study.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.

Term	Definition
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
CCI [redacted]	
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than 1 primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study	Study with objectives not linked to the data of another study.

Term	Definition
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: "Study intervention" and "study treatment" are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2b, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Dose Finding study to evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of GSK1070806 SC injection in Adult Participants with Moderate to Severe Atopic Dermatitis.

Brief Title:

A dose finding study to investigate the safety and effectiveness of GSK1070806 in adult participants with moderate to severe atopic dermatitis.

Rationale: Refer to Section 2.1.

Atopic Dermatitis

AtD is a chronic inflammatory skin disease characterized by eczematous lesions and intense pruritus, and is associated with skin barrier dysfunction and immune dysregulation. Intense pruritus results in sleep deprivation, signs of anxiety and depression, impaired QoL and reduced productivity.

AtD is considered to be a heterogeneous disease with primary T-helper cell T_H2/T_H22-skewing and variable T_H1/T_H17 contribution. Changes in the transcriptional profile of AtD have been observed with a number of experimental / approved therapies that have also shown clinical efficacy including cyclosporine, TCS, JAKi, phosphodiesterase 4 inhibitor, dupilumab, ustekinumab, and fezakinumab. The AtD skin proteome shows an inflammatory and vascular-endothelial signature (even in non-lesional skin), emphasizing the need for early treatment.

Treatment(s) and Unmet Medical Need

Owing to involvement of multiple cytokines in AtD, broad acting therapeutics and specific antagonists have been or are being developed; these include JAKi such as Cibinqo (abrocitinib), Rinvoq (upadacitinib) and monoclonal antibodies targeting IL-13 (Adtralza [tralokinumab] and Ebglyss [lebrikizumab]) and the IL-4Rα (Dupixent [dupilumab]), OX40 and IL-31. However, the currently approved advanced targeted therapies focus on modulating the Th2 pathway (anti-IL4Rα, anti-IL-13 and JAKi). Despite multiple treatment options, many patients remain in need of more effective, safer, and more convenient therapies.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To evaluate the efficacy of GSK1070806 CCI versus placebo in adults with moderate to severe AtD.	PCFB in the EASI to Week 16.
Secondary	
To evaluate the efficacy of GSK1070806 across the dose range versus placebo by characterizing the longitudinal dose-response relationship in adults with moderate to severe AtD.	PCFB in the EASI at each time point.
To further evaluate the impact of GSK1070806 CCI and across the dose range versus placebo in adults with moderate to severe AtD.	• Achieving EASI Reduction of ≥75% from Baseline at Week 16 • Achieving IGA score of 0 or 1 and a reduction from baseline ≥2 points at Week 16 • CFB in PP-NRS at Week 16 • Achieving PP-NRS Reduction of ≥4 points from Baseline at Week 16
To further evaluate the efficacy of GSK1070806 CCI and across the dose range versus placebo in adults with moderate to severe AtD.	Achieving EASI Reduction of ≥50%/90%/100% from Baseline at Week 16. Achieving SCORAD Reduction of ≥50%/75% from Baseline at Week 16. CFB to Week 16 for the following measures: • BSA • SCORAD
To assess the impact of GSK1070806 CCI and across the dose range versus placebo on Health Related-Quality of Life (HR-QoL), depression and anxiety, fatigue, sleep, WPAI and pain as measured by a range of PROs in adults with moderate to severe AtD.	CFB to Week 16 for the following PRO measures: • SP-NRS • PROMIS-Sleep disturbance 8b • FACIT-Fatigue • BFI-item 3 • POEM • DLQI • HADS • WPAI-AD
To assess the safety of GSK1070806 CCI and across the dose range in adults with moderate to severe AtD.	• Occurrence of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI) • Change from baseline in key laboratory parameters. • Occurrence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 hematological/clinical chemistry abnormalities.

Refer to Section 3 for the full list of objectives, endpoints, and estimands.

Overall Design: This is a Phase 2b, randomized, double-blind, parallel group, placebo controlled, dose finding study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics (target engagement) of GSK1070806 in biologic naive and biologic experienced adults with moderate to severe AtD.

Eligible adult participants (≥18 years of age) with moderate-to-severe AtD for at least 1 year, as defined by the AAD Consensus Criteria, with an EASI Score of ≥16, an IGA score of ≥3 and a BSA of ≥10% will be enrolled.

The study will enroll biologic naive and biologic experienced participants who will be randomized in a 2:1:1:1:2 ratio to receive either placebo CCI SC (n=50), GSK1070806 CCI SC (n=25), CCI SC (n=25), CCI SC (n=25) or CCI SC (n=50). Please note that all participants will receive blinded study treatment (GSK1070806 or placebo) at baseline and CCI to maintain the blind, therefore, participants randomised to CCI treatment arm will receive blinded placebo at CCI

Refer to Section 4.1.

Number of Participants: Approximately 50 participants per arm in the placebo and GSK1070806 CCI arms are aimed to be recruited. The sample size for the intermediate dose regimens (n=25) is supported by a pharmacometric simulation re-estimation analysis using an integrated D-E-R model. Therefore, approximately 175 participants in total are aimed to be recruited.

Refer to Section 9.5.

Data Monitoring/Other Committee: The study includes an internal Data Review Committee (iDRC). Refer to Section 10.1.6.

1.2. Schema

Figure 1 Study design overview

1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities

Screening

Procedure	Screening (Day -28 to Day -1)	Notes Please also refer to Table 9. Screening may be performed across 1 or more visits if needed.
Informed consent	X	
Inclusion and exclusion criteria	X	
Demography	X	
Atopic Dermatitis/Medical/Medication/Drug/Alcohol history	X	
Full Physical examination including height and weight	X	
Vital signs	X	
12-lead ECG	X	Single ECG to be taken; Triplicate if QTc prolonged
CLINICAL ASSESSMENTS		
Investigator's Global Assessment (IGA)	X	
Eczema Area and Severity Index (EASI)	X	
Body Surface Area (BSA)	X	
PATIENT REPORTED OUTCOME MEASURES [v]		eDiary completion should be started once the participant passes all the other screening assessments, on or prior to Day-14 to meet the minimum requirements detailed below and Inclusion Criteria 7. eDiary dispensation and training can be completed before the participant passes all the other screening assessments.
Peak Pruritus Numerical Rating Scale (PP-NRS)	X	Daily record in an e-Diary from Day -14 to Day -1
Skin Pain Numerical Rating Scale (SP-NRS)	X	Daily record in an e-Diary from Day -14 to Day -1
Brief Fatigue Inventory (BFI-item 3)	X	Daily record in an e-Diary from Day -14 to Day -1
DIGITAL ASSESSMENT (Optional)		
CCI [redacted]		
Urinalysis	X	See Table 9

Procedure	**Screening (Day -28 to Day -1)**	**Notes** **Please also refer to Table 9.** **Screening may be performed across 1 or more visits if needed.**
Pregnancy test (serum, WOCBP) or FSH/Estradiol (serum, WONCBP)	X	See Appendix 4.
HIV, Hepatitis B and C screening	X	
Hematology, Clinical chemistry, Coagulation profile	X	See Table 9
TB screening (QuantiFERON)	X	
SAE assessment	X	SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product (non-study drug) will be recorded from the time a participant consents to participate in study.

Treatment and Follow-up

Procedure	Treatment												Safety Follow-up				
CCI [redacted]																	
CCI	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Visit window			±1 day				±2 days						±3 days			NA	NA
Outpatient visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X[a]																
Physical examination (Full/Brief)[b]	X[c]							X[c]				X			X	X	X[d]
12-lead ECG[e]	X							X				X			X	X	X
Vital signs	X[f]		X	X	X	X	X	X[f]	X	X	X	X	X	X	X	X	X
Hematology, clinical chemistry, coagulation profile (see Table 9)	X[c]			X		X		X[c]	X	X		X	X	X	X	X	X
Urinalysis (see Table 9)	X[c]			X		X		X[c]	X	X		X	X	X	X	X	X
Urine Pregnancy test [g]	X[c]			X		X		X[c]	X	X		X	X	X	X	X	X
Randomization	X																
CCI [redacted]																	
CLINICAL ASSESSMENTS [c]																	
IGA - Investigator's Global Assessment	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
EASI - Eczema Area and Severity Index	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Treatment												Safety Follow-up				
CCI [redacted]																	
CCI [redacted]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Visit window			**±1 day**				**±2 days**						**±3 days**			**NA**	**NA**
BSA - Body Surface Area	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
SCORAD – Scoring Atopic Dermatitis	X			X		X		X		X		X	X	X	X	X	X
PATIENT REPORTED OUTCOME MEASURE [v]																	
PP-NRS – Peak Pruritus Numerical Rating Scale	X	Daily: (eDiary)														X	X
SP-NRS – Skin Pain Numerical Rating Scale	X	Daily: (eDiary)														X	X
BFI-item 3 – Brief Fatigue Inventory	X	Daily: (eDiary)														X	X
PROMIS-Sleep Disturbance 8b	X					X		X		X		X	X	X	X	X	X
PGIS-SD - Patient Global Impression of Severity (Sleep Disturbance)	X					X		X		X		X	X	X	X	X	X
FACIT-Fatigue	X					X		X		X		X	X	X	X	X	X
PGIS-Fatigue - Patient Global Impression of Severity (Fatigue)	X					X		X		X		X	X	X	X	X	X
PGIS-nocturnal scratching - Patient Global Impression of Severity	X							X				X				X	

Procedure	Treatment												Safety Follow-up				
CCI [redacted]																	
CCI	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Visit window			**±1 day**				**±2 days**						**±3 days**			**NA**	**NA**
PGIC-nocturnal scratching - Patient Global Impression of Change								X				X				X	
DLQI – Dermatology Life Quality Index	X					X		X		X		X	X	X	X	X	X
POEM – Patient Oriented Eczema Measure	X	Weekly (eDiary)														X	X
HADS – Hospital Anxiety and Depression Scale	X					X		X		X		X	X	X	X	X	X
WPAI-AD – Work Productivity and Activity Impairment Questionnaire	X					X		X		X		X	X	X	X	X	X
ACQ-5 – Asthma Control Questionnaire [i]	X											X			X	X	X
CCI [redacted]																	

Procedure	Treatment												Safety Follow-up				
CCI																	
CCI	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Visit window			±1 day				±2 days						±3 days			NA	NA
CCI																	
OTHER ASSESSMENTS																	
CCI																	
PK and PD (Target engagement, TE) [r]	X[c]	X[x]	X		X		X	X[c]	X	X		X	X	X	X	X	X
CCI																	
Immunogenicity	X[c]				X		X	X[c]		X		X	X		X	X	X
CCI																	
Serious AE and AE [u]	<----------														---------->	X	X
Concomitant medication	<----------														---------->	X	X

BL: Baseline, EOS: End of Study, EW: Early Withdrawal, UV: Unscheduled Visit, NA: Not Applicable, ECG: Electrocardiogram, SC: Subcutaneous, PROMIS: Patient-Reported Outcomes Measurement Information System, FACIT: Functional Assessment of Chronic Illness Therapy, RNA: Ribonucleic Acid, CCI, PK: Pharmacokinetics, PD: Pharmacodynamics, CCI AE: Adverse Event

a. Re-check clinical status before dose of study medication to ensure participants remains eligible.
b. Full Physical Examinations should be performed at Screening and Week 28. Brief physical examination at CCI
c. Samples/assessments at CCI to be done pre-dose.
d. A targeted (symptom-directed) physical examination may be conducted at the discretion of the Investigator at a visit where no physical examination has been scheduled or at unscheduled visits. This will be reported as an unscheduled assessment. Any abnormal clinically significant finding will be recorded as an AE in the eCRF.
e. CCI if possible. Note for all ECG assessments: Single ECGs to be taken. Triplicate only if QTc prolonged.
f.
g. WOCBP only. A serum test will be performed if required by local regulations (e.g.: country or IRB/EC)
h. Participants will be observed for approximately 2 hours post dose.
i. Only in patients with comorbid asthma at baseline
j. CCI .
k. CCI that is representative of the participant's atopic dermatitis involvement, outside of the CCI , such as the back or lower extremities. Please note that the same area should be CCI at all follow-up visits.
l. Capture CCI of the CCI at baseline, at week 16, and upon completion/withdrawal from the study. Only perform CCI of the CCI at Week 4 and Week 8 if the participant has CCI at baseline
m. CCI of the CCI area should be captured, at any treatment follow-up visit, in participants experiencing a worsening of pre-existing, or new onset, of CCI throughout the duration of the study.
n. CCI at baseline only, both samples to be taken prior to dosing. CCI .
o. Not in China
p. CCI at baseline only, prior to dosing. CCI
q. CCI
r. CCI throughout the study period.
s. This sample can be taken at any time point if blood volumes become restricting on Day 1. CCI
t. Only those CCI which CCI in CCI can measure will be done in CCI
u. SAEs and AEs will be collected from the start of study intervention until the final follow up visit
v. PROs administered on site should be administered before other clinical assessments or procedures, and before administration of study treatment. The PROs will be administered to participants in different regions based on the availability of translated versions.
w. CCI
x. PK/TE collection acceptable 24-96 h post-dose
y. CCI , analysis will be performed subject to availability and validation of CCI

Note: If following withdrawal of study treatment or withdrawal from the study, the participant agrees to continued assessments, however, does not agree to continue in-person visits during the remainder of the study or safety follow-up, a modified follow-up must be arranged to ensure the collection of endpoints and safety information (e.g., telephone contact).

2. INTRODUCTION

GSK1070806 is a potent anti-IL-18 monoclonal antibody that is being developed for the treatment of AtD [see GSK1070806 Investigator's Brochure].

2.1. Study rationale

Atopic Dermatitis

AtD is a chronic 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 QoL and reduced productivity [Yosipovitch , 2019].

AtD is considered to be a heterogeneous disease with primary T-helper cell T_H2/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 cyclosporine [Khattri , 2014], TCS [Brunner, 2016], JAKi [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 varies globally depending on region and healthcare capabilities although studies of AtD disease severity are limited [Fuxench, 2019]. A study of AtD patients in the US estimated the distribution of mild, moderate, and severe disease among patients at 60%, 29%, and 11% respectively [Fuxench, 2019].

In the US, 3 studies report that AtD is prevalent in approximately 7-8 percent adults [Silverberg, 2015; Barbarot, 2018; Sacottte, 2018; Fuxench, 2019].

From a 2017 study investigating the burden of AtD in the US, it was estimated that total annual burden of AtD (direct, indirect and costs due to QoL) was over $5 billion dollars [Adamson , 2017]. In the US, adults with AtD have almost $5000 more in annual healthcare costs compared to adults without AtD [Manjelievskaia, 2021].

Treatment(s) and Unmet Medical Need

Owing to involvement of multiple cytokines in AtD, broad acting therapeutics and specific antagonists have been or are being developed; these include JAKi such as Cibinqo (abrocitinib), Rinvoq (upadacitinib) and monoclonal antibodies targeting IL-13 (Adtralza [tralokinumab] and Ebglyss [lebrikizumab]) and the IL-4Rα (Dupixent [dupilumab]), OX40 and IL-31. However, the currently approved advanced targeted therapies focus on modulating the Th2 pathway (anti-IL4Rα, anti-IL-13 and JAKi). Despite multiple treatment options, many patients remain in need of more effective, safer, and more convenient therapies.

Dupixent (Dupilumab) is a fully human mAB directed against the IL-4Rα subunit licensed 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 [Beck, 2014; Thaci, 2015; Simpson, 2016b; Blauvelt, 2017; de Bruin-Weller, 2018; Cork, 2020; Simpson, 2020]. However, dupilumab has been associated with hypersensitivity, allergic reactions, conjunctivitis and keratitis, joint pain (arthralgia), and opportunistic infections from parasites [Lobefaro , 2022] and head and neck dermatitis [Vittrup, 2023].

Adtralza (Tralokinumab) is indicated for the treatment of moderate-to-severe AtD in adult and adolescent who are candidates for systemic therapy and has demonstrated modest efficacy in clinical studies [Wollenberg, 2021]. Safety concerns included hypersensitivity, conjunctivitis and keratitis, and parasitic infections.

Cibinqo (Abrocitinib) is a JAKi indicated for the treatment of adults with refractory, moderate to severe AtD and has demonstrated significant improvements in clinical outcomes [Simpson, 2020; Bieber, 2021]. AEs have been reported in about 60% of treated participants [Lobefaro , 2022], including serious infections, malignancy, MACE, and thrombosis.

Rinvoq (Upadacitinib), a selective JAKi has recently received an indication for treatment of severe AtD in individual older than 12 years who are candidates for systemic therapy and is associated with significant improvement in clinical outcomes [Guttman-Yassky, 2021]. Acne and upper respiratory tract infections were the most common side effects reported [Lobefaro , 2022]. Other safety concerns included serious infections, malignancy, MACE, thrombosis, and GI perforations.

Although it was reported that the IGA 0/1 end point significantly underestimated the positive treatment effects associated with dupilumab [Silverberg, 2019], these data suggest that there remains an unmet medical need. Alternative therapies continue to be explored for participants 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 Th1/Th2 driven AtD (a broader approach) and for which relatively infrequent dosing may also be possible. Treatment of AtD requires standardization among clinicians: further studies are needed to evaluate the complex relationship between AtD severity, comorbidities, and therapeutic choices [Lobefaro , 2022].

2.2. Background

Rationale for a potential role of IL-18 in AtD

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 participants with AtD and correlated with disease severity [Inoue, 2011]. In preclinical models, overexpression of IL-18 induces skin inflammation, while neutralization of IL-18 can prevent development of an AtD-like phenotype suggesting that IL-18 may have potential in clinical disease [Konishi, 2002; Plitz, 2003; Kawase, 2003; Terada, 2006; Antonopoulos, 2008; Röse, 2012; Ricardo-Gonzalez, 2018; Chen, 2020]. 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 IgG1 antibody, which was previously explored in a FTiH and an exploratory study in T2DM and DGF following renal transplantation [Mistry, 2014; McKie, 2016; Wlodek, 2021]. A phase 1b study enrolled participants with moderate to severe AtD is completed (refer to Section 2.3 for more details). A study exploring CCI [redacted] safety, PK, and PD is being conducted in healthy participants of European / Caucasian, Japanese and Chinese ancestry [see GSK1070806 Investigator's Brochure].

Study 219538 in Atopic Dermatitis

The aim of this study is to explore GSK1070806 across a range of doses and regimes in adult participants with moderate to severe AtD who have previously been treated with medicated topical treatments or a biologic therapy.

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), and supported with data from the 1 month and a 26 week SC repeat dose toxicology study in cynomolgus monkeys, and on prior clinical experience in T2DM and DGF following CCI [redacted] CCI [redacted] and CCI [redacted] of GSK1070806, respectively [see GSK1070806 Investigator's Brochure]. In addition, a Ph1b study 215253 in which CCI [redacted] of GSK1070806 CCI [redacted] was administered has completed. This was a multi-centre, 12-week, randomized, double-blind, parallel-group, placebo-controlled study to investigate efficacy and safety of GSK1070806 in participants with moderate-to-severe AtD.

This study assessed the impact of [redacted] of GSK1070806 [redacted] administered intravenously in 2 groups of participants with moderate-to-severe AtD:

- Biologic Naive Group (Group 1): Participants naive to biologic treatment and had failed topical therapies.
- Dupi-IR Group (Group 2): Participants who were not adequately responsive (or were intolerant) to dupilumab.

All participants must have washed out topical therapies (corticosteroids, calcineurin inhibitors, PDE4 inhibitors) for at least 7 days prior to dosing on Day 1.

The primary endpoint was the PCFB in the EASI in the Biologic Naive group (Group 1) participants and was assessed at Week 12.

A total of 34 participants were enrolled into the study, 30 within the Biologic Naive group and 4 within the Dupi-IR group. The study achieved its primary objective, demonstrating a positive treatment effect on the primary endpoint (PCFB in the EASI score at Week 12 in Biologic Naive group). A positive treatment effect was observed across all efficacy endpoints in both the Biologic Naive group and the Dupi-IR group. A positive treatment effect was observed in the exploratory PRO endpoints including Itch (PP-NRS) and QoL (DLQI). No safety concerns related to administration of GSK1070806 were observed in the study. No ADAs were observed in the study.

More detailed information about the potential benefits and risks of GSK1070806 can be found in the IB [GSK1070806 Investigator's Brochure].

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks associated with Study Intervention [GSK1070806]		
Infections	IL-18 plays a role in host defence against microbial pathogens. IL-18 primes both innate and acquired immunity to viruses and other intracellular pathogens. As a result, there is a theoretical risk that blocking of IL-18 signalling by GSK1070806 may increase a participant's susceptibility to bacterial, viral, or other types of infections. **Non-Clinical Data:** In a 4-week monkey toxicology study, *Shigella flexneri* infection occurred in monkeys that received IV GSK1070806 at all doses, and in vehicle control monkey (0 [vehicle control], CCI [redacted] No infections were observed at doses CCI [redacted] in the SC 26-week toxicology study. **Clinical Data:** Events of infection, including serious infections in Study 204824 in patients following renal transplant, have been reported in completed trials. No causal association has been established.	**Eligibility Criteria:** Exclusion of participants with: • Chronic or acute infection requiring treatment with oral or IV antibiotics, antivirals, anti-protozoal, or antifungals within 4 weeks before the Screening visit or anytime between the Screening and Baseline visits. • Superficial skin infections within 1 week before the Screening visit or Active infections (including localized infections), or history of recurrent infections (excluding recurrent fungal infections of the nail bed). • Known, pre-existing or suspected parasitic infection within 6 months before the Screening visit. • Symptomatic herpes zoster within 3 months prior to screening • Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., TB, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per the Investigator's judgment. **Monitoring:** • Serious infections and opportunistic infections are categorized as AESIs. • Participants will be monitored for signs of infection. • Instructions will be provided to participants as to the signs and symptoms of infection, and to contact site personnel should they develop any infection. • Serious infections and opportunistic infections will be captured on a specific eCRF to further characterize the events.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Temporary Discontinuation: • Temporarily discontinue the study intervention for serious infections or opportunistic infections until the infection has resolved. **Withdrawal Criteria:** • Permanently discontinue the study intervention for new latent or active TB infection. • Other serious or severe infection AEs, exclusively at the discretion of the Investigator, preferably after consultation with the Medical Monitor.
Hypersensitivity Reactions	The administration of any mAb has the potential to induce local or systemic immunologic reactions. **Non-Clinical Data:** No evidence of hypersensitivity reactions was observed in non-clinical studies following IV (bolus) or SC injection. **Clinical Data:** GSK1070806 has been administered to humans via IV infusion and no serious hypersensitivity reactions have been reported in completed clinical studies.	**Eligibility Criteria:** Exclusion of participants with: • History of an allergic reaction or significant sensitivity to any constituents of the study drug (including excipients). • History of significant allergies to mAbs • Clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA, dermatosis, toxic epidermal necrolysis or Stevens-Johnson syndrome, and exfoliative dermatitis. **Monitoring:** • Serious hypersensitivity reactions are categorized as AESIs. • Instructions will be provided to participants as to the signs and symptoms of a hypersensitivity reaction and to seek immediate medical care should they develop. • Participants will be monitored for approximately 2 hours post dosing after each SC injection. • Serious hypersensitivity reactions will be captured on a specific eCRF to further characterize the events. **Withdrawal:** Permanently discontinue study intervention for serious hypersensitivity reactions related to GSK1070806.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Injection site reactions	SC injections, including injections of mAbs, may be associated with local reactions such as swelling, induration, or pain. **Non-Clinical Data:** No macroscopic or microscopic changes indicative of local infusion site intolerance were observed at the IV (bolus) infusion sites in the 4 week toxicology study. In the 26-week study, minimal perivascular mononuclear cell infiltration was observed at the SC injection site at GSK1070806 doses CCI **Clinical Data:** GSK1070806 was administered to humans via IV infusion, and no infusion site reactions were observed in completed studies. The SC injection route of administration has not been studied.	**Monitoring:** • ISRs are categorized as AESIs. • Participants will be monitored for approximately 2 hours post dosing after each SC injection. Monitor for ISRs throughout study. • ISRs will be captured on a specific eCRF to further characterize the events. If the participant is receiving other permitted SC medication, the study treatment should be administered in a different location.
Immunogenicity	Monoclonal antibodies may induce ADAs, which have the potential to induce adverse reactions or affect the PK of GSK1070806. **Non-Clinical Data:** No ADAs were detected in cynomolgus monkeys following CCI IV administrations at doses up to CCI. In a SC 26-week toxicology study in monkeys, ADAs were noted in monkeys who received GSK1070806 at CCI and CCI. ADAs observed in monkeys is not considered to be indicative of ADAs in humans. **Clinical Data:** Three of 57 healthy participants (5.3%) who received GSK1070806 had ADAs post dosing (Study A18110040). Two of 32 healthy participants (6%) of Asian or European/Caucasian ancestry who received GSK1070806 had ADAs post dosing (Study 218841). There was no apparent change in the individual PK or safety profile of GSK1070806. No ADAs were detected in completed studies in participants with T2DM (Study A18116378) or participants with AtD (Study 215253).	**Monitoring:** Blood samples will be drawn for ADAs to GSK1070806 according to the SoA. In addition to scheduled immunogenicity assessments, 'event-driven' testing will be performed in the context of serious hypersensitivity reactions or AEs deemed to be clinically significant in the opinion of the investigator, resulting in discontinuation from study intervention.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Vaccine Effects	IL-18 has the potential to modulate the human immune system and thus response to vaccines. There is a theoretical possibility that blocking of IL-18 signalling by GSK1070806 may increase a participant's susceptibility to infections to which they have been previously vaccinated or, in the case of a live vaccine, allow proliferation of the virus. **Non-clinical Data:** In a 26-week toxicology study with GSK1070806 administered SC at doses CCI , monkeys generated both primary and secondary responses to KLH immunization, albeit with reduced IgM and IgG titres compared with IgM and IgG titres observed in controls. **Clinical Data:** Vaccine effects have not been formally tested in clinical studies with GSK1070806.	Live or live attenuated vaccines must not be administered to participants from 30 days prior to the first dose of study intervention and for 5 half-lives CCI after dosing has completed. Investigators should review and update the vaccination status of potential participants as per local guidelines for adult vaccination including against COVID-19, influenza, herpes zoster, haemophilus influenzae type b, and pneumococcus prior to the first dose of study intervention. If indicated, non-live vaccines (e.g., inactivated influenza vaccines) may be administered while receiving study treatment based on an assessment of the benefit/risk (e.g., possible risk of decreased immune response). **Eligibility Criteria:** Exclusion of participants who received live or live attenuated vaccine(s) within 30 days prior to first dose of study intervention or planned during the study. **Withdrawal Criteria**: Administration of a live or live attenuated vaccine during study.
Effects on Blood Pressure	**Non-clinical Data:** There was no apparent change in BP in a CCI nonclinical safety pharmacology study and a 4- week toxicology study in monkeys (CCI administered CCI). **Clinical Data:** Events of hypertension have been reported in completed trials. No causal association has been established.	**Eligibility Criteria:** Exclusion of participants who have uncontrolled hypertension. **Monitoring:** Vital signs are routinely monitored in the study according to the SoA.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Reproductive Toxicity-	GSK1070806 is not considered genotoxic. **Non-clinical Data:** A reproductive toxicology study has not been conducted. Non-clinical modelling suggested that the likely transferable drug concentration for sperm to female via the vaginal tract is negligible. **Clinical Data:** No pregnancies were reported in completed studies. The effect of GSK1070806 on human pregnancy is unknown.	**Eligibility Criteria:** A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies: • Is a WONCBP. See Section 10.4. OR • Is a WOCBP and using a contraceptive method as described in Section 10.4 during the study intervention period and for at least CCI after the last dose of study intervention (please note, however, that WOCBP wishing to be considered for the LTE, should maintain highly effective contraceptive use). A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at screening. **Monitoring:** • Urine pregnancy testing (or serum as required by local regulations) of WOCBP throughout the study per SoA. See Section 8.3.5 Pregnancy Testing. • Collection of pregnancy information. Pregnancy information to be followed to determine outcome. • Report AE/SAE for any pregnancy complication or elective termination. **Withdrawal Criteria:** • Permanently discontinue study intervention in the event of pregnancy.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks associated with Study Procedures		
Blood draws	Venous access in some participants may be problematic and the needles used may cause bruising (ecchymosis) around the access site.	• The whole blood volume that will be collected from each participant over the course of the study is provided in the ICF. • At visits to collect whole blood samples, 1 or more samples of sufficient volume will be collected and divided into suitable portions for the various analyses such as PD biomarkers. • CCI [redacted] will only be collected from those consenting to participate in this research. • Whole blood samples will be collected by site personnel experienced in phlebotomy.
CCI [redacted]		

2.3.2. Benefit assessment

Participants may or may not experience benefit in improved symptoms of AtD and clinical presentation following administration 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 participants intolerant or unresponsive to currently available treatments for AtD, or those who have lost access.

2.3.3. Overall benefit-risk conclusion

There remains an unmet medical need for the effective treatment of AtD in participants who inadequately responded to medicated topical treatments such as TCS and TCI or who have had previous experience with biologic therapies such as dupilumab and tralokinumab.

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 with moderate to severe AtD who are candidates for systemic therapy.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1. Objectives and Endpoints

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of GSK1070806 CCI versus placebo in adults with moderate to severe AtD.	PCFB in the EASI to Week 16.
Secondary	
To evaluate the efficacy of GSK1070806 across the dose range versus placebo by characterizing the longitudinal dose-response relationship in adults with moderate to severe AtD.	PCFB in the EASI at each time point.
To further evaluate the impact of GSK1070806 CCI and across the dose range versus placebo in adults with moderate to severe AtD.	• Achieving EASI Reduction of ≥75% from Baseline at Week 16 • Achieving IGA score of 0 or 1 and a reduction from baseline ≥2 points at Week 16 • CFB in PP-NRS at Week 16 • Achieving PP-NRS Reduction of ≥4 points from Baseline at Week 16
To further evaluate the efficacy of GSK1070806 CCI and across the dose range versus placebo in adults with moderate to severe AtD.	Achieving EASI Reduction of ≥50%/90%/100% from Baseline at Week 16. Achieving SCORAD Reduction of ≥50%/75% from Baseline at Week 16. CFB to Week 16 for the following measures: • BSA • SCORAD
To assess the impact of GSK1070806 CCI and across the dose range versus placebo on Health Related-Quality of Life (HR-QoL), depression and anxiety, fatigue, sleep, WPAI and pain as measured by a range of PROs in adults with moderate to severe AtD.	CFB to Week 16 for the following PRO measures: • SP-NRS • PROMIS-Sleep disturbance 8b • FACIT-Fatigue • BFI-item 3 • POEM • DLQI • HADS • WPAI-AD
To assess the safety of GSK1070806 CCI and across the dose range in adults with moderate to severe AtD.	• Occurrence of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI) • Change from baseline in key laboratory parameters.

Objectives	Endpoints
	• Occurrence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 hematological/clinical chemistry abnormalities.
Exploratory	
To explore the onset and maintenance of improvements in pain intensity of GSK1070806 CCI and across the dose range versus placebo in adults with moderate to severe AtD	• Achieving SP-NRS Reduction of ≥4 points from baseline at Week 16 • Achieving SP-NRS Reduction of ≥4 points from baseline at each scheduled timepoint up to Week 28
To further evaluate the efficacy over time of GSK1070806 CCI and across the dose range versus placebo in adults with moderate to severe AtD.	At each scheduled timepoint up to Week 28: • PCFB EASI • CFB EASI • CFB BSA • CFB SCORAD At each scheduled timepoint up to Week 28: • Achieving IGA score of 0 or 1 and a reduction from baseline ≥2 points • Achieving EASI Reduction of ≥50/75/90/100% from Baseline • Achieving SCORAD Reduction of ≥50%/75% from Baseline (SCORAD50/75).
To further evaluate the PRO measures over time of GSK1070806 CCI and across the dose range versus placebo in adults with moderate to severe AtD.	Achieving PP-NRS Reduction ≥4 Points from baseline at each scheduled timepoint up to Week 28. CFB to Week 16 in ACQ5 CFB at each scheduled timepoint up to Week 28 for the following PRO measures: • PP-NRS • SP-NRS • PROMIS-Sleep disturbance 8b • FACIT-Fatigue • BFI- item 3 • POEM • DLQI • HADS • WPAI-AD • ACQ5

Objectives	Endpoints
CCI [redacted]	
To further evaluate the efficacy of GSK1070806 CCI and across the dose range placebo in adults with moderate to severe AtD on other measures of efficacy.	• Time to onset of IGA score of 0 or 1 and a reduction from baseline ≥2 points • Time to onset of EASI Reduction of ≥75% from baseline • Time to a ≥50% increase (worsening) in EASI score relative to baseline. • Time to first use of rescue therapy
To assess the PK concentration-time profile of SC GSK1070806 CCI and across the dose range in adults with moderate to severe AtD.	• GSK1070806 PK concentrations in serum over time • PK parameters: area under the concentration-time curve over the dosing interval (AUC (0-tau)), maximum observed concentration (Cmax), time of occurrence of Cmax (tmax)
To assess the PD profile (TE) of SC GSK1070806 CCI and across the dose range in adults with moderate to severe AtD.	• Total IL-18 concentrations in serum over time. • Free IL-18 concentrations in serum at baseline • IL-18BP in serum at baseline
To assess the potential for ADA formation.	• Incidence of pre-existing ADAs. • Incidence of treatment-emergent ADAs
To investigate the effect of GSK1070806 CCI and across the dose range versus placebo on nocturnal scratching measured by CCI (in a subset of participants in selected countries), and to collect evidence to support the clinical validation of the nocturnal scratch measures including sensitivity to change over time and concurrent validity through comparison to other measures (PROs and other clinical outcomes).	• CFB in CCI measures to Week 16 (e.g., number of scratching events, scratching time, etc.) • Correlations between CCI measures, PROs (e.g., PP-NRS, PROMIS-sleep disturbance 8b, FACIT-Fatigue, WPAI-AD, or nocturnal scratch PGIS and PGIC) and other clinical measures (e.g., EASI)

3.2. Estimands

This section describes the estimand strategy for the efficacy and safety objectives.

3.2.1. Estimand Strategy for Efficacy Objectives

Estimand 1 – Primary estimand	
Clinical question of interest	What is the treatment difference for GSK1070806 CCI vs. placebo with or without use of non-medicated background treatments as measured by PCFB in the EASI score to Week 16 in participants with moderate to severe AtD (either biologic naïve or experienced); regardless of discontinuation of investigational treatment for any reason but where use of rescue therapy for AtD before Week 16 is considered a negative outcome? Rationale: This clinical question of interest is designed to evaluate the difference in treatment response of GSK1070806 CCI vs. placebo with or without use of non-medicated background treatments where the use of rescue therapy for AtD results in a negative outcome, irrespective of permanent intervention discontinuation for any reason. The composite strategy explicitly recognizes that use of rescue therapy constitutes a failure of the treatment to manage the participant's disease and avoids reporting results reflecting use of an additional medicated treatment rather than a placebo.
Treatment Condition	SC GSK1070806 CCI vs. placebo administered CCI with or without use of non-medicated background treatments regardless of permanent treatment discontinuation for any reason (treatment policy strategy).
Endpoint	PCFB to Week 16 in EASI where any use of rescue medication is considered an unfavourable outcome.
Population	Participants with moderate to severe AtD (either biologic naïve or experienced) who have previously been treated with medicated topical treatments only or 1 biologic therapy.
Strategy for ICEs	• ICE: permanent treatment discontinuation CCI Strategy: treatment policy • ICE: use of rescue therapy for AtD before Week 16 Strategy: composite; use of rescue therapy is considered a negative outcome, and post-ICE assessments are imputed as the participant's worst observation (from baseline or post-baseline assessments) • ICE: treatment discontinuation due to extreme administrative and operational disruptions (e.g., situations such as pandemic illness, or war causing lockdown or site closure and restricting access to the study medication) Strategy: hypothetical
Population-level summary	Difference (GSK1070806 CCI with or without use of non-medicated background treatments – placebo with or without use of non-medicated background treatments) in mean percent change between treatment conditions.

Additional Estimand For The Primary Efficacy Objective

One additional estimand for the primary objective will be defined (estimand 2). The attributes follow the primary estimand (estimand 1) except for the endpoint definition and the strategy for ICE of use of rescue therapy.

Estimand 2 – Additional Estimand to the Primary	
Endpoint	PCFB to Week 16 in EASI
Strategy for ICEs	• ICE: use of rescue therapy for AtD before Week 16 Strategy: treatment policy

Rationale: This additional estimand is designed to evaluate the treatment effect attributable to GSK1070806 CCI with or without use of non-medicated background treatments, irrespective of permanent treatment discontinuation or use of rescue therapy before Week 16. This provides evidence of efficacy regardless of whether participants took the drug as per the protocol and is most closely reflective of usual clinical practice.

3.2.2. Estimand Strategy for Secondary Dose Response Objective

Estimands for the dose- response objective	
Clinical question of interest	What is the longitudinal dose-exposure response for GSK1070806 across the dose range vs. placebo with or without use of non-medicated background treatments as measured by PCFB in the EASI score at each time point in participants with moderate to severe AtD (either biologic naive or experienced); had discontinuation of investigational treatment for any reason not occurred or had rescue therapy not been administered for AtD before Week 16?
Treatment Condition	SC GSK1070806 across the dose range vs. placebo administered CCI with or without use of non-medicated background treatments.
Endpoint	PCFB at each scheduled timepoint in EASI.
Population	Participants with moderate to severe AtD (either biologic naive or experienced) who have previously been treated with medicated topical treatments only or 1 biologic therapy.
Strategy for ICEs	• ICE: permanent treatment discontinuation CCI • ICE: use of rescue therapy for AtD before Week 16 • ICE: treatment discontinuation due to extreme administrative and operational disruptions (e.g., situations such as pandemic illness, or war causing lockdown or site closure and restricting access to the study medication Strategy: hypothetical Note: Observed PK/PD values will be used for modelling purposes.
Population-level summary	Difference (Each dose of GSK1070806 with or without use of non-medicated background treatments – placebo with or without use of non-medicated background treatments) in mean percent change between treatment conditions.

3.2.3. Estimand Strategy for Secondary Efficacy Objectives

Continuous secondary efficacy objectives

These estimands (continuous) for the secondary efficacy objectives follow the attributes, including the handling strategies for all ICEs, of the primary estimand (estimand 1) except for the treatment condition, endpoints, and population-level summary, as described below.

Estimands (continuous) for secondary efficacy objectives	
Treatment Condition	SC GSK1070806 CCI and across the dose range vs. placebo administered CCI with or without use of non-medicated background treatments regardless of permanent treatment discontinuation for any reason (treatment policy strategy).
Endpoints	CFB to Week 16 in: • PP-NRS • BSA • SCORAD • SP-NRS • PROMIS-Sleep disturbance 8b • FACIT-Fatigue • BFI-item 3 • POEM • DLQI • HADS • WPAI-AD where any use of rescue medication before Week 16 is considered an unfavourable outcome.
Population-level summary	Difference (Each dose of GSK1070806 with or without use of non-medicated background treatments – placebo with or without use of non-medicated background treatments) in mean change between treatment conditions.

Binary secondary efficacy objectives

These estimands are applicable to the binary secondary efficacy objectives. The treatment condition, endpoints, strategy for handling use of rescue therapy ICE and population-level summary differ from the primary estimand (estimand 1) and are detailed below.

Estimands (binary) for secondary efficacy objectives	
Treatment Condition	SC GSK1070806 CCI and across the dose range vs. placebo administered CCI with or without use of non-medicated background treatments regardless of permanent treatment discontinuation for any reason (treatment policy strategy).
Endpoints	At Week 16: • Achieving IGA score of 0 or 1 and a reduction from baseline ≥2 points without use of rescue therapy for AtD • Achieving EASI reduction of ≥50%/75%/90%/100% from baseline without use of rescue therapy for AtD • Achieving PP-NRS reduction of ≥4 points from baseline without use of rescue therapy for AtD

Estimands (binary) for secondary efficacy objectives	
	• Achieving SP-NRS reduction of ≥4 points from baseline without use of rescue therapy for AtD • Achieving SCORAD reduction of ≥50%/75% from baseline without use of rescue therapy for AtD
Strategy for ICEs	• ICE: use of rescue therapy for AtD before Week 16 Strategy: composite; use of rescue therapy is considered a negative outcome, and post-ICE assessments are imputed as non-responder
Population-level summary	Difference (Each dose of GSK1070806 with or without use of non-medicated background treatments – placebo with or without use of non-medicated background treatments) in proportions between treatment conditions.

These additional estimands will follow the attributes of the estimands for binary secondary efficacy objectives except for endpoints and the strategy for ICE of use of rescue therapy.

Additional estimands (binary) for secondary efficacy objectives	
Endpoints	At Week 16: • Achieving IGA score of 0 or 1 and a reduction from baseline ≥2 points • Achieving EASI reduction of ≥75 from baseline • Achieving PP-NRS reduction of ≥4 points from baseline
Strategy for ICEs	• ICE: use of rescue therapy for AtD before Week 16 Strategy: treatment policy

Note: Population for endpoints 'achieving PP-NRS reduction of ≥4 points from baseline' and 'achieving SP-NRS reduction of ≥4 points from baseline' will include only the subset of participants with a PP-NRS/SP-NRS ≥4 points at baseline respectively.

3.2.4. Estimand Strategy for Safety Objectives

Estimands for safety objectives	
Clinical question of interest	What is the difference in safety for GSK1070806 CCI and across the dose range vs. placebo with or without use of non-medicated background treatments as measured by occurrence of AEs, SAEs, AESIs, and grade ≥3 hematological/clinical chemistry abnormalities, as well as change from baseline in key laboratory parameters in participants with moderate to severe AtD (either biologic naive or experienced); regardless of discontinuation of investigational treatment for any reason or use of rescue therapy for AtD before Week 16? Rationale: This clinical question of interest is designed to evaluate the safety of GSK1070806 CCI and across the dose range vs placebo with or without use of non-medicated background treatments, irrespective of permanent treatment discontinuation or use of rescue therapy for AtD before Week 16. This provides comparison of safety regardless of whether participants took the drug as per the protocol and is most closely reflective of usual clinical practice.
Treatment Condition	SC GSK1070806 CCI and across the dose range vs placebo administered CCI with or without use of non-medicated background treatments regardless of use of rescue therapy for AtD before Week 16 or permanent treatment discontinuation for any reason (treatment policy strategy).
Endpoints	• Occurrence of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI) • Change from baseline in key laboratory parameters • Occurrence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 hematological/clinical chemistry abnormalities (CTCAE).
Population	• Participants with moderate to severe AtD (either biologic naive or experienced) who have previously been treated with medicated topical treatments only or 1 biologic therapy.
Strategy for ICEs	• ICE: permanent treatment discontinuation CCI • ICE: use of rescue therapy for AtD before Week 16 • ICE: treatment discontinuation due to extreme administrative and operational disruptions (e.g., situations such as pandemic illness, or war causing lockdown or site closure and restricting access to the study medication) Strategy: treatment policy
Population-level summary	• AEs, SAEs: number and % of participants with at least 1 event by System Organ Class and Preferred Term for each treatment arm • CFB in key laboratory parameters: mean for each treatment arm and timepoint

Additional estimands for safety objectives

For key safety endpoints, overall AEs and overall SAEs only, these estimands will use the "while on treatment" approach, i.e., any safety events which occur post discontinuation of study intervention which are not classified as treatment emergent will be excluded. Treatment emergent events are events which occur CCI a participant's last dose.

4. STUDY DESIGN

4.1. Overall design

This is a Phase 2b, randomized, double-blind, parallel group, placebo controlled, dose finding study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics (target engagement) of GSK1070806 in biologic naive and biologic experienced adults with moderate to severe AtD.

The study will enroll approximately n=175 biologic naive and biologic experienced participants who will be randomized in a 2:1:1:1:2 ratio to receive either placebo CCI SC (n=50), GSK1070806 CCI SC (n=25), CCI SC (n=25), CCI SC (n=25) or CCI SC (n=50). Please note that all participants will receive blinded study treatment (GSK1070806 or placebo) at baseline and CCI to maintain the blind, therefore, participants randomised to CCI treatment arm will receive blinded placebo at CCI

It is anticipated that approximately CCI of the participants would be biologic experienced, however, a maximum of approximately CCI biologic naive participants (across the whole study) will be enrolled. Participants will be stratified by Region (China vs Japan vs Rest of World), and CCI

The biologic naive population is defined as participants who have no prior exposure to a biologic treatment for atopic dermatitis (such as dupilumab, tralokinumab or lebrikizumab) and have experienced an inadequate response to a stable regimen of prescription topical medication or for whom prescription topical medications are not tolerated.

The biologic experienced population is defined as participants who have had previous exposure to a single biologic treatment (such as dupilumab, tralokinumab or lebrikizumab) for atopic dermatitis but subsequently stopped the biologic treatment either due to:

- non-response, partial response, loss of efficacy

or

- intolerance or AEs

Note: exposure to only 1 previous biologic for atopic dermatitis is permitted; with no prior treatment with oral JAKi. Previous exposure to topical JAKi is permitted. Please refer to Section 5.2.2 for details of wash-out requirements.

Eligible adult participants (≥18 years of age) with moderate-to-severe AtD for at least 1 year, as defined by the AAD Consensus Criteria [Eichenfield, 2014] (see Appendix 8), with an EASI Score of ≥16, an IGA score of ≥3 and a BSA of ≥10% will be enrolled.

The study will have a 4-week screening period, a CCI [redacted]. Participants who complete the treatment period will be followed up for CCI [redacted] post completion. Participants who prematurely withdraw from the treatment period will be followed up for at least CCI [redacted] (5 half-lives) post last dose (Refer to Section 1.2 for Design Schema). At the discretion of the Investigator, participants may be followed up after completion of the follow-up period if continued safety monitoring is required following an AE or abnormal laboratory result for example, until such time that the event is considered to have normalized, stabilized or returned to baseline.

All SC injections of study medication will be administered in the clinic. The study treatment will be administered into the abdomen or thigh. Participants will remain in the clinic for safety monitoring for approximately 2 hours after each administration of study treatment. Participants will be observed for AEs including systemic reaction (i.e., allergic [type 1 hypersensitivity] reaction and other systemic reactions) and local ISRs.

Any ongoing medicated topical treatments, such as TCS, will be required to be washed out during the screening period with no medicated topical treatment use permitted within 7 days prior to baseline and throughout the CCI [redacted] treatment period. Medicated topical treatments will be permitted from Week 16 in line with local guidelines and the investigator's usual prescribing patterns. If the use of medicated topical treatments is required prior to Week 16, please refer to Section 6.9.3 for guidance.

The overall duration for a participant is not expected to exceed 32 weeks.

CCI [redacted]

The primary endpoint of PCFB in the EASI will be measured at Week 16. In addition, efficacy will be measured throughout the duration of the study via the assessment of EASI, IGA, SCORAD.

QoL and impact of disease will be assessed using the POEM, DLQI and HADS, FACIT Fatigue, BFI- item 3, Pruritus, Sleep, Pain, and WPAI-AD measures.

Participants with comorbid asthma will be asked to complete ACQ-5 at baseline, Week 16 and Week 28 (study completion or withdrawal) to monitor any changes in asthma control over the duration of the study period.

Safety will be assessed by monitoring AEs, physical examination, pulse, BP and temperature, ECGs, serum chemistry, hematology, coagulation and urinalysis. Serum and blood samples will be collected for PK and PD analysis, immunogenicity, and assessment of biomarkers.

Biomarkers will also be evaluated at baseline from CCI and CCI to assess prediction of treatment response.

CCI will also be studied as optional assessments at selected sites to CCI and activity/sleep quality respectively.

Several interim analyses may be included for non-binding futility, or to assess efficacy for internal decision making and/or confirming/adjusting dose regimens, CCI or to initiate or support Phase 3 planning activities. The sample size, number of treatment arms or dose regimens may be adjusted as a result of an interim analysis.

The study will appoint an iDRC, independent to the study team, that will review interim data periodically throughout the trial to determine appropriate recommendations for study conduct and enabling activity for the wider development plan.

4.2. Scientific rationale for study design

4.2.1. Rationale for Randomized, double-blind, placebo-controlled design

GSK1070806 is an experimental drug. The inclusion of a placebo arm will ensure blinding of any attribution of treatment to potential safety signals whilst also providing control data for the comparison of efficacy and biomarkers.

4.2.1.1. Rationale for Study Populations

Enrolled participants will have a recent history of inadequate response to medicated topical treatment or be contraindicated for medicated topical treatments (biologic naive) or have a history of prior exposure to a single biologic therapy and experienced either an inadequate therapeutic response, or an intolerance or adverse effect, and are candidates for systemic therapy.

4.2.1.2. Duration of Treatment / Follow-Up Period

The duration of the Treatment Period is CCI (see both this Section 4.2 “Efficacy

Endpoints” and Justification for Dose: Section 4.3) allowing participants sufficient time to demonstrate a therapeutic response across endpoints and to support dose identification.

GSK1070806 has shown an average terminal half-life of CCI after CCI administration of CCI in patients with AtD. Therefore, following participants for CCI CCI after administration of last dose of GSK1070806 CCI allows safety monitoring to continue for more than 5 half-lives in this disease population (see Justification for Dose, Section 4.3).

Previous clinical studies have shown an CCI PD effect for at least CCI weeks after a CCI of GSK1070806, suggesting that even if GSK1070806 concentrations are expected to be very low at this time, GSK1070806 may still retain some pharmacological activity. Therefore, monitoring patients up to CCI is considered important to allow PD effect to start recovering.

4.2.1.3. Randomization Ratio

The study will enroll approximately n=175 participants, stratified by region (Japan, China and Rest of World) and CCI Participants will be randomized in a 2:1:1:1:2 ratio to receive either placebo CCI SC (n=50), GSK1070806 CCI SC (n=25), CCI SC (n=25), CCI SC (n=25) or CCI SC (n=50).

4.2.2. Rationale for Efficacy Endpoints

The primary endpoint is PCFB in the EASI at Week 16.

EASI (see Section 8.2.1.1) 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 and experimental drugs Crisaborole [Bissonnette, 2019], Dupixent [Beck, 2014], Upadacitinib [Guttman-Yassky, 2020a], Lebrikizumab [Guttman-Yassky, 2020b] and Abrocitinib [Simpson, 2020b] and will allow for indirect comparison to other therapies.

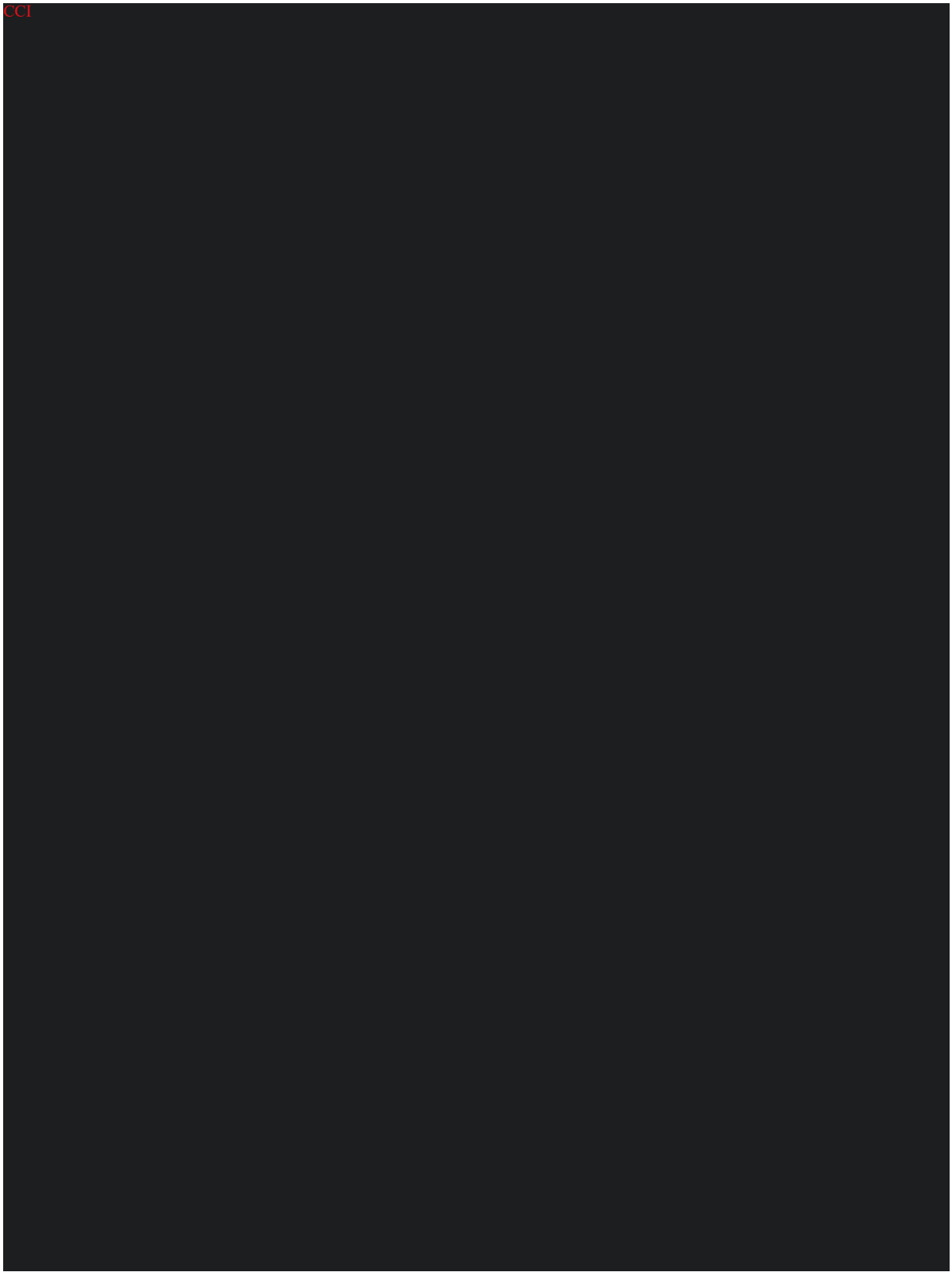
Similarly, the IGA response is an accepted FDA regulatory endpoint. Clinical scores will be measured throughout the study to ensure preliminary assessment of the onset, extent and duration of clinical response and this measure will be included as a key secondary efficacy endpoint.

SCORAD is a validated clinical tool for assessing the extent and intensity of AtD and is included as a secondary endpoint.

4.2.3. Rationale for PROs

Nearly two-thirds (62.9%) of moderate to severe AtD participants report itching for at least 12h each day, with 60.5% of participants 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 [Yosipovitch , 2019]. Eight additional PRO instruments have been introduced to collect qualitative and meaningful data on sleep disturbance (PROMIS-Sleep Disturbance [Lei, 2020]), fatigue (FACIT-Fatigue) and (BFI-item 3 [Mendoza, 1999]), anxiety and depression (HADS), signs, symptoms and impacts of AtD (POEM), work productivity and activity impairment (WPAI) and asthma control as measured by ACQ-5. Lastly, the DLQI covers the impact of AtD on general aspects of daily living [Finlay, 1994], see details in Section 8.2.2.

CCI



CCI [redacted]

4.2.6. Participant input into design

Feedback on study design has been obtained by conducting a patient engagement survey. The study was well-received overall, and the general design and requirements were acceptable.

It is GSK's intent to continually engage participants which may influence future study designs for this disease area and aim to improve the patient experience within clinical research.

4.3. Justification for dose

The dose range and regimens have been chosen to allow a full exploration of the D-E-R of GSK1070806 in AtD participants by selecting doses and regimens that are predicted to encompass a wide range of free IL-18 TE (reductions compared to baseline levels). This will facilitate selecting the optimal effective/safe dose(s) and regimen(s) for investigation in Phase 3 using the longitudinal PK and clinical efficacy data collected from all the dose regimens in the current study.

GSK1070806 TE has been demonstrated in healthy participants across of range of doses and AtD participants at a CCI [redacted] level. CCI [redacted]

CCI

SC doses CCI

SC CCI

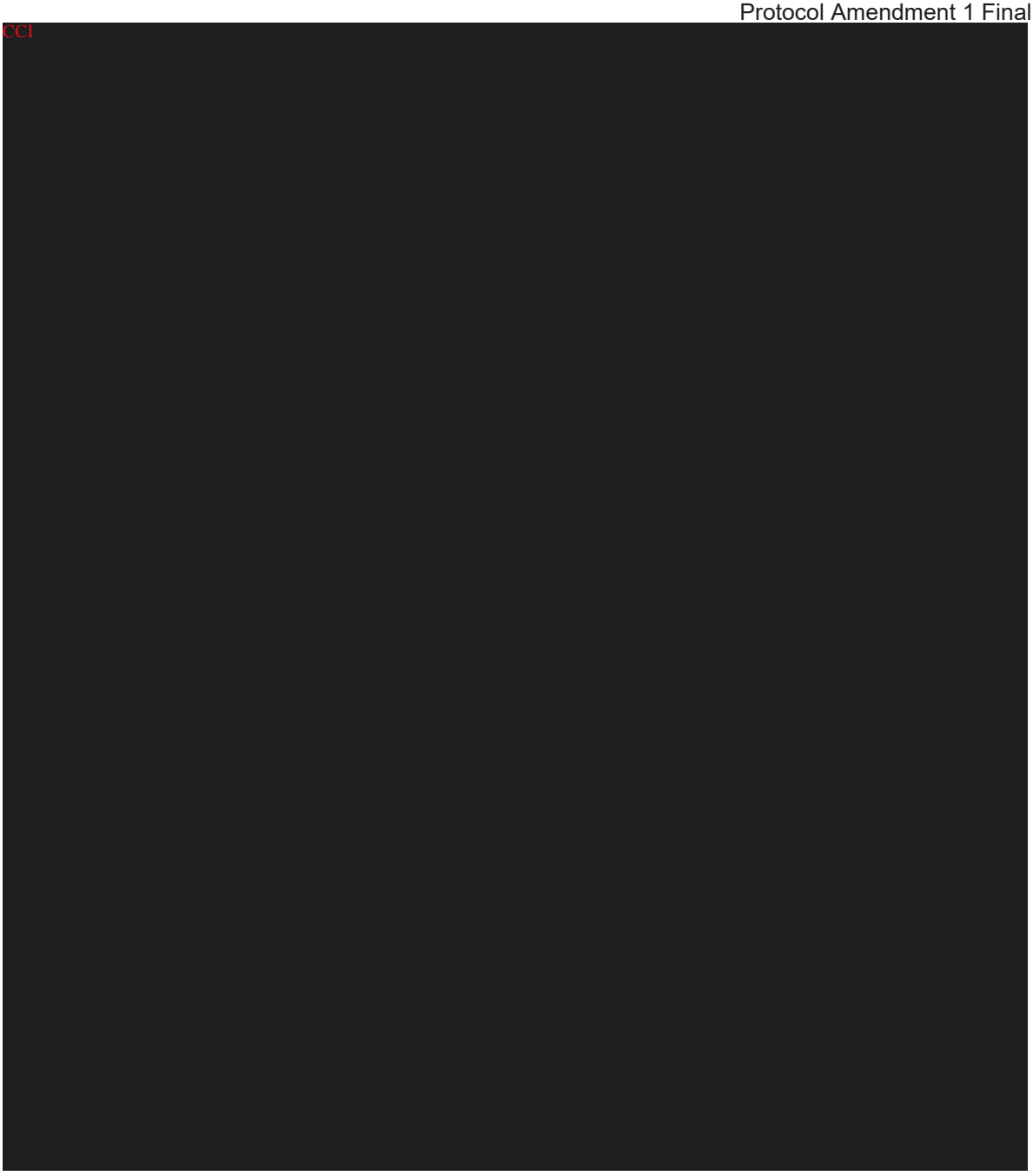
CCI

CCI SC CCI .

CCI

Through an integrated analysis of longitudinal data from all doses and regimens it is predicted that there will be a full understanding of D-E-R relationship across the CCI -fold dose range (total of CCI of GSK1070806 which will facilitate dose selection for future studies in this population.

CCI



4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed the last scheduled procedure shown in the SoA (Week 28).

The end of the study is defined as the date of the last visit of the last participant according to the SoA.

5. STUDY POPULATION

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

5.1. Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Participant and/or their LAR must sign and date an informed consent.
2. Adult participants 18 years to 75 years of age
   - Country specific requirement: Participants from South Korea are required to be aged at least 19 years or greater in the study. Participants from Thailand are required to be aged at least 20 years or greater in the study.
3. BMI within the range 18 - 39.9 kg/m^2 (inclusive).
4. Disease Characteristics
   - AtD defined by the AAD Consensus Criteria [Eichenfield, 2014] (see Appendix 8).
   - Diagnosis of AtD ≥1 year
   - An IGA score ≥3 at both the Screening and Baseline visits
   - AtD involvement of ≥10% BSA at both the Screening and Baseline visits
   - EASI score ≥16 at both the Screening and Baseline visits
   - Baseline pruritus numerical rating scale average score for maximum intensity of at least 3, based on the average of daily pruritus numerical rating scale scores for maximum itch intensity reported during the 7 days prior to randomization.
5. AtD Medications:
   - Biologic experienced participants: may have had exposure to 1 biologic therapy for atopic dermatitis such as, dupilumab, tralokinumab or lebrikizumab. Such participants must meet at least 1 of the following conditions:
     - Participants who stopped treatment due to non-response, partial response, loss of efficacy.
     - Participants who stopped treatment due to intolerance or AEs.

     Participants who have had prior exposure to a biologic therapy could have received it in either a marketed setting, or a research setting with documentation of the participants treatment allocation confirming prior exposure to active biologic therapy and not placebo.

   OR

- Biologic naive participants: who in addition to an inadequate response to optimization of non-pharmacological measures such as moisturizers, must meet at least 1 of the following conditions:
  - Participant with a recent history (≤6 months prior to the Screening visit) of inadequate response to a stable regimen of prescription topical medication
  - Participants for whom prescription topical medications are not tolerated
  - Participants where there is a concern for potential side effects, such as skin thinning or increased risk of hypothalamic-pituitary-adrenal suppression.

  Note: Inadequate response to a stable regimen of prescription topical medication (such as medium to high potency TCS or TCI) is defined as failure to achieve and maintain remission or low disease activity state (equivalent to an IGA score =0 [clear] to 2 [mild]) despite treatment for the recommended duration as per label or for the maximum duration recommended for the participant's treatment, whichever is shorter.

6. Apply a stable dose of non-medicated topical moisturizer at least twice daily for ≥7 days prior to the baseline visit.
7. Completed electronic diary entries for PP-NRS for a minimum of 4 of 7 days preceding randomization.
8. Willing and able to comply with all clinic visits and study-related procedures and questionnaires (able to read and understand the PRO questionnaires and able to use electronic devices)
9. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   - A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:
     - Is a WONCBP as defined in Section 10.4.

       OR
     - Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention period and for at least [redacted] after the last dose of study intervention (please note, however, that WOCBP wishing to be considered for the LTE, should maintain highly effective contraceptive use). The investigator should evaluate 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 pregnancy test (urine or serum as required by local regulations) at screening and within 24 hours before the first dose of study intervention.
     - If a urine test is positive or cannot be confirmed as negative (e.g., an ambiguous result) a serum pregnancy test is required. In such case, 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.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1. Medical Conditions

1. History of anaphylaxis as defined by the Sampson Criteria [Sampson, 2006]
2. History of significant allergies to monoclonal antibodies
3. Clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA, dermatosis, toxic epidermal necrolysis or Stevens-Johnson syndrome, and exfoliative dermatitis).
4. Other types of eczema such as allergic contact dermatitis
5. Any other concomitant skin disorder (e.g., generalized erythroderma such as Netherton's Syndrome, or psoriasis), pigmentation, or extensive scarring that in the opinion of the investigator may interfere with the evaluation of AtD lesions or compromise participant safety.
6. Chronic or acute infection requiring treatment with oral or IV antibiotics, antivirals, anti-protozoal, or antifungals within 4 weeks before the Screening visit or anytime between the Screening and Baseline visits.
7. Superficial skin infections within 1 week before the Screening visit or active infections (including localized infections), or history of recurrent infections (excluding recurrent fungal infections of the nail bed)
8. Known, pre-existing or suspected parasitic infection within 6 months before the Screening visit.
9. Symptomatic herpes zoster within 3 months prior to screening
10. Uncontrolled hypertension.
11. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
12. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., TB, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution or unusually frequent, recurrent, or prolonged infections, per the Investigator's judgment.
13. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years

14. Breast cancer within the past 10 years
15. History or presence of significant medical illness including but not limited to cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurological, or psychiatric disorders which in the opinion of the investigator would interfere with the study procedures and/or assessments.

5.2.2. Prior/Concomitant Therapy

16. Previously treated with any oral JAKi or other kinase inhibitors, experimental or approved (e.g., tofacitinib, abrocitinib, baricitinib, upadacitinib, filgotinib, peficitinib).
17. Prior treatment with any of the medications or treatments listed below within the indicated periods before the baseline visit.

Medication or Treatment	Timeframe prior to baseline visit
Use of medicated moisturizers (prescribed or over-the-counter) that are likely to impact participant's AtD	1 week
Herbal or traditional treatments likely to impact participants AtD	1 week
TCS or TCI or topical JAKi	1 week
Systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate, or any immunosuppressive therapy	4 weeks
Any biologic treatment for AtD, including but not limited to, dupilumab, tralokinumab, lebrikizumab or nemolizumab.	13 weeks for Dupilumab 15 weeks for Tralokinumab 18 weeks for Lebrikizumab 12 weeks for Nemolizumab For other biologics: 5 half-lives (if known) or [redacted], whichever is longer.
Specific dermatological treatments include phototherapy, treatment with phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA])	4 weeks
Regular use (more than 2 visits per week) of a tanning booth/parlor	4 weeks
Any investigational drug	8 weeks or within 5 half-lives (if known), whichever is longer
Treatment with a live or live attenuated vaccine	30 days of the baseline visit or planned to receive such vaccines during the study
Any other biologic treatment including but not limited to TNF inhibitors (e.g., etanercept, adalimumab), IL inhibitors (e.g., tocilizumab, anakinra) or T-cell inhibitors (e.g., abatacept) Please note that inclusion of any prior biologic other than those mentioned in Inclusion Criteria #5 should be discussed with the Medical Monitor prior to enrollment.	5 half-lives (if known) or [redacted], whichever is longer
B Cell-Depleting biologics, including rituximab	6 months

18. Uncontrolled chronic disease that might require bursts of oral corticosteroids, e.g., co-morbid severe uncontrolled asthma (defined by an ACQ-5 score ≥1.5 or a history of ≥2 asthma exacerbations within the last 12 months requiring systemic [oral and/or parenteral] corticosteroid treatment or hospitalization for >24 hours).

5.2.3. Prior/Concurrent Clinical Study Experience

19. Prior exposure to GSK1070806.
20. History of an allergic reaction or significant sensitivity to any constituents of the study drug (including excipients).

5.2.4. Diagnostic Assessments

21. Presence of HbsAg or HbcAb at screening or within 3 months prior to first dose of study intervention
    a. In addition, country specific requirement for participants from Japan and China sites: positive for HbsAb AND positive for HBV DNA
22. Positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained
23. Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing
24. Positive HIV antibody test
25. 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.
26. QTcF >450 msec or QTcF >480 msec in participants with bundle branch block at screening or Day 1 visit.
27. Have any of the following specific abnormalities on screening laboratory tests:
    a. ALT >1.5x ULN
    b. Total bilirubin >1.5xULN; Participants with Gilbert's syndrome can be included with total bilirubin >1.5xULN as long as direct bilirubin is ≤1.5xULN
    c. Hemoglobin <10 g/dL (100 g/L)
    d. Evidence of renal insufficiency, indicated by estimated creatinine clearance <60 mL/min/1.73m^2 at screening
    e. Total white blood cell count <3.0 x 10^9/L (<3000/mm^3)
    f. Absolute neutrophil count of <1.5 x 10^9/L (<1500/mm^3)
    g. Absolute lymphocyte count of <0.8 x 10^9 /L (<800/mm^3)
    h. Platelet count of <100 x 10^9/L (<100,000/mm^3)

28. In the Investigator's opinion, any clinically significant laboratory results from the chemistry, hematology or urinalysis tests obtained at the screening visit.

5.2.5. Other Exclusion Criteria

29. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.
30. Participants will be excluded from the optional CCI [redacted] sub-study if they have a history of severe skin allergy or hypersensitivity.
31. Participants with known allergy to CCI [redacted]
32. Planned surgery which requires general anesthesia that would take place during the study. Planned surgery which requires only local anesthesia, and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and participant safety.

5.3. Lifestyle considerations

5.3.1. Meals and dietary restrictions

No specific restrictions.

5.3.2. Caffeine, alcohol, and tobacco

There are no restrictions on ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate). However, extensive use of caffeine, alcohol, and tobacco should be avoided. In addition, changes in tobacco usage should also be avoided during the study.

Participants who use tobacco products will be instructed that smoking will not be permitted while they are in the site.

5.4. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, protocol deviations, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants are required to sign a new ICF and should be assigned a new participant number for every screening/rescreening event. Previously assigned participant numbers are to be recorded in the participants' eCRF.

All screening procedures and assessments should be repeated for rescreened participants.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational interventions, marketed products, placebo, intended to be administered to a study participant according to the study protocol.

6.1. Study interventions administered

An overview of the study interventions is provided in table below. Investigators should note the following:

Each participant will receive CCI SC CCI [redacted]

At each dosing visit, the injection will be administered in either the abdomen (at or under the level of and about 2 inches away from the navel) or thigh (anterior). As much as possible, avoid areas of skin with AtD lesions.

The injections must be performed at the site after completion of all pre-dose study assessments as per SoA including clinical assessments, ePROs, CCI [redacted]

All participants must receive general safety monitoring for approximately 2 hours after each dose CCI [redacted]. Safety monitoring will include monitoring of symptoms and signs for systemic hypersensitivity and local ISRs.

For ease of monitoring and documentation of any ISR by the investigator, a different anatomical site can be chosen at the CCI [redacted] visit, but this is not mandated. CCI [redacted], if the participant chooses the same anatomical site, it is recommended that the injection is administered >2 cm apart from the 1st dosing injection site. The participant must also be encouraged to choose a site with the most SC fat.

Unblinded pharmacist/unblinded authorized site staff will dispense the study medication and unblinded authorized site staff will administer the product.

Table 3 Study Interventions Administered

Intervention Label	CCI				Placebo
Study intervention name:	GSK1070806 Injection, 100 mg/mL	GSK1070806 Injection, 100 mg/mL	GSK1070806 Injection, 100 mg/mL	GSK107080 6 Injection, 100 mg/mL	Placebo 0.9% sodium chloride injection
Unit Dose Strength	100 mg/mL	100 mg/mL	100 mg/mL	100 mg/mL	0.9%
Dose levels	CCI				0.9% sodium chloride (SC) single injection
	SC injection	SC injection	CCI SC injection	CCI SC injection	
Type	Drug	Drug	Drug	Drug	Other
Dose formulation	CCI				Solution for injection; single dose placebo SC injection
Route of Administration	SC	SC	SC	SC	SC
Use	IMP	IMP	IMP	IMP	Placebo
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.	Provided centrally by the sponsor.	Provided centrally by the sponsor.	Provided locally by the study site, subsidiary, or designee.
Presentation	Study Intervention will be provided in CCI Each CCI will be labelled as required per country requirement.	Study Intervention will be provided in CCI. Each CCI will be labelled as required per country requirement.	Study Intervention will be provided in CCI. Each CCI will be labelled as required per country requirement.	Study Intervention will be provided in CCI. Each CCI will be labelled as required per country requirement.	Study intervention will be purchased commercially and used in its commercial container closure systems.
Type (study intervention or control)	Study intervention	Study intervention	Study intervention	Study intervention	Control

6.2. Preparation, handling, storage, and accountability

For the required dose, the study intervention will be administered through SC injection. 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 Pharmacy Manual.

The investigator or designee must confirm appropriate conditions (e.g., temperature) 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 unblinded authorized site staff may supply, prepare, or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions CCI with access limited to the investigator and authorized site staff.

The investigator, or authorized site staff 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 interventions are provided in the Pharmacy 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.

A MSDS/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

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

6.3. Assignment to study intervention

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits as summarized in the SoA. At screening a unique participant number will be assigned to any participant who has at least 1 screening procedure performed, other than informed consent. The unique participant number will be used to identify individual participants during the course of the study. Participants who meet the eligibility criteria will be randomized to a treatment group centrally through the IWRS, RAMOS NG. Randomization will be in accordance with a randomization schedule generated by GSK Randomization Office, prior to the start of the study, using validated internal software. Once a randomization number and/or participant number have been assigned to a participant, they will not be reassigned to any other participant in the study.

6.4. Blinding

Blinded study with unblinded pharmacist/unblinded authorized site staff who is dispensing intervention and/or unblinded authorized site staff who is administering the medication.	Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an unblinded authorized site staff will be responsible for the dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization. Also, an unblinded authorized site staff will administer the drug product as per the pharmacy manual and the syringe must be shielded from the participant to avoid unblinding. In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately.
Emergency unblinding	This is a double-blind study in which participants, investigator and the blinded site staff are blinded to study intervention. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact GSK to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded. If the investigator is unable to access the intervention system, they can contact the GSK helpdesk based on the information provided in the pharmacy manual. A physician other than the investigator (e.g., an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information as per participant card.

PK and PK PD studies	Designated independent representative(s) may be unblinded for preparing population [CCI redacted], including but not limited to: concentration-time data, dosing information, baseline demographic characteristics, and vital sign, laboratory, and PD information]. Details of [CCI redacted] data access will be specified in a separate analysis plan.
Primary analysis and reporting	Primary analysis and reporting will take place after the target number of participants have completed their week 16 (or early withdrawal) visit. GSK staff who have direct contact with sites will remain blinded to individual participant allocation until the end of study.

If the participant's intervention code is unblinded by the investigator or treating physician, the participant may continue in the study, however, must be withdrawn from study treatment. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

GSK's Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 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.

6.5. Study intervention compliance

Pharmacy manual should be followed when preparing study intervention for study participants.

When participants are dosed at the site, they will receive study intervention directly from the authorized unblinded site staff, under medical supervision via SC route. 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 the authorized unblinded site staff.

6.6. Dose Modification

[CCI redacted]

6.7. Continued access to study intervention after the end of the study

[CCI redacted]

CCI

[redacted]

6.8. Treatment of overdose

For this study, any dose of GSK1070806 greater than the planned top dose in the study, 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.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities following dosing until End of Study or until resolution, at the Investigator's discretion.
- Document the quantity of the excess dose in the eCRF.

6.9. Prior and concomitant therapy

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

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal/traditional supplements or remedies) or other specific categories of interest (topical therapies for AtD) that the participant is receiving at the time of screening 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, frequency and route of administration

6.9.1. Permitted Concomitant Therapies

Participants are to be instructed to apply a stable dose of non-medicated topical moisturizer or emollients at least twice daily for ≥7 days prior to the baseline visit.

Non-medicated moisturizers or emollients are to be used during the study. Participants may continue their current non-medicated over-the-counter moisturizer regimen, if approved by the Investigator.

The use of concomitant medications for other medical conditions (e.g., hypertension, diabetes, and hypercholesterolemia) is permitted during this study.

Routine inhaled treatments, such as inhaled corticosteroids and bronchodilators to control asthma are permitted.

The following concomitant therapies are permitted under the conditions described:

- Antihistamines, oral or topical, (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.
- Other concomitant medication may be considered on a case-by-case basis by the investigator (and in consultation with the Medical Monitor if required).
- Medicated topical treatments (such as TCS) will be permitted from Week 16 to Week 28

Every effort should be made to maintain permitted concomitant therapies at a stable dose/regime throughout the treatment period to Week 16.

6.9.2. Prohibited Medications

Medications prohibited between Screening and Week 16 are as follows, owing to their potential to confound safety and efficacy assessments:

- Topical treatments:
  - TCS (e.g., hydrocortisone, betamethasone)
  - TCI (e.g., tacrolimus, pimecrolimus)
  - Topical PDE4 inhibitors (e.g., crisaborole)
  - Topical JAKi (e.g. ruxolitinib)
  - Any other medicated topical treatment or herbal/traditional remedies likely to impact the participants AtD.

Medications prohibited between Screening and Week 28 are as follows, owing to their potential to confound safety and efficacy assessments:

- Systemic treatments (Oral or injectable):
  - Immunosuppressants:
    - Corticosteroids (e.g., prednisolone, budesonide)
    - Calcineurin inhibitors (e.g., tacrolimus, cyclosporin)
    - JAKi (e.g., abrocitinib, baricitinib, upadacitinib)
    - IMDH inhibitors (e.g., mycophenolate mofetil)
    - Monoclonal Antibodies (e.g., dupilumab, tralokinumab, lebrikizumab)

  - Any other immunosuppressive therapy or biologic including, but not limited to, TNF inhibitors (e.g., entanercept, adalimumab), IL inhibitors (e.g., tocilizumab, anakinra), B-cell inhibitors (e.g., rituximab) or T-cell inhibitors (e.g., abatacept)

- Other treatments:
  - Phototherapy
  - Live or Live attenuated vaccines
  - Planned or anticipated major medical procedures or surgeries should be avoided during the trial.
  - Regular use (more than 2 visits per week) of a tanning booth/parlor should be avoided.

Participants who experience intolerable AtD symptoms, please refer to section "rescue" (Section 6.9.3) for guidance.

If a participant requires any of the prohibited medications described above to address an urgent clinical need, these should be discussed with Medical Monitor if this is possible without delaying the adequate treatment of the participant.

6.9.3. Rescue Medications

Investigators should attempt to manage participants with non-medicated treatments such as moisturisers or emollients, however, investigators are allowed to rescue participants who are experiencing unacceptable or worsening symptoms of AtD at any time if absolutely required. Prior to initiating rescue, it is recommended to increase the frequency of non-medicated treatments such as emollient at least twice a day or more in an effort to control symptoms.

If not controlled, consider the addition of low/moderate potency TCS (e.g., triamcinolone acetonide 0.1% cream, hydrocortisone 1% cream). Investigators may also select to use TCIs and/or crisaborole where approved, although use of this during the study is not encouraged. If TCIs are prescribed, use should be limited to problem areas only (e.g., face, neck, folds, genital areas, etc.).

In participants who do not improve sufficiently with the provided rescue topical therapy after 7 days, a higher potency TCS may be used.

If topical rescue therapy as described above fails to sufficiently control AtD symptoms, then oral systemic medications may be used as rescue (e.g., corticosteroids, cyclosporine, methotrexate); however, the investigational product will be required to be permanently discontinued for the remainder of the study duration and the participant will not be eligible for the separate LTE study.

Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit can be used for this purpose if necessary.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if possible, continue other study procedures (e.g., safety or immunogenicity) planned in the study protocol according to the visit schedule described in the SoA (Section 1.3). If the participant does not agree to continue in-person visits, a modified follow-up must be arranged to ensure the collection of endpoints (including ePROs where possible [i.e., those captured on an eDiary]) and safety information (e.g., telephone contact, retrieval of vital status information through medical records). See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

In the event of any of the following, the participant must be withdrawn from study intervention:

- Serious hypersensitivity reactions
- New latent or active TB infection
- Other serious or severe infection AEs, exclusively at the discretion of the Investigator, preferably after consultation with the Medical Monitor.
- Liver event stopping criteria – see Section 7.1.1
- QTc stopping criteria – see Section 7.1.2
- The participant requires major surgery; surgery which requires general anesthesia at any point throughout the study period.
- Pregnancy – see Section 8.4.6
- Inability to adhere to protocol-specified restrictions or procedures at the discretion of the Investigator after consultation with the Medical Monitor.
- Withdrawal of informed consent
- Lack of efficacy (as assessed by Investigator)

The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the list below:

Reasons
AE
Lack of efficacy
Lost to follow-up
Participant Reached Protocol-Defined Treatment Stopping Criteria
Physician Decision
Pregnancy
Protocol Deviation
Site Terminated by Sponsor
Study Terminated by Sponsor
Withdrawal by Participant
Other
Death

Participants who withdraw from study intervention will not be eligible to participate in CCI

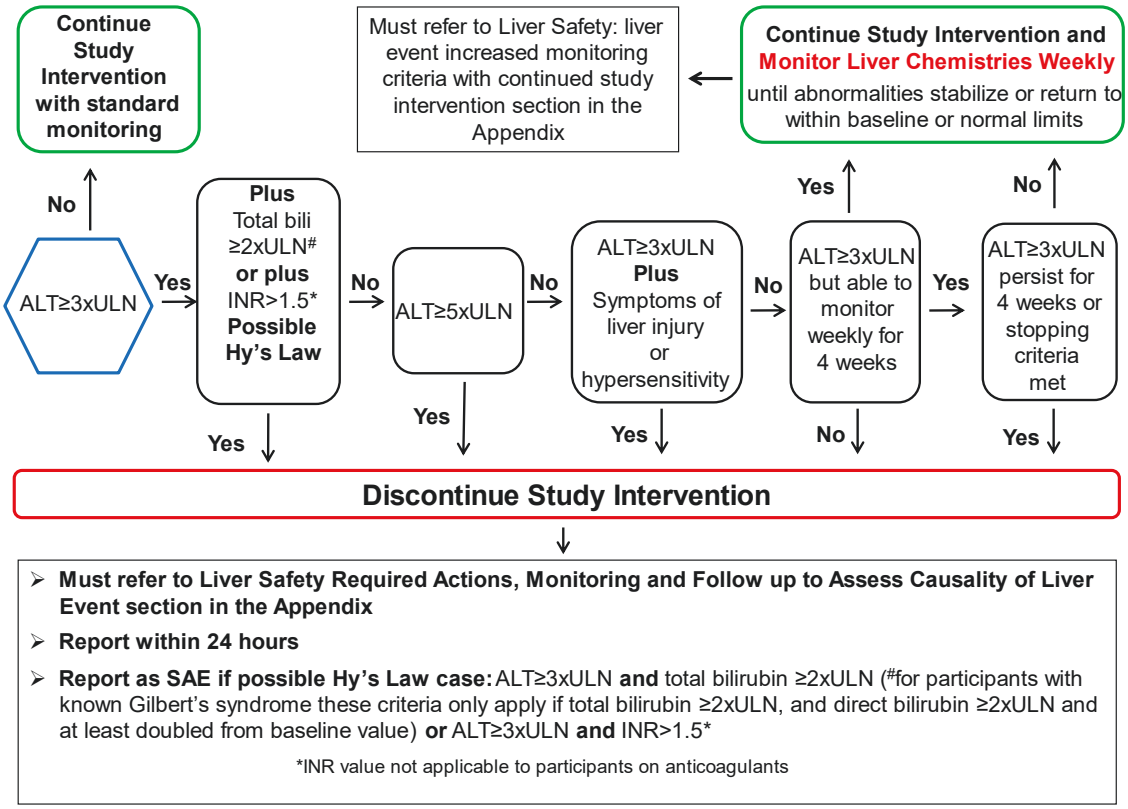
7.1.1. Liver event stopping criteria

Liver event stopping criteria with increased monitoring and required follow-up assessments have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of the study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in best interest of the participant.

Figure 4 Liver event study intervention stopping criteria and liver event increased monitoring criteria with continued study intervention algorithm



ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

Refer to Section 10.6.1 for required liver safety actions, monitoring and follow-up to assess causality of liver event.

Participants who do not meet protocol-specified liver event stopping criteria but met protocol-defined increased monitoring criteria may continue study intervention with increased (weekly) liver chemistry monitoring. Refer to Section 10.6.2 for required liver event increased monitoring criteria with continued study intervention.

7.1.2. QTc Stopping criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment, the investigator or qualified designee will determine if the participant can continue the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A participant who meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study intervention:

- QTc >500 msec OR Uncorrected QT >600 msec
- CFB of QTc >60 msec
- For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

7.1.3. Temporary discontinuation

- Serious infections, opportunistic infections, or suspected TB:
  - If a serious infection, opportunistic infection, or suspected TB develops, temporarily delay study intervention until the infection resolves and discuss further management with the Medical Monitor prior to administering the study intervention.

7.1.4. Rechallenge

7.1.4.1. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant is not allowed in this study.

7.2. Participant discontinuation/withdrawal from the study

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

A participant may discontinue from the study intervention at any time at the participant's own request for any reason (or without providing a reason). Investigators will make all reasonable attempts to encourage the participant to continue participating in the study, with visits as shown in the SoA, regardless of discontinuation from study intervention.

Furthermore, a participant may concurrently or subsequently withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of discontinuing from the study, if possible, an EW visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. 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, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant discontinuation/ withdrawal from the study will be documented in the eCRF based on the list below:

Reasons
AE
Lack of efficacy
Lost to follow-up
Participant Reached Protocol-Defined Treatment Stopping Criteria
Physician Decision
Pregnancy
Protocol Deviation
Site Terminated by Sponsor
Study Terminated by Sponsor
Withdrawal by Participant
Other
Death

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.5.5).

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant 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, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at least 3 telephone calls, and if necessary, a tracked 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, the participant 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 of the participant 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.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- 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. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, is provided in the ICF.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as year of birth, sex, race, and ethnicity in the participant's medical record and the eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant and review of the participant's medical record. Record any pre-existing conditions, signs and/or symptoms present prior to study start in the eCRF.

8.2. Efficacy Assessments

8.2.1. Clinical Assessments

Refer to Section 1.3 for the scheduling of Clinical Assessments.

8.2.1.1. Eczema Area and Severity Index (EASI)

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

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

Assessors must be trained by an approved vendor at the Sponsor's direction prior to conducting this assessment. A single assessor (if possible) should be assigned for each participant throughout the study for as many visits as possible, to avoid inter-assessor variability in scoring.

8.2.1.2. Investigator Global Assessment (IGA)

IGA for AtD 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:

Score	Grade	Definition
0	Clear	Minor, residual discoloration; no erythema or induration/papulation; no oozing/crusting; no edema.
1	Almost Clear	Trace, faint pink erythema with barely perceptible induration/papulation and no oozing/crusting; no edema.
2	Mild	Faint-pink erythema with papulation and edema perceptible upon palpation and no oozing/crusting; minimal induration.
3	Moderate	Pink-red erythema with definite edema of skin papules and plaques; there may be some oozing/crusting; palpable induration.
4	Severe	Deep/bright red erythema with significant swelling and obvious raised borders of papules and plaques with oozing/crusting; significant induration.

The IGA must be conducted prior to conducting the EASI and BSA assessments.

Assessors must be trained by an approved vendor at the Sponsor's direction prior to conducting this assessment. A single assessor (if possible) should be assigned for each participant throughout the study for as many visits as possible, to avoid inter-assessor variability in scoring.

8.2.1.3. Body Surface Area (BSA)

The BSA assessment estimates the extent of disease or skin involvement with respect to AtD and is expressed as a percentage of total body surface. BSA will be determined by the Investigator or designee using the patient palm = 1% rule.

Assessors must be trained by an approved vendor at the Sponsor's direction prior to conducting this assessment. A single assessor (if possible) should be assigned for each participant throughout the study for as many visits as possible, to avoid inter-assessor variability in scoring.

8.2.1.4. Scoring Atopic Dermatitis (SCORAD)

SCORAD is a clinical tool to assess the extent and severity of AtD. The tool comprises of 3 components:

- Part A: extent of disease (investigator assessed), scored as 0 to 102%.
- Part B: intensity of 6 signs of AtD, which include erythema, oedema/papulation, excoriation, lichenification, oozing/crusting and dryness. These signs are investigator assessed and graded as 0 to 3. Signs scores of 0 correspond to none, 1 correspond to mild, 2 correspond to moderate, and 3 correspond to severe.
- Part C: assessments of pruritus (itch) and sleep loss. These symptoms are participant/caregiver assessed and reported as the average value for the last 3 days or nights using a visual analogic scale (VAS) (0–10).

To compute the total score, the following SCORAD index formula is used: A/5 + 7B/2 + C. In this formula A is defined as the extent (0-100), B is defined as the intensity (0-18) and C is defined as the subjective symptoms (0-20). The maximum SCORAD score is 103.

8.2.2. Patient Reported Outcomes (PROs)

Refer to Section 1.3 for the scheduling of PROs. The PROs will be administered to participants in different regions based on the availability of translated versions.

8.2.2.1. Peak Pruritus Numerical Rating Scale (PP-NRS)

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

Participants need to complete the assessment once daily in their e-Diary at approximately the same time each day from 14 days before Day 1 through Week 28. The weekly score is based on the average of daily PP-NRS scores for maximum itch intensity reported during the 7 days prior. The weekly score will be set to missing if there are fewer than 4 daily scores recorded in the 7 days prior. Percentage of patients with a PP-NRS of ≥4 points at baseline who achieve a ≥4 -point reduction from baseline to Week 16 will be analyzed.

8.2.2.2. Skin Pain Numerical Rating Scale (SP-NRS)

SP-NRS is a patient reported measure assessing **worst** level of skin pain (in the past 24 hours) using an 11-point scale (from 0 to 10), with 0 being no pain and 10 being the worst pain imaginable.

Participants need to complete the assessment once daily in their e-Diary at approximately the same time each day from 14 days before Day 1 through Week 28 and are asked the following question in their local language: "Please rate your skin pain severity by circling the number that best describes your worst level of skin pain (for example, discomfort or soreness) in the past 24 hours."

8.2.2.3. The Brief Fatigue Inventory (BFI)-Item 3

The BFI is a self-administered questionnaire developed to assess fatigue severity for use both in clinical screening and clinical trials [Mendoza, 1999]. The BFI has 9 items. BFI item 3 assesses the **worst** level of fatigue related concepts (i.e., tiredness, weariness) during the past 24 hours. Participants report their worst level of fatigue daily, for the previous 24 hours, using a numerical rating scale ranging from 0 (no fatigue) to 10 (as bad as you can imagine).

Participants need to complete the assessment once daily in their e-Diary at approximately the same time each day from 14 days before Day 1 through Week 28 and are asked the following question in their local language: “Please rate your fatigue (weariness, tiredness) by circling the 1 number that best describes your worst level of fatigue during past 24 hours.”

8.2.2.4. The Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance

The PROMIS Short Form Sleep disturbance 8b is a PRO instrument designed to assess self-reported sleep disturbance for which the recall period is the past 7 days.

The items are rated on a 5-point verbal rating scale. Items are summed giving a range in raw score from 8 to 40, with higher scores indicating greater severity of sleep disturbance.

Raw scores are converted to T-scores [Lei, 2020]. The T-score rescales the raw score into a standardized score with a mean of 50 and a SD of 10.

8.2.2.5. Patient Global Impression of Severity (PGIS)-Sleep Disturbance

The PGIS-Sleep Disturbance is a single item scale that allows participants to rate the overall severity in their sleep disturbance as caused by AtD. It measures static, current state patient global impression of overall severity of sleep disturbance. It is used as an anchor in analyses to evaluate threshold of clinically meaningful within-patient change and may be used for additional validation analyses.

8.2.2.6. The Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-Fatigue)

The FACIT-Fatigue scale is a short, 13-item measure that assesses self-reported fatigue and its associated impact for daily activities over the past week. The items are rated on a 5-point Likert-type scale (i.e., 4 = not at all to 0 = very much). The scale range is 0 to 52, with 0 being the worst possible score and 52 being the best possible score (indicating no fatigue) [Montan, 2018].

8.2.2.7. Patient Global Impression of Severity (PGIS)-Fatigue

The PGIS-Fatigue is a single item scale that allows participants to rate the overall severity in their fatigue as caused by AtD. It measures static, current state patient global impression of overall severity of fatigue. It is used as an anchor in analyses to evaluate threshold of clinically meaningful within-patient change and may be used for additional validation analyses.

8.2.2.8. Patient Global Impression of Severity and Change (PGIS and PGIC)-nocturnal scratching

These scores will be used as an anchor to support determination of the MCID for the CCI -based nocturnal scratch. PGIS and PGIC on nocturnal scratch should be assessed for all participants to help understand the impact, if any, of wearing the CCI device on their night-time scratching.

8.2.2.9. 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 QoL 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 (not at all) to 3 (very much).

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

8.2.2.10. Patient Oriented Eczema Measure (POEM)

POEM is a 7-item questionnaire that assesses symptoms of dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping over the last week. The scoring symptom ranges from 0 (absent disease) to 28 (severe disease). Higher score indicates poor QoL.

8.2.2.11. Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-reported questionnaire which measures depression and generalized anxiety, in the past week. Each item on the questionnaire ranges from 0 (no, not at all) to 3 (yes, definitely). The scale ranges from 0 to 21, with lower score indicating better QoL.

8.2.2.12. Work Productivity and Activity Impairment Questionnaire-Atopic Dermatitis (WPAI-AD)

The WPAI-AD is a validated, patient-reported, quantitative assessment of absenteeism (work time missed), presentism (reduced on-the-job effectiveness), work productivity loss and activity impairment due to a specific health problem.

8.2.2.13. Asthma Control Questionnaire (ACQ-5)

ACQ-5 measures adequacy of clinical asthma control. It is a 5-item questionnaire that is scored on a 7-point Likert scale with a recall period of 1 week. The ACQ-5 has been shown to reliably measure asthma control and distinguish participants with well-controlled asthma (score ≤0.75 points) from those with uncontrolled asthma (score ≥1.5 points). The total ACQ-5 score is the mean score of all questions, a lower score indicated better asthma control.

The ACQ-5 would be assessed only in participants with known history of asthma.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA. The participant will be encouraged to always contact the site in case of any AE.

8.3.1. Physical examination

- A full physical examination will include, at a minimum:
  - General Appearance
  - Head & Neck (Ears, Nose & Throat)

  - Respiratory System
  - Cardiovascular System
  - Gastrointestinal System
  - Neurological System
  - Musculoskeletal System
  - Lymphatic Body Systems
  - Skin (except Atopic Dermatitis)
- A brief physical examination will include:
  - Cardiovascular system
  - Lungs
  - Abdomen (including liver and spleen)
  - Skin (except Atopic Dermatitis)
- A targeted (symptom-directed) physical examination may be conducted at the discretion of the Investigator and will be reported as an unscheduled assessment. Any abnormal clinically significant finding will be recorded as an AE in the eCRF.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests).
- Blood pressure and pulse measurements will be assessed in semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure, pulse measurements and respiratory rate should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- All blood pressure readings will be recorded in source documents and in the eCRF.

8.3.3. Electrocardiograms

- 12-lead ECG(s) 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 QTc intervals. Refer to Section 7.1.2 for QTc stopping criteria and any additional QTc readings that may be necessary.

- ECG measurements will be made after the participant has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments followed by other study procedures. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.
- Paper ECG traces will be recorded at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip. Paper ECG traces are required to be maintained at the site with other source documents.
- If a routine ECG demonstrates a prolonged QT interval, obtain 2 more ECGs (triplicate) as closely as possible in succession, but no more than 2 minutes apart, and then use the averaged QTc values of the 3 ECGs to determine whether the participant should be discontinued from the study intervention (but not from the study). Refer to Section 7.1.2 for QTc stopping criteria.
- All ECGs will be read locally, and paper ECGs will be kept at study sites as source documents.
- If the ECG machine does not automatically calculate the QTc interval according to Fridericia's formula (QTcF), site staff should use the below equation to manually calculate the QTcF and document the result in the participant's medical record.
    - $QTcF = QT/\sqrt[3]{((60)/HR)}$ QTcF result in msec,
    - QT in msec, HR in bpm

8.3.4. Clinical safety laboratory tests

- See Section 10.2 Appendix 2 for the list of clinical laboratory tests to be performed in accordance with lab manual and the SoA (Section 1.3).
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with 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 after the last dose of study intervention should be repeated as deemed necessary and until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Section 10.3.1 and Section 10.3.2).
    - 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.

- 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), then the results must be recorded.

8.3.5. Pregnancy testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Female participants of childbearing potential must perform a urine pregnancy test within 24 hours before each dose of study intervention (or a serum pregnancy test if required by local regulations (e.g.: country or IRB/EC). Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative on the days of drug administration (i.e., CCI [redacted]
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at specific intervals per the SoA (Section 1.3) during study intervention period for all WOCBP. If a urine test is positive or cannot be confirmed as negative (e.g., an ambiguous result) a serum pregnancy test is required. In such case, the participant must be excluded if the serum pregnancy result is positive.
- Urine pregnancy testing (or serum if 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.
- Refer to Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.3.6. Study safety monitoring and Committee

- Participant safety will be continuously monitored by the Medical Monitor, designated Safety Lead (or delegate) and sponsor's internal committee, throughout the study. Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit-risk profile of the product.
- The study will include an iDRC that will conduct the interim analysis and review interim data periodically throughout the trial to determine appropriate recommendations for study conduct and enabling activity for the wider development plan in accordance with the iDRC Charter.

8.4. Adverse Events (AEs), serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information, see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up all AEs OR AEs that are serious, considered related to the study intervention, or that caused the participant to discontinue the study intervention or study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR).

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, SAE, and other safety information

SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study.

All AEs and SAEs will be collected from the start of study intervention until follow-up visit at the timepoints specified in the SoA.

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 immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in this section.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

See Section 8.4.8 for contact information.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

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 and AEs of special interest (as defined in Section 8.4.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.5.5.

8.4.4. Adverse Events of Special Interest

The potential risks of GSK1070806 are discussed in Section 2.3.1.

AESIs for GSK1070806 include:

- Serious infections
- Opportunistic infections
- Serious hypersensitivity reactions
- ISRs

8.4.5. 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.3.
- 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

Table 4 Timeframes for submitting SAE and pregnancy reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAE	24 hours*‡	electronic Adverse Events Report	24 hours*	Electronic Adverse Events Report
Pregnancy	24 hours*	paper pregnancy notification report	24 hours *	Paper pregnancy follow-up report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡ Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.4.6. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

- Details of all pregnancies in female participants will be collected after the start of study intervention and for at least [redacted] after the last dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- 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 female 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. See Table 4 for reporting timeframes.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.7. CV and death events

For any CV events detailed in Section 10.3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the eCRF within 1 week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

8.4.8. Contact information for reporting SAEs, AESIs and pregnancies

Table 5 Contact information for reporting SAEs, AESIs and pregnancies

Study contact for questions regarding SAEs, AESIs and pregnancies Contact GSK's local and/or medical contacts
Contact for reporting SAEs, AESIs and pregnancies. Email: oax37649@gsk.com Fax: +44(0) 20 81814780

8.4.9. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/ caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.5. Pharmacokinetics

Blood samples for PK analysis of GSK1070806 will be collected at the time points specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each blood sample collection will be recorded in the CRF. Instructions for the collection, processing, storage, and shipment of the samples will be described in the Lab Manual.

These samples may also be used for assay validation purposes related to this study and future assessments will be limited to explore other conditions where this mechanism of action may play a role and/or to develop new methods and tests. All samples will be retained for a maximum of 20 years after the last participant completes the trial.

8.6. Pharmacodynamics

Serum and plasma samples will be collected for the measurement of Total IL-18, CCI [redacted] at the time points specified in the SoA (Section 1.3). The actual date and time of each blood sample collection will be recorded in the CRF. Instructions for the collection, processing, storage, and shipment of the samples will be described in the Lab manual.

These samples may also be used for assay validation purposes related to this study and future assessments will be limited to explore other conditions where this mechanism of action may play a role and/or to develop new methods and tests. All samples will be retained for a maximum of 20 years after the last participant completes the trial.

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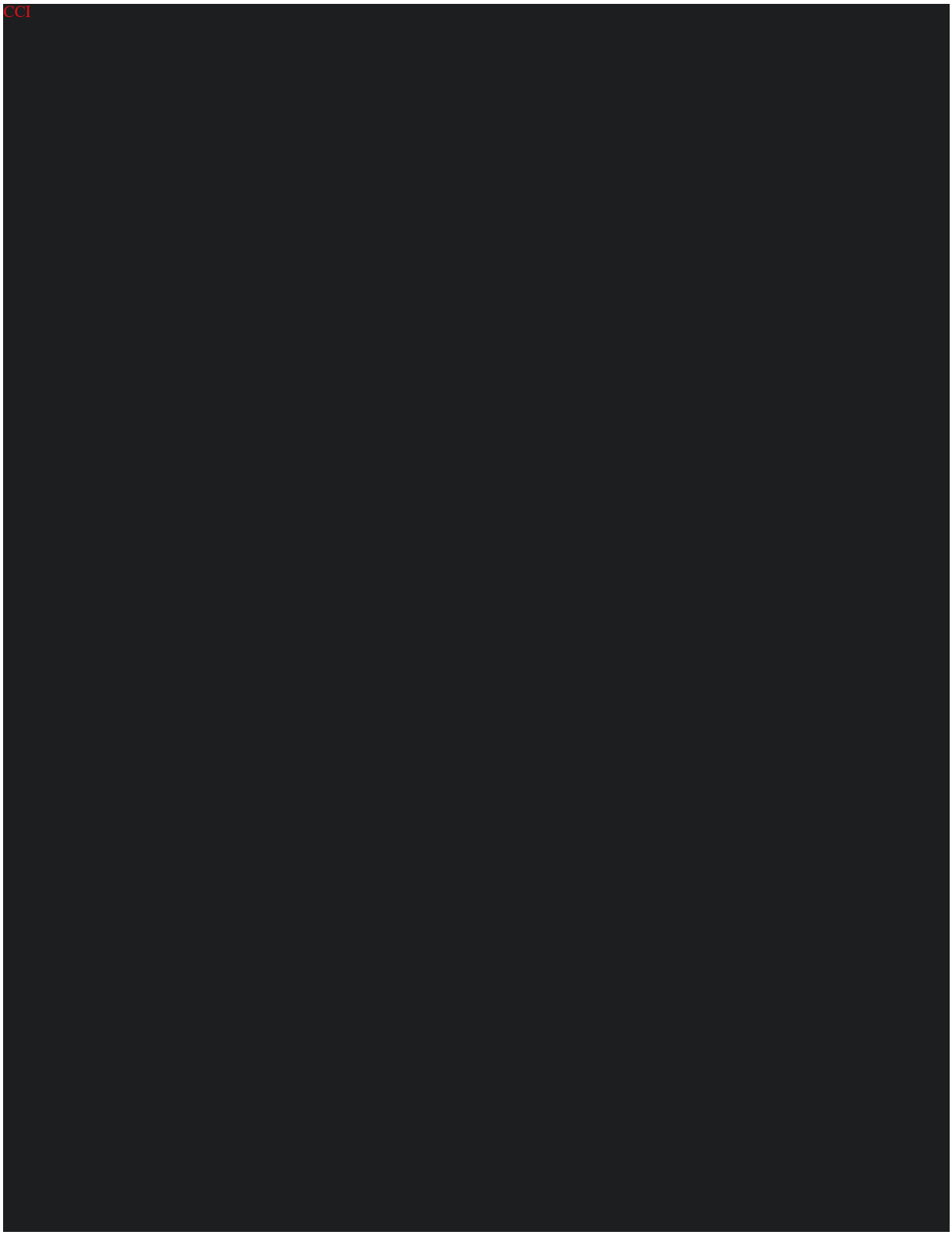

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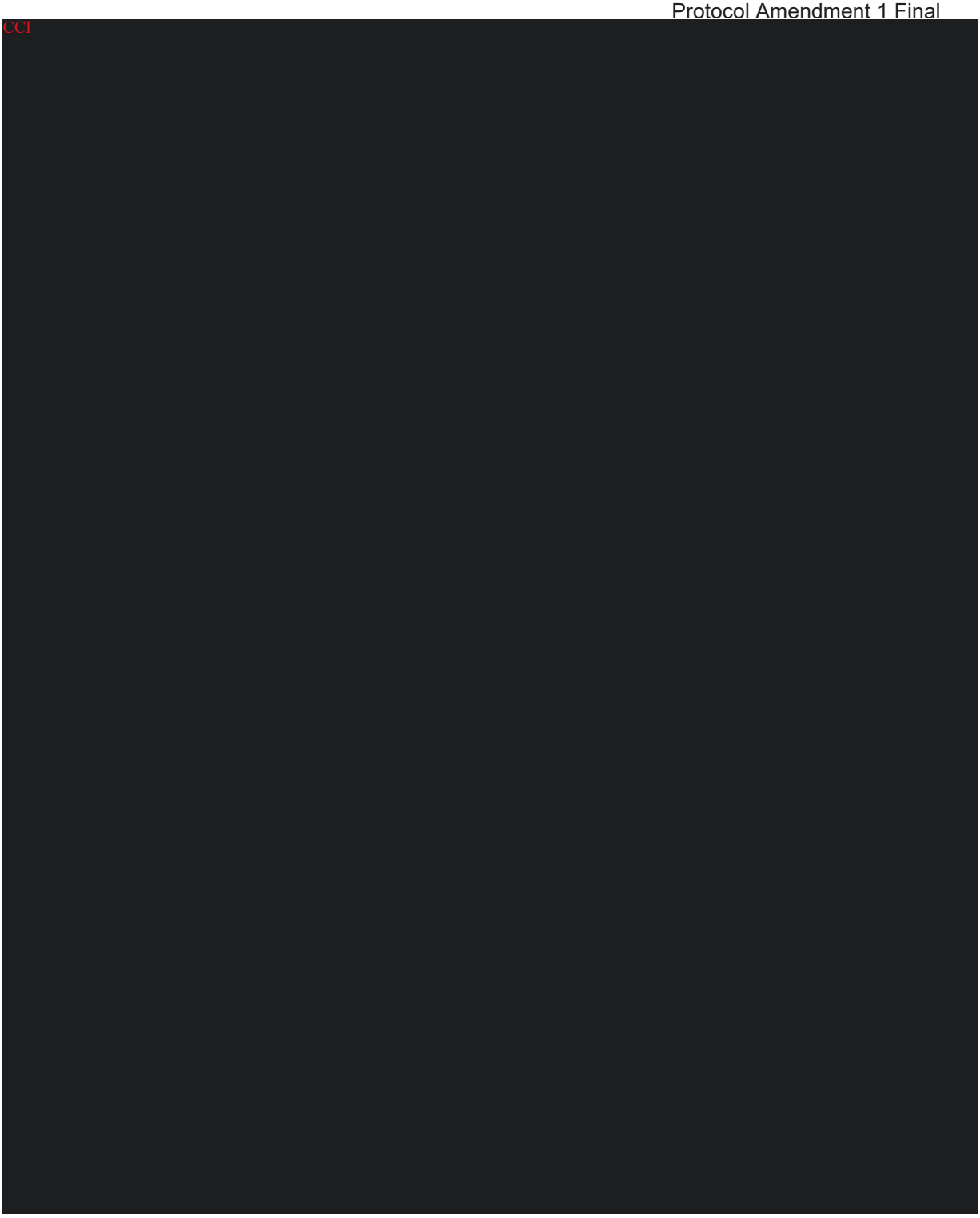

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8.9. Immunogenicity assessments

Antibodies to GSK1070806 will be evaluated in serum samples collected 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.

Serum samples will be screened for antibodies binding to GSK1070806 and the titre of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of GSK1070806. These samples may also be used for assay validation purposes related to this study and future assessments will be limited to explore other conditions where this mechanism of action may play a role and/or to develop new methods and tests.

Samples may be stored for a maximum of 20 years after the last participant completes the trial.

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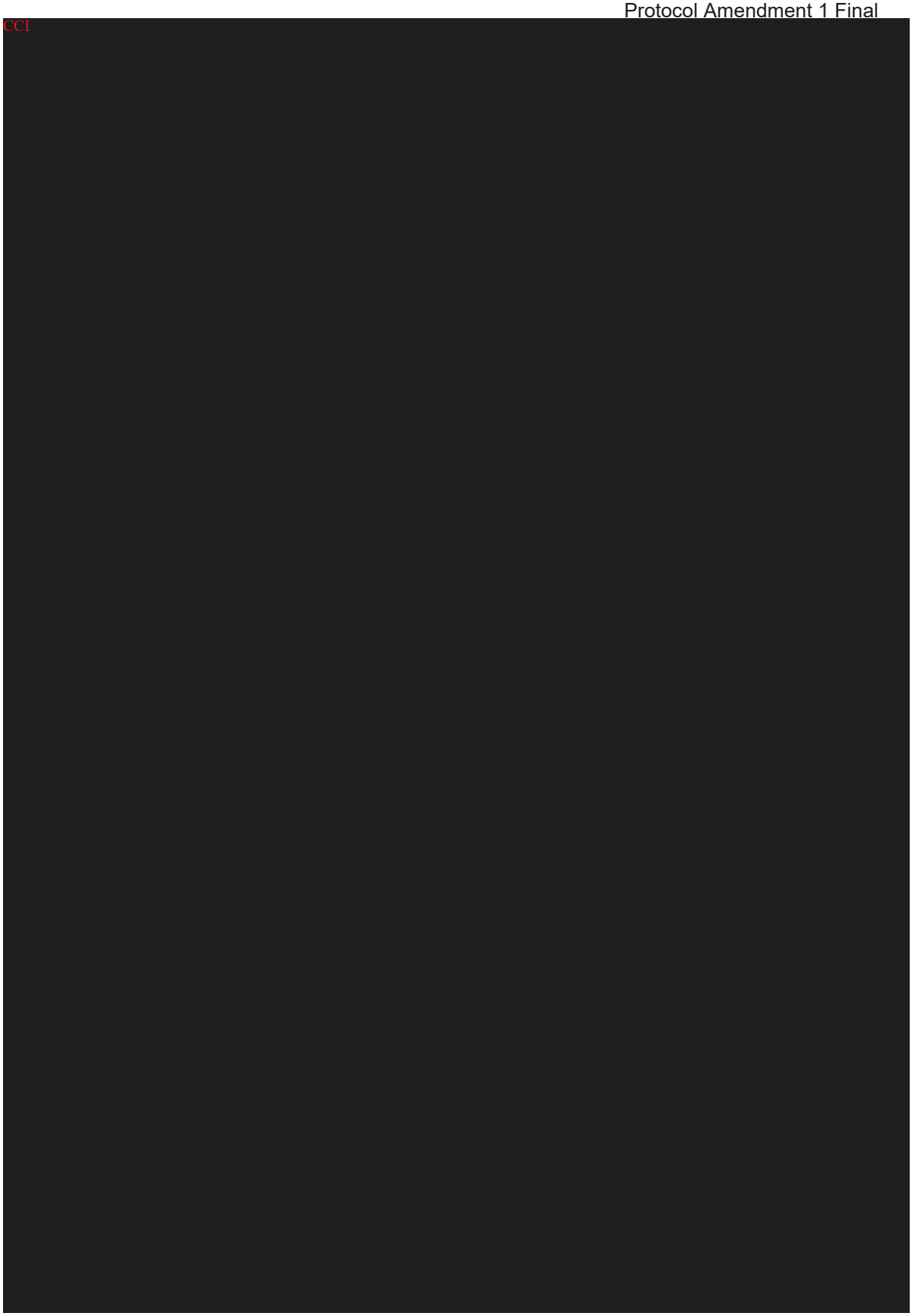

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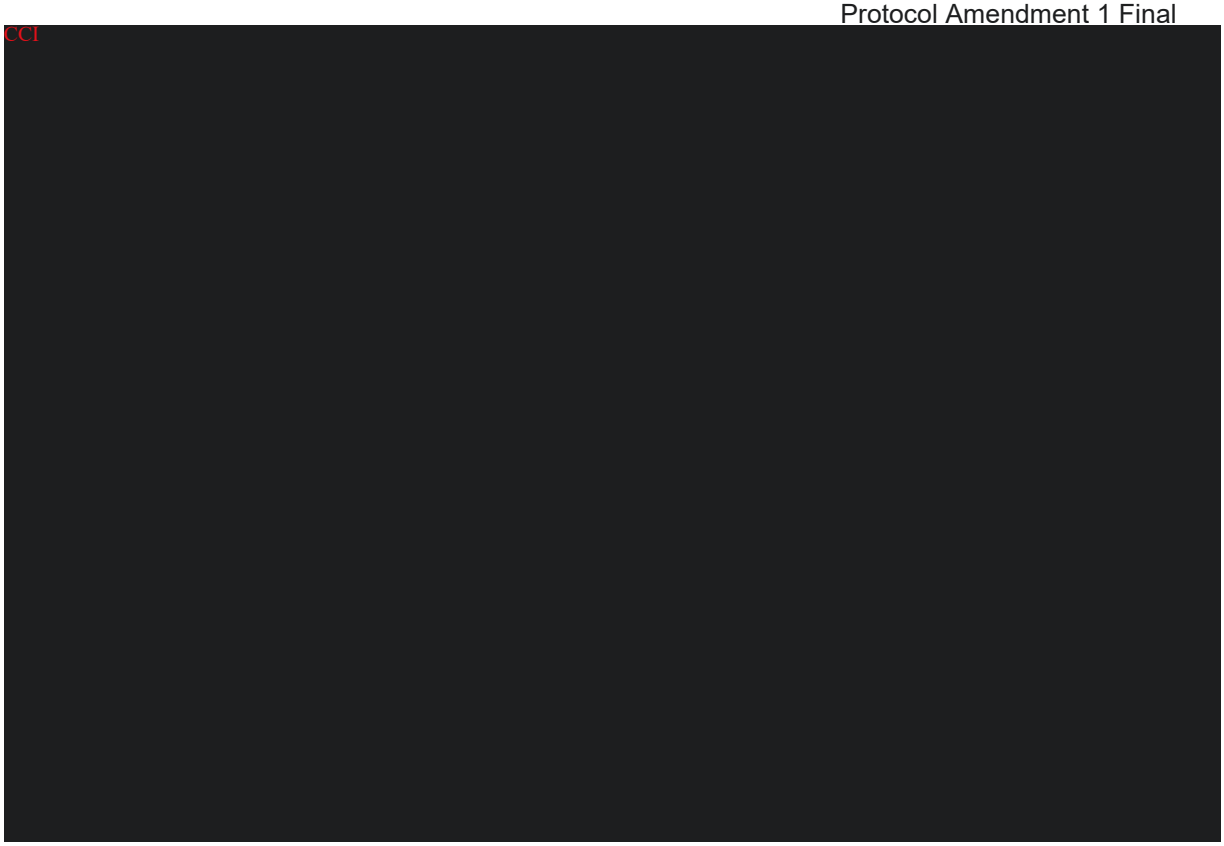

8.12. Health economics or medical resource utilization

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The SAP 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.

9.1. Statistical hypotheses

An estimation approach with no hypothesis testing will be used to address the primary objective. For the primary estimand, a Bayesian analysis will be utilized with a non-informative prior for the true treatment difference. It is assumed that the PCFB EASI follows a normal distribution with a non-informative prior for the true treatment difference. The primary assessments of interest are the point estimates of the treatment difference in PCFB EASI and 95% credible intervals; in addition, posterior probabilities that the true treatment difference in each active treatment arm versus placebo is greater than a range of clinically meaningful differences given the observed differences will be provided. Comparisons relative to the key secondary/exploratory objectives will be assessed using probability inference approaches.

9.1.1. Multiplicity Adjustment

An estimation approach with no hypothesis testing will be performed and therefore multiplicity adjustments are not applicable.

9.2. Analysis Sets

Table 6 Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	Study Population
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Randomized	• All participants who were randomly assigned to study intervention in the study. • This population will be based on the treatment the participant was randomized to. • All participants who receive a treatment randomization number will be considered to have been randomized.	Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
Safety	• All participants who received at least 1 dose of study intervention. • This population will be based on the treatment the participant actually received. In the situation where CCI [redacted] treatments were received; the participant will be assigned to the treatment of highest dose received. Full details will be provided in the SAP. • Note: Participants who were not randomized but received at least 1 dose of study treatment should be listed.	Safety Biomarker PD
Full Analysis Set (FAS)	• All randomized participants who received at least 1 dose of study treatment. • This population will be based on the treatment the participant was randomized to.	Study Population Efficacy
PK	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	PK
Immunogenicity	• All participants in the Safety analysis set who had at least 1 Immunogenicity sample collected with analysis result.	Immunogenicity
CCI [redacted]		Study Population Efficacy

9.3. Statistical analyses

9.3.1. General considerations

The SAP 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. Any changes to the original planned analysis given in this section of the protocol will be described in the SAP and/or the CSR.

All statistical analyses will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely accepted statistical or graphical software as required. Data will be presented in listings, tables, and figures. Binary and categorical variables expressed as n (%), and continuous variables as presented as mean with standard deviation or as median with interquartile range, depending on distribution.

The primary study analysis and reporting will be conducted when all randomized participants have completed their Week 16 (or Early Withdrawal) study visit. An end of study analysis will take place when all randomized participants have completed the study (including the off-treatment follow-up period). Recruitment may continue to include additional participants, increasing by up to 15% of the target sample size, if regional and/or CCI [redacted] recruitment targets have not been met. Consequently, the primary analysis may be delayed accordingly.

Unless otherwise specified, baseline will be the last value/assessment before the first dose of study treatment (Day 1 pre-dose). If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used as the baseline. If baseline data is missing, no derivation will be performed, and baseline will be set to missing.

For the cases that repeated measurement model is employed to analyze the data, an unstructured correlation matrix will be considered to account for multi-collinearity of repeated measurements data.

Non-informative priors will be used for the Bayesian analyses, with full details provided in the SAP.

9.3.2. Primary endpoint analysis

The primary endpoint is PCFB in the EASI score measured at Week 16. Further details of the estimands are described in Section 3.

A Bayesian repeated measures linear model will be fitted to the PCFB response at CCI [redacted] including baseline EASI score, region (China versus Japan, versus Rest of World), CCI [redacted], week (categorical) and treatment as well as interactions for treatment-by-week, baseline EASI score-by-week using an unstructured covariance matrix to handle repeated measures.

The treatment difference for GSK1070806 CCI [redacted] from placebo at Week 16 from this model will be summarized as Mean, SD, Median and 95% credible interval of the posterior distribution.

For the primary estimand, all data collected after the ICE of use of rescue therapy (before Week 16) is ignored and imputed with the participant's worst observation across all their previous observations prior to the ICE (including baseline and post-baseline).

All data collected after the ICE of treatment discontinuation due to extreme administrative or operational disruptions is ignored and as per the hypothetical strategy will be imputed under an MAR assumption.

All data collected after the ICE of permanent treatment discontinuation for any reason before [redacted] will be included. All data that is missing due to this ICE, under the treatment policy strategy, will be imputed based on participants who discontinued treatment and had no missing data under an MAR assumption conditioning on treatment discontinuation status.

Any missing data will be imputed under an MAR assumption.

Full details will be provided in the SAP.

9.3.2.1. Definition of endpoints/estimands

Refer to Section 3.1 and Section 8.2 for primary endpoints, and refer to Section 3.2 for estimands.

9.3.2.2. Supplementary/supportive analysis

Subgroup analysis

Subgroups may be explored for stratification factors and other key baseline/disease characteristics, repeating the primary and some secondary analyses detailed in Section 9.3.2 and Section 9.3.3, respectively. Further details to be provided in the SAP.

9.3.3. Secondary endpoint(s)/estimand(s) analyses

Efficacy across the dose range vs placebo and longitudinal dose-response relationship

A D-E-R analysis based on a longitudinal drug-disease model will be used to describe the time course of serum GSK1070806 concentrations and individual EASI response. A non-linear mixed effects modelling approach, including direct and/or indirect response models will be applied to explore the relationship between exposure, target engagement and overall efficacy (EASI). Covariate analysis will include exploration of stratification factors and other key disease characteristics and efficacy endpoints (IGA, PP-NRS). This analysis may incorporate prior information from previous studies to support the prediction of treatment response after different doses and dosing regimens. Secondary PK parameters (AUC, Cmax, Css) and predicted median PCFB in the EASI per dose regimen level will be derived along with the 95% confidence intervals. Further details of the analysis will be provided in the SAP.

Safety analysis

The strategy for handling ICEs is described in Section 3.

No formal statistical testing will be performed on safety data. Unless specified, safety data from the treatment period and the off-treatment follow-up will be summarized together.

AEs will be coded using the MedDRA coding dictionary and summarized by preferred term and treatment. Separate summaries will be provided for all AEs, drug-related AEs, SAEs, AESIs and AEs leading to permanent discontinuation of study intervention or withdrawal from the study.

Laboratory data, immunogenicity data, ECG and vital signs will be presented in tabular and/or graphical format and summarized descriptively according to GSK standards at each time point. No imputations for missing data will be performed for the reporting of safety.

Efficacy analysis

Details of the estimands for the secondary efficacy endpoints are described in Section 3.

The CFB in PP-NRS at CCI [redacted] will be analyzed using a Bayesian repeated measures model including baseline PP-NRS score, baseline disease severity (IGA score), region, prior treatment experience, week (categorical) and treatment as well as interactions for treatment-by-week, baseline-by-visit using an unstructured covariance matrix to handle repeated measures. The difference from placebo at Week 16 from this model will be summarized as Mean, SD, Median and 95% credible interval of the posterior distribution.

The occurrence of ≥75% reduction from baseline in the EASI score (achieving EASI75) at Week 16 without the use of rescue medication will be analyzed using a Bayesian logistic model including baseline EASI score (continuous), region, prior treatment experience, and treatment and a binary variable (with 1 if ≥75% reduction from baseline without the use of rescue medication and 0 otherwise) as response. The 95% credible interval of the posterior distribution will be presented as well as posterior median and 95% credible intervals for the true difference in proportion of responders (a range of doses and regimens of GSK1070806 – placebo) and adjusted posterior median and 95% credible intervals of the true response rate for each treatment group using the back-transformation of the logit.

To analyze the occurrence of achieving an IGA score of 0 or 1 and ≥2 change from baseline at Week 16 without the use of rescue medication, the same approach as described for EASI75 above will be used. A binary variable with 1 if IGA score is 0 or 1 and ≥2 change from baseline without the use of rescue medication and 0 otherwise will be used as response.

To analyze the occurrence of achieving a reduction in PP-NRS ≥4 points at Week 16 without the use of rescue medication, the same approach as described for EASI-75 and IGA0/1 above will be used. A binary variable with 1 if PP-NRS score is ≥4-point reduction from baseline without the use of rescue medication and 0 otherwise will be used as response.

9.3.4. Tertiary/exploratory/other endpoint(s)/estimand(s) analysis

Details will be provided in the SAP.

9.4. Interim analyses

Prior to the primary study analysis, interim analyses may occur.

An iDRC, independent to the study team, will be appointed for this study to review the interim analysis data in an unblinded manner. Specific details regarding all interim analyses, including pre-specified futility criteria based on efficacy thresholds, will be outlined in the interim analysis charter, along with the outline of how the iDRC will ensure data integrity and appropriate quality control of data prior to making decisions and an outline of the committee membership. Interim analyses to assess futility, efficacy or doses/regimens may be conducted and importantly any available clinical data may be assessed, and the totality of available evidence will provide supportive information for consideration prior to any decision. Full details of the interim analyses will be described in the iDRC charter.

9.4.1. Sequence of interim and other planned analyses

For any interim, the decision criteria will be prospectively specified in the iDRC charter.

Planned or additional interim analyses may include or occur for non-binding futility or to assess efficacy for internal decision making and/or confirming/adjusting dose regimens, CCI [redacted] or to initiate or support Phase 3 planning activities. Therefore, the sample size, number of treatment arms or dose regimens may be adjusted as a result of an interim analysis.

For any interim, an estimation approach with no hypothesis testing will be performed and therefore multiplicity adjustments are not applicable.

9.5. Sample size determination

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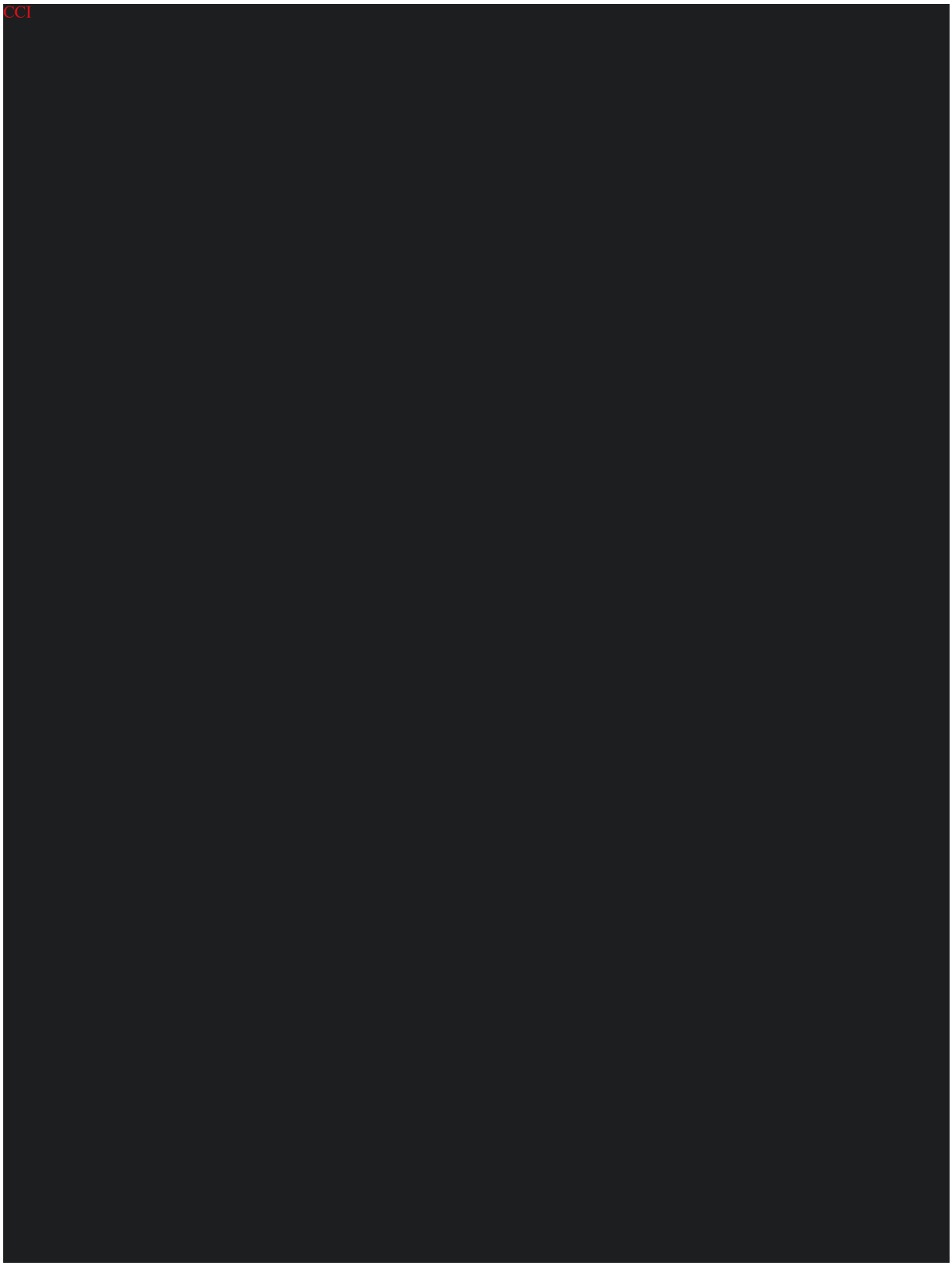

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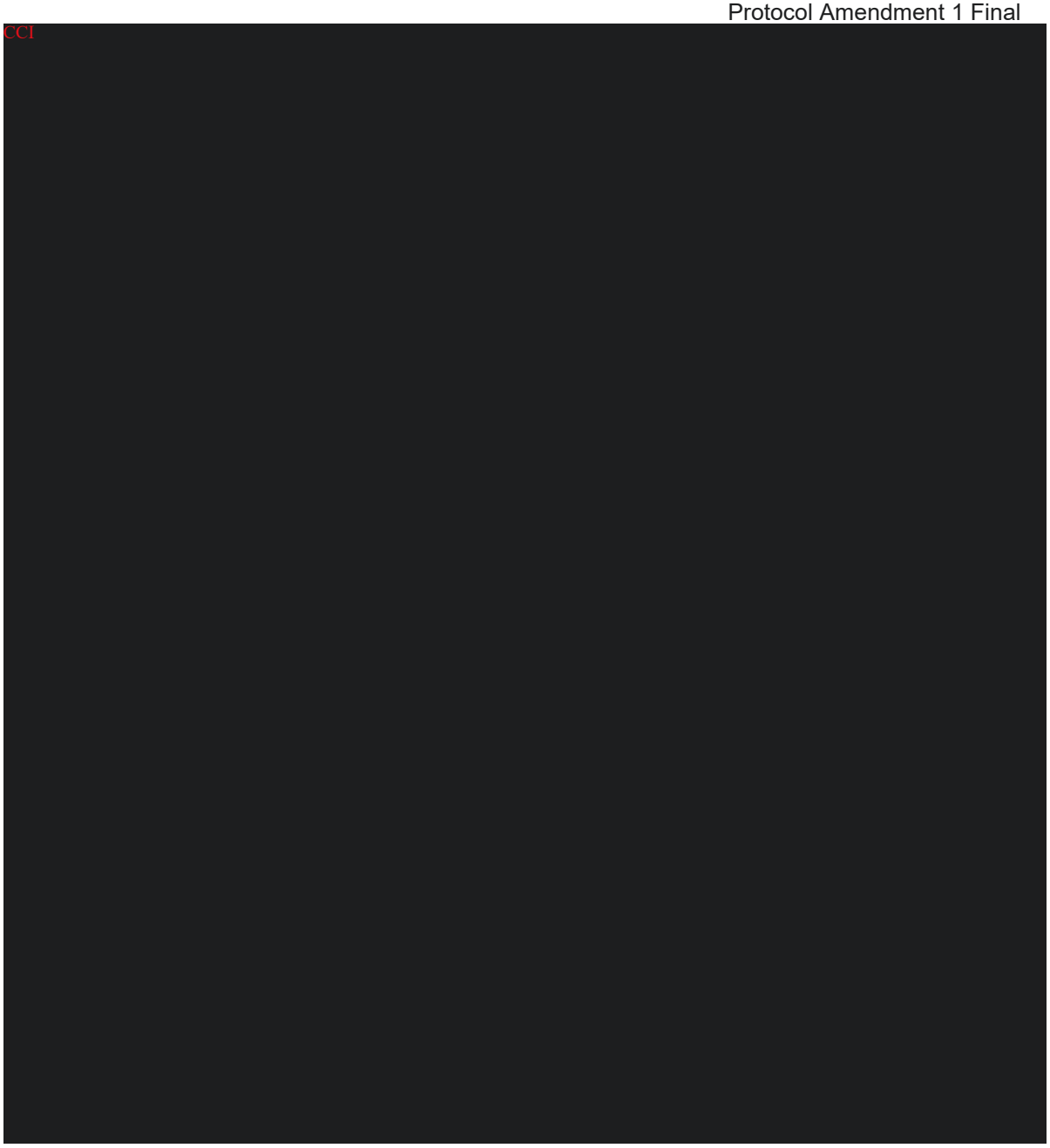


10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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 the following:
  - 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 ICH 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 IRB/IEC 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, as applicable:
  - 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/IEC
  - Notifying the IRB/IEC of SAEs 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (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 the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants/LAR and answer all questions regarding the study.
- Potential participants/LAR must be informed that their participation is voluntary. They or their LARs will be required to physically sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant/LAR.
- By default, collected samples for the study will be stored for a maximum of 20 years. This storage period begins when the last participant completes the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.
- The medical record must include a statement that physical informed consent was obtained before the participant was enrolled in the study and the date the physical consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF during their participation in the study.
- A physical copy of the ICF must be provided to the participant or their LAR.
- Participants who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. 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.
- In case of an unexpected pregnancy, participant must be informed that PI such as date of birth and sex of the baby will be collected as part of the safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment strategy

Feedback from participants with AtD on the proposed study design was solicited. Prior to selecting a site for inclusion in the study, data will be gathered to understand the numbers of participants that they may be able to enroll from their own participant database and networks. Sponsor may develop participant recruitment materials and support materials including participant card, but not limited to recruitment poster / flyer, appointment reminder card, thank you card etc. Sponsor may consider direct to healthcare practitioner engagement and referrals for participation, to support enrollment activities at sites. Sponsor may consider direct to patient digital advertisements to drive and recruit participants to a prescreening website to complete a questionnaire to determine if they pre-qualify for the study and refer themselves to the closest study site.

These items will provide basic study information and site contact information which are designed to assist with recruitment.

Recruitment will be monitored throughout the study and mitigation plans put in place if needed.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. 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.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant/LAR must be informed that their 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/LAR(s), that their data will be used as described in the informed consent.
- The participant/LAR must be informed that their 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.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees structure

An iDRC will be appointed for this study. The iDRC review interim data periodically throughout the trial to determine appropriate recommendations for study conduct and enabling activity for the wider development plan in accordance with the DRC Charter. No study personnel with direct contact with sites or site staff will be involved in the iDRC. Full details of the data to be reviewed, the frequency of review and members of the committee will be included in the Internal Data Review Committee Charter, to be finalized before study start.

- In line with routine pharmacovigilance, a SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information and will review blinded safety data at appropriate intervals during the study.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.

- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs 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 eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the QTL Report in Veeva vTMF: 01.01.03 to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- 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, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and Central Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- 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 CSR/ equivalent summary unless local regulations or institutional policies require a different 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. In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.

- When copies of source documents are shared externally for review by a central reader mechanism (e.g., expert reader), documents are stored by the external body for 25 years.

10.1.9. Source documents

- For this study, there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- 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 eCRF 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 source data acknowledgment
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF 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.
- Source data are shared with third parties contracted by GSK for review by a central reader mechanism (e.g., expert reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, imaging reports, ECG reports, etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the participant information redaction strategy are provided in the relevant third party manuals and/or study plans. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.10. Study and Site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

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 (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily 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 temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 9 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.
- Investigators must document their review of each laboratory safety report.

Table 9 Protocol-required safety laboratory tests

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	White blood cell (WBC, absolute)			
	Reticulocyte Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Calcium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Alkaline phosphatase[1]	Gamma-Glutamyl Transferase (GGT)	Albumin
	Sodium			
	Estimated Creatinine Clearance/glomerular filtration rate (CKD-EPI[2])			
Coagulation Profile	• International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT), Fibrinogen			

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood, protein, or leukocyte is abnormal)
Pregnancy testing	Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in WONCBP only). • Serology: HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) • Hepatitis B DNA (Hep B DNA) and hepatitis B surface antibody (HbsAb) (Japan & China only) • Hepatitis C virus antibody -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay (or other third generation immunoassay) or Hepatitis C Virus RNA test (either quantitative or qualitative) should be reflexively performed on the same sample to confirm the result) • QuantiFERON-TB Gold / QuantiFERON-TB Gold PLUS

NOTES:
1. If alkaline phosphatase is elevated, consider fractionating.
2. Chronic Kidney Disease Epidemiology Collaboration creatinine equation 2021 (CKD-EPI 2021) will be used for calculating and reporting eGFR. For participants from Japan sites, the Japanese coefficient (0.813) -modified CKD-EPI will be used for calculating and reporting eGFR. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

All planned laboratory testing will be performed at GSK's laboratory or in a laboratory designated by GSK.

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.

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). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition 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. • Events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen). • "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 AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the 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, admission for routine examination).
- 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. Pre-existing diseases will be recorded in the medical history section of the eCRF**.**
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	**Is a congenital anomaly/birth defect in the offspring of a study participant**
f.	**Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)**
g.	**Is a suspected transmission of any infectious agent via an authorized medicinal product**
h.	**Other situations:** • Possible Hy's Law case: ALT ≥3x ULN AND total bilirubin ≥2x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or 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 1 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 (CV) event definition:
Investigators will be required to fill out the specific CV event page of the eCRF 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. Definition of TEAE

TEAE Definition:
• A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.5. Recording, assessment and follow-up of AEs, SAEs, AESIs and pregnancies

10.3.5.1. 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 reports, 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.

10.3.5.2. Assessment of intensity

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

- **Mild:**
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:**
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant**.**

- **Severe:**
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention**.**

10.3.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. 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 their 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 1 of the criteria used when determining regulatory reporting requirements.

10.3.5.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.5.5. Follow-up of AEs, SAEs, AESIs, pregnancies or any other events of interest

- 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.
- 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.
- After the initial AE, SAE, AESI, pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in the Section 8.4.4) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.
- Other nonserious AEs must be followed until the event is resolved or until the participant is lost to follow-up.

Follow-up during the study

AEs/SAEs/AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the event is resolved.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report and the AE Report, if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.5.7.

10.3.5.6. Updating of SAE, AESI, and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, AESI, or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.8).

10.3.5.7. Reporting of SAEs, AESIs, and pregnancies

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an 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 offline 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 offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.8.

SAE Reporting to GSK via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/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 timeframes.
- Contacts for SAE reporting can be found in Section 8.4.8.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential (WOCBP)

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

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2. Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenarchal: Tanner stage 1 (prepubertal)
- Permanently sterile due to 1 of the following procedures:
  a. Documented hysterectomy
  b. Documented bilateral salpingectomy
  c. Documented bilateral oophorectomy

For permanently sterile individuals 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. If reproductive status is questionable, additional evaluation should be considered.

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

- Postmenopausal female:

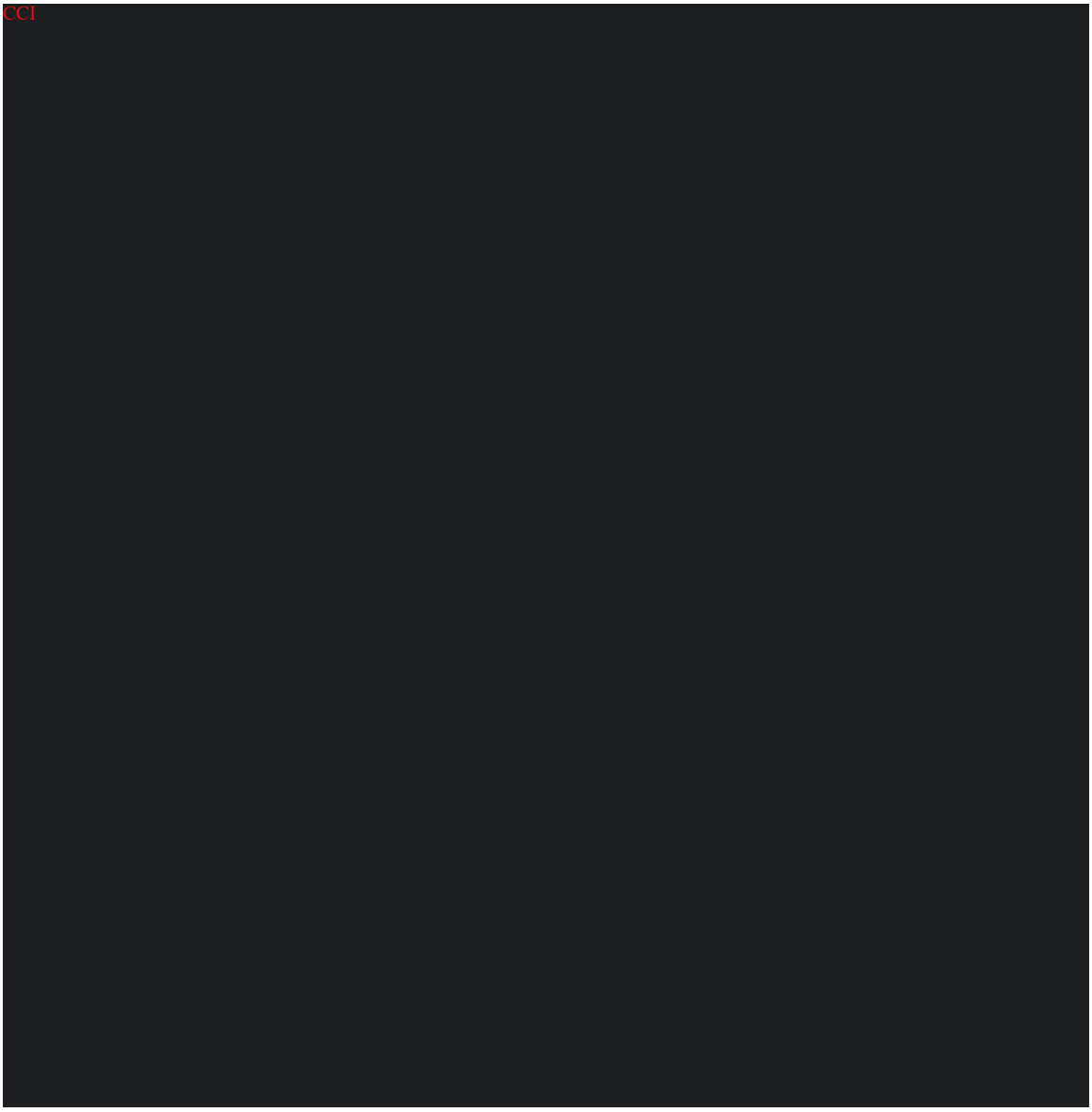
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 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 enrollment.

10.4.2. Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE CLINICAL 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/ligation
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 (e.g., medical assessment of the surgical success for vasectomy). If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: Documentation for a male partner can come from medical history interview with the participant..
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 ovulation[c] • Oral • Intravaginal • Transdermal • Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • 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 clinical 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. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: 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).

CCI



10.6. Appendix 6: Liver safety requirements and guidelines

10.6.1. Liver safety: required actions, monitoring and follow-up to assess causality of liver event

Required actions, monitoring, and follow-up to assess causality of liver event

<table>
<tr><th colspan="3">Liver event study intervention stopping criteria</th></tr>
<tr><td>ALT absolute</td><td colspan="2">ALT ≥5xULN</td></tr>
<tr><td>ALT increase</td><td colspan="2"><u>Unable to monitor weekly for 4 weeks:</u>
ALT ≥3xULN

<u>Able to monitor weekly:</u>
ALT ≥3xULN that persists for 4 weeks

Note: if values reduce to <3xULN or return to within baseline or normal limits for 2 consecutive weekly assessment, weekly monitoring may return to regular per protocol schedule.</td></tr>
<tr><td>Bilirubin[1,2]</td><td colspan="2">ALT ≥3xULN and total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT ≥3xULN and INR >1.5</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required actions, monitoring and follow-up to assess causality of liver event</th></tr>
<tr><th colspan="2">Actions and monitoring</th><th>Follow-up to assess causality of liver event</th></tr>
<tr><td colspan="2">• Immediately discontinue study intervention
• Report the event to GSK within 24 hours.
• Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2].
• Perform liver event follow-up to assess causality of liver event.
• Monitor the participant liver chemistries (see MONITORING).

MONITORING:
If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up to assess liver event causality within 24 hours.
• Monitor participants twice weekly until liver chemistries reduce to <3xULN for ALT, <2xULN for total bilirubin or ≤1.5 for INR or return to or remain within baseline or normal limits.
• A specialist or hepatology consultation is recommended.</td><td>• Viral serology[4].
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG (IgG or gamma globulins).
• Blood sample for PK analysis[5].
• Serum CPK and LDH, GGT, GLDH, and serum albumin.
• 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 liver event form.
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications.
• Record alcohol use on the liver event alcohol intake form.</td></tr>
</table>

For all other stopping criteria (bilirubin <2xULN and INR ≤1.5): • **Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up to assess liver event causality within 24-72 hours.** • **Monitor participants weekly until liver chemistries reduce to <3xULN for ALT or return to or remain within baseline or normal limits.** **RESTART and/or RECHALLENGE** • **Do not restart and/or rechallenge participant with study intervention since not allowed per protocol; continue participant in the study for any protocol-specified follow-up assessments.**	**If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 obtain the following in addition to the assessments listed above:** • **Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury.** • **Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease, complete liver imaging forms.** • **Liver biopsy may be considered and discussed with local specialist if available:** – **In patients when serology raises the possibility of AIH.** – **In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention.** – **In patients with acute or chronic atypical presentation.** • **If liver biopsy conducted, then complete liver biopsy form.**

AIH = Autoimmune hepatitis; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CPK = Creatine phosphokinase; CRF = Case report form; DNA = Deoxyribonucleic acid; DILI = Drug-induced liver injury; GGT = Gamma glutamyl transferase; GLDH = Glutamate dehydrogenase; GSK = GlaxoSmithKline Biologicals SA; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; HDV = Hepatitis D virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M; INR = International normalized ratio; LDH = Lactate dehydrogenase; PCR = Polymerase chain reaction; PK = Pharmacokinetic; RNA = Ribonucleic acid; SAE = Serious adverse event; ULN = Upper limit of normal.

1. Serum bilirubin fractionation should be performed if testing is available. 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 total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) 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 IgM antibody; HBsAg and HBcAb (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody and RNA PCR test. HBV DNA quantification, and HDV antibody should be measured if participant known to be HBsAg and/or HBcAb positive prior to onset of the liver event or subsequently found to be HBsAg positive on investigation following the liver event. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed and if this is feasible).

5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to 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 laboratory manual.

10.6.2. Liver safety: liver event increased monitoring criteria with continued study intervention

Liver event increased monitoring criteria and actions with continued study intervention	
Criteria	**Actions**
ALT ≥3xULN and <5xULN and bilirubin <2xULN or INR ≤1.5, without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss participant safety. • Participant can continue study intervention. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they stabilize (i.e., ALT or AST <3xULN and no increases in total bilirubin and INR) or return to or remain within baseline or normal limits. • If at any time participant meets the liver event stopping criteria, proceed as described above. • If, after 4 weeks of monitoring, stopping criteria have not been met but any of the monitored liver chemistry (ALT, AST, alkaline phosphatase, total bilirubin and INR) remains abnormal/above baseline, monitor participants twice monthly until they stabilize or return to within baseline or normal limits. Alternatively, the monitoring can return to standard as per protocol when the investigator and medical monitor agree that values are stable or no longer significantly abnormal (this may require local investigation of potential causes for liver chemistry abnormality).

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GSK = GlaxoSmithKline Biologicals SA; INR = International normalized ratio; ULN = Upper limit of normal.

10.7. Appendix 7: Country-specific requirements

10.7.1. Japan specific requirement:

Japanese individuals living in Japan (defined as all Japanese until their grandparents on consanguinity) are eligible for this study in Japan.

For evidence of active or past hepatitis B infection participants from Japan are required to test for HBsAb in addition to HBsAg and HBcAb. Participants from Japan are not eligible if positive for HBsAb and consequently positive for HBV DNA.

Chronic Kidney Disease Epidemiology Collaboration equation 2021 (CKD_EPI 2021) will be used for calculating and reporting eGFR. For participants from Japan, the Japanese coefficient (0.813) modified CKD-EPI will be used for calculating and reporting eGFR.

10.7.2. China specific requirement

For evidence of active or past hepatitis B infection participants from China are required to test for HBsAb in addition to HBsAg and HBcAb. Participants from China are not eligible if positive for HBsAb and consequently positive for HBV DNA.

10.7.3. South Korea specific requirement

Modified inclusion criterion 2 for participants in South Korea: In South Korea, a participant must be at least 19 years of age inclusive at the time of signing the informed consent.

Contraception period increased from CCI to CCI to align with local regulatory requirement to adopt a more conservative approach considering the variance in half-life estimate in a previous study of a small group of healthy participants who received a higher dosage of GSK1070806.

In South Korea, a WOCBP must use a contraceptive method that is highly effective, with a failure rate of <1% during the study intervention period and for at least CCI after the last dose of study intervention.

In South Korea, details of all pregnancies in female participants will be collected after the start of study intervention and for at least CCI after the last dose of study intervention.

10.7.4. Thailand specific requirement

Modified inclusion criterion 2 for participants in Thailand: In Thailand, a participant must be at least 20 years of age at the time of signing the informed consent.

10.7.5. French specific requirement

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

10.7.5.1. Concerning the "SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA"

A participant will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code L.1124-1).

It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the participant is affiliated to or beneficiary of a social security category.

Participants will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the ICF. Participants not completing the study for whatever reason could be compensated generally on a pro rata basis.

10.7.5.2. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol**

  ⇒ Concerning the **process for informing the subject**, the following text is added:

  French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject written consent. It also contains a reference to the single scientific and ethical regulatory authorisation.

  ⇒ Concerning the **management of the Patient ICFs**, the following text is added:

  French Patient Informed Consent Form is in duplicate.

  The first page of the Patient ICF is given to the investigator. The copy is kept by the patient.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

  In accordance with Article R.1123-69 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- **INFORMATION TO THE HOSPITAL PHARMACIST**

  In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g., included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

- **ETHNIC ORIGIN**

  In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

  In accordance with the French Public Health Code – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

10.7.5.3. Concerning the "DATA MANAGEMENT" the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction, and opposition on their own data through GSK (Clinical Operations Department).

10.7.5.4. Concerning Data Privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with 1 of the methodology of reference (MR-001) or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

Additional inclusion criterion for participants in France: A participant is eligible to be included in the study only if they are either affiliated to or a beneficiary of a social security category.

10.7.5.5. INVESTIGATIONAL PRODUCT ACCOUNTABILITY, RECONCILIATION, AND DESTRUCTION

In specific situations where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor' to verify and document IP accountability, the following applies:

*"During the conduct of the Study, IP will be destroyed by the Institution prior to a GSK "**monitor**" conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GSK with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).*

10.8. Appendix 8: American Academy Of Dermatology (AAD) Consensus Criteria for Atopic Dermatitis, Eichenfield 2014

ESSENTIAL FEATURES—Must be present:

- Pruritus
- Eczema (acute, subacute, chronic)
  - Typical morphology and age-specific patterns*
  - Chronic or relapsing history

**Patterns include:*

1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions

IMPORTANT FEATURES—Seen in most cases, adding support to the diagnosis:

- Early age of onset
- Atopy
  - Personal and/or family history
  - Immunoglobulin E reactivity
- Xerosis

ASSOCIATED FEATURES—These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:

- Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- Ocular/periorbital changes
- Other regional findings (e.g., perioral changes/periauricular lesions)
- Perifollicular accentuation/lichenification/prurigo lesions

EXCLUSIONARY CONDITIONS—It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

Adapted from Eichenfield, 2014.

10.9. Appendix 9: Protocol amendment history

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1 EU-1	05 February 2024
Amendment 1 KOR-1	05 January 2024
Original Protocol	03 August 2023

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

Amendment 1 EU-1 (05 February 2024)

Overall rationale for the current Amendment: The protocol has been amended based on the EU CTR review requests. The main substantial change includes an additional exclusion criterion: History of an allergic reaction or significant sensitivity to any constituents of the study drug (including excipients). In addition, the protocol was amended to indicate that future research will be limited to explore other conditions where this mechanism of action may play a role and/or to develop new methods and tests to align with the current main ICF and the optional genetic research ICF.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 2.3.1 Risk assessment; Section 7.1 Discontinuation of study intervention	Included the terms 'exclusively', 'preferably' in the sentence referring to Withdrawal criteria related to serious or severe AEs	For better clarity about one of the 'Withdrawal Criteria' related to serious or severe AEs
Section 2.3.1 Risk assessment; Section 5.2.3 Prior/Concurrent Clinical Study Experience	Added the exclusion criterion, "History of an allergic reaction or significant sensitivity to any constituents of the study drug (including excipients)"	As per EU CTR request, added this exclusion criterion for clarity.
Section 5.2.4 Diagnostic Assessments	Modified the sentence, "Participants with Gilbert's syndrome can be included with total bilirubin >1.5xULN as long as direct bilirubin is ≤1.5xULN"	To clarify that the participants with Gilbert's syndrome can be included in the study.
Section 6.9.2 Prohibited Medications	Revised the text on to how to address an urgent clinical need.	Presentation updated for completeness of information.
Section 7.1 Discontinuation of study intervention	Added the discontinuation criteria of 'withdrawal of informed consent', and 'lack of efficacy (as assessed by Investigator'	To ensure consistency across the document about the discontinuation criteria.
Section 8.3.2 Vital signs	Deleted the word 'oral'	Updated for clarity around temperature assessment.

Section # and title	Description of change	Brief rationale
CCI [redacted]		

Amendment 1 KOR-1 (05 January 2024)

Overall rationale for the Amendment 1 KOR-1: Contraception period increased to align with local regulatory requirement to adopt a more conservative approach considering the variance in half-life estimate in a previous study of a small group of healthy participants who received a higher dosage of GSK1070806.

Summary of changes table of previous amendments (Amendment 1 KOR-1)

Section # and title	Description of change	Brief rationale
2.3.1 Risk assessment Reproductive Toxicity	**Eligibility Criteria:** • Is a WOCBP and using a contraceptive method as described in Section 10.4 during the study intervention period and for at least CCI [redacted] after the last dose of study intervention (please note, however, that WOCBP wishing to be considered for the LTE, should maintain highly effective contraceptive use).	Contraception period increased to align with local regulatory requirement.
5.1. Inclusion Criteria	9. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. • Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention period and for at least CCI [redacted] after the last dose of study intervention.	Same as above
8.4.6 Pregnancy	• Details of all pregnancies in female participants will be collected after the start of study intervention and for at least CCI [redacted] after the last dose of study intervention.	Pregnancy data collection period increased to align with contraception period.
10.7.2 South Korea specific requirement	Modified reproductive toxicity in risk assessment and inclusion criterion 9 for participants in South Korea: In South Korea, a WOCBP must use a contraceptive method that is highly effective, with a failure rate of <1% during the study intervention period and for at least CCI [redacted] after the last dose of study intervention. Modified pregnancy data collection period for participants in South Korea: In South Korea, details of all pregnancies in female participants will be collected after the start of study intervention and for at least CCI [redacted] after the last dose of study intervention.	Added clarification for changes specific to South Korea

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