CLINICAL STUDY PROTOCOL

Primary Study Intervention(s)	GSK1070806
Other Study Intervention(s)	Not Applicable
Study Identifier	220723
EU CT Number	2023-508474-29-00
Approval Date	02 Aug 2024
Title	Long-Term Extension Study (AtDvance) to Evaluate the Safety and Efficacy of GSK1070806 in Participants with Moderate to Severe Atopic Dermatitis.
Compound Number/Name	GSK1070806
Brief Title	Long-Term Study (AtDvance) to Evaluate GSK1070806 in Atopic Dermatitis.
Sponsor	GlaxoSmithKline 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 information can be found in the local study contact information document.

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- 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 site agreement.
- To comply with local bio-safety legislation.
- 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 supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- If applicable, to acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of GSK and the express written informed consent of the participant.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate 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.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

Study identifier	220723
EU CT number	2023-508474-29-00
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Title	Long-Term Extension Study (AtDvance) to Evaluate the Safety and Efficacy of GSK1070806 in Participants with Moderate to Severe Atopic Dermatitis.
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACQ	Asthma control questionnaire
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AtD	Atopic dermatits
AxMP	Auxiliary medicinal product
BP	Blood pressure
CFB	Change from baseline
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
DCT	Decentralized trial
D-E-R	Dose-Exposure-Response
DGF	Delayed graft function
DLQI	Dermatology Life Quality Index
EASI	Eczema area and severity index
ECG	Electrocardiogram
eCRF	Electronic case report form
EoS	End-of-study
EW	Early withdrawal
FDA	Food and Drug Administration, United States of America
FSFV	First subject first visit
FTiH	First-time in human
GCP	Good clinical practices
GI	Gastrointestinal
GSK	GlaxoSmithKline
HADS	Hospital Anxiety and Depression Scale
HbsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council on Harmonisation
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
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
ISR	Injection site reaction

Abbreviation	Definition
IV	Intravenous
JAKi	Janus activation kinase inhibitors
KLH	Keyhole limpet hemocyanin
LSLV	Last Subject Last Visit
LTE	Long-term extension
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
NIMP	Non-investigational medicinal product
NQ	Non-quantifiable
PCFB	Percent change from baseline
PD	Pharmacodynamic
PDE4	Phosphodiesterase-4
Ph2	Phase 2
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 [redacted]	
QoL	Quality of life
QTc	Corrected QT interval
QTcF	QT interval according to Fridericia's formula
QTL	Quality tolerance limit
RAMOS	Registration and Medication Ordering System
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SoA	Schedule of activities
SPFQ	Study Participant Feedback Questionnaire
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
TMDD	Target-mediated drug disposition
TNF	Tumor necrosis factor
US	United States of America
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 until the participant's qualifying Ph2 parent study has been analyzed or reported. Unblinding may also occur when required in case of a SAE.
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.
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
NIMP/AxMP	A NIMP or AxMP 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 /product(s)/control). Synonym: subject
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.
Remote visit	This term refers to the visit conducted in the place other than the study site.
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/LSLV	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:

Long-Term Extension, Study (AtDvance) to Evaluate the Safety and Efficacy of GSK1070806 in Participants with Moderate to Severe Atopic Dermatitis.

Brief Title:

Long-Term Study (AtDvance) to evaluate GSK1070806 in Atopic Dermatitis.

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

Overall Design: Refer to Section 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

CCI

1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities

	Treatment period year 1 and 2 (from Week 0 to Week 104)																																	Continue with Week 108	Unscheduled visit	Unscheduled call	Early withdrawal
Week	CCI																																				
Visit window																																					
Visit																																					
Day																																					
Outpatient visit	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X			
Telephone consultation								X		X		X		X		X		X		X		X		X		X		X		X							
CCI																																					
Inform consent (h)	X																																				
Inclusion/exclusion criteria	X	X																																			
Medical history/demographics		X																																			
Physical examination (Full/Brief) (i,j)		X			X		X				X				X				X				X				X						X (j)		X
12-lead ECG		X			X		X								X																		X		X
Vital signs		X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Hematology, clinical chemistry, coagulation profile		X	X	X	X	X	X				X				X				X				X				X						X		X
Urinalysis		X	X	X	X	X	X				X				X				X				X				X						X		X
Urine pregnancy test (k)		X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X				X		X
Serology															X (l)																				X (l)		
TB testing															X																						
PK (m)		X			X		X				X				X																				X		X
PD (Target engagement, TE), Total IL-18 (m)		X			X		X				X				X																				X		X
Immunogenicity (m)		X			X		X				X				X								X												X		X
SAE and AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Concomitant meds		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Treatment allocation		X																																			
Dispensing and return of eDiary device		X					X																														
Study Participant Feedback Questionnaire - SPFQ (optional)				X											X														X							
CLINICAL ASSESSMENTS																																					
IGA - Investigator's Global Assessment		X	X	X	X	X	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		X		X		X		X		X
PATIENT REPORTED OUTCOME MEASURE (n)																																					
PP NRS		Daily in participants e-diary							X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
SP NRS (p)																																					
POEM		X		X	X	X	X				X				X												X						X		X
DLQI		X		X	X	X	X				X				X												X						X		X
PROMIS-Sleep Disturbance 8b		X		X	X	X	X				X				X												X						X		X
WPAI-AD		X		X	X	X	X				X				X												X						X		X
HADS		X		X	X	X	X				X				X												X						X		X

	Treatment period year 3 and 4 (from Week 108 to Week 208)																														
Week	CCI																														
Visit window																															
Visit																															
Day																															
Outpatient visit		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Telephone consultation	X		X		X		X		X		X		X		X		X		X		X		X		X		X				
CCI																															
Physical examination (Full/Brief) (i,j)		X				X				X				X				X				X				X			X (j)		X
12-lead ECG																													X		X
Vital signs		X		X		X		X		X		X		X		X		X		X		X		X		X			X		X
Hematology, clinical chemistry, coagulation profile		X								X								X											X		X
Urinalysis		X								X								X											X		X
Urine pregnancy test (k)		X		X		X		X		X		X		X		X		X		X		X		X		X			X		X
Serology	X (l)																												X (l)			
TBs testing										X												X									
PK (m)																													X		X
PD (Target engagement, TE) (m)																													X		X
Immunogenicity (m)		X								X								X											X		X
SAE and AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Participant Feedback Questionnaire - SPFQ (optional)									X													X									
CLINICAL ASSESSMENTS																															
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	
PATIENT REPORTED OUTCOME MEASURE (n)																															
PP NRS		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
POEM										X												X							X		X
DLQI										X												X							X		X
PROMIS-Sleep Disturbance 8b										X												X							X		X
WPAI-AD										X												X							X		X
HADS										X												X							X		X

Continue with Week 212

	Treatment period year 5 (from Week 212 to Week 264)														Safety follow-up period						
Week	CCI																		**Unscheduled visit**	**Unscheduled call**	**Early wihtdrawal**
Visit window																					
Visit																					
Day																					
Outpatient visit		X		X		X		X		X		X		X				X			
Telephone consultation	X		X		X		X		X		X		X		X	X	X				
CCI																					
Physical examination (Full/Brief) (i,j)		X				X				X				X				X	X (j)		X
12-lead ECG																		X	X		X
Vital signs		X		X		X		X		X		X		X				X	X		X
Hematology, clinical chemistry, coagulation profile								X				X						X	X		X
Urinalysis								X				X						X	X		X
Urine pregnancy test (k)		X		X		X		X		X		X		X				X	X		X
Serology	X (l)																		X (l)		
TB testing								X													
PK (m)																			X		X
PD (Target engagement, TE) (m)																			X		X
Immunogenicity (m)								x										X	X		X
SAE and AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Participant Feedback Questionnaire - SPFQ (optional)								X										X			X
CLINICAL ASSESSMENTS																					
IGA - Investigator's Global Assessment		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
PATIENT REPORTED OUTCOME MEASURE (n)																					
PP NRS		X		X		X		X		X		X		X				X	X		X
POEM								X										X	X		X
DLQI								X										X	X		X
PROMIS-Sleep Disturbance 8b								X										X	X		X
WPAI-AD								X										X	X		X
HADS								X										X	X		X

NOTE: While on site, study procedures should be conducted preferably in the following order:

- Participant reported outcomes.
- Physician reported-outcomes.
- SAEs/AEs and concomitant medications recording.
- ECG, physical examination, vital signs.
- Blood and urine sampling (All PK, PD and immunogenicity sampling must be done before dosing).
- Dosing.

a. Visit 1 (for consent) will be preferably the visit before, but no later than the End of Study (EoS) visit in the qualifying Ph2 parent study.
b. Visit 1 window can be up to 28 days. In case TCS washout needs to be initiated during EoS visit of qualifying Ph2 parent study this window can be extended up to 37 days (28 days + 9 days).
c. If Visit 2 is on the same day as EoS visit from the qualifying Ph2 parent study (or within 3 days), laboratory samples, efficacy and safety assessments (including weight collection) do not need to be repeated.
d. In case TCS wash-out is to be initiated at EoS visit in qualifying Ph2 parent study, Day 1 visit is to be performed at the latest 9 days after EoS visit of qualifying Ph2 parent study. In such case, all efficacy assessments (IGA, EASI, PROs) are to be conducted again at Day 1 visit. If no TCS wash-out is needed or if the TCS wash-out is completed at EoS visit of qualifying Ph2 parent study, this EoS visit can also be Day 1 visit of the LTE (all D1 assessments and samplings will be from the EoS visit from qualifying Ph2 parent study) and the Day 1 dosing can take place.
e. Should the participant not be able to stay for Day 1 dosing and the post-dose safety monitoring period of 2h, then Day 1 visit needs to take place within 3 days after EoS visit of Ph2 parent study. If Day 1 visit is later than 3 days after EoS visit of parent, then efficacy assessments (IGA, EASI, PROs) will have to be repeated.
f. Participants will be observed for approximately 2 hours post dose CCI [redacted]. Thereafter, post dose monitoring duration will be at investigator's discretion.
g. For participants on CCI [redacted], placebo injection for blinding purpose will be stopped at the time their qualifying Ph2 parent study is analyzed or reported.
h. Participation to the LTE to be discussed and LTE ICF signed during the visit before EOS visit from the qualifying Ph2 parent study.
i. Full physical examination will be performed at Day 1, EW visit and EOS visit (W280). Brief physical examination will be done at all other visits. Full physical examination can be done at the discretion of the Principal Investigator if deemed necessary.
j. 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.
k. WOCBP only. Urine pregnancy test will be done pre-dose. A serum test will be performed if required by local regulations (e.g.: country or IRB/EC).
l. Serologies described in Appendix 2 (Section 10.2) to be performed if required per local regulations or Investigator's discretion.
m. Pre-dose sampling
n. PROs administered on site should be administered before other clinical assessments or procedures, and before administration of study treatment.
o. In the first CCI [redacted] of the LTE, after qualifying Ph2 parent study is analyzed or reported: W0, W8, and W16 visits remain mandatory. W2, W4, and W12 visits can be replaced at PI discretion by telephone visits to assess AE, SAE, and concomitant medications.
p. After qualifying Ph2 parent study is analyzed or reported, SP-NRS might be removed.

2. INTRODUCTION

GSK1070806 is a potent anti-IL-18 monoclonal antibody that is being developed for the treatment of AtD [see GSK Document No.: RPS-CLIN-052602].

2.1. Study rationale

Atopic Dermatitis (AtD)

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 TH2/TH22-skewing and variable TH1/TH17 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 of 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].

Treatments 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 Olumiant (Baricitinib) monoclonal antibodies targeting IL-13 (Adtralza [tralokinumab] and 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, 2020a]. 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, 2020b; 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.

Olumiant (Baricitinib), an oral reversible and selective Janus kinase (JAK)1/JAK2 inhibitor, is indicated for the treatment of moderate-to-severe AtD in adult patients. In clinical trials of once-daily baricitinib 2 mg and 4 mg as monotherapy or in combination with topical corticosteroids, baricitinib showed significant clinical efficacy with acceptable safety [Guttman-Yassky, 2019; Reich, 2020; Simpson, 2020c; Simpson, 2021; Bieber, 2022].

Although it was reported that the Investigator´s Global Assessment (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 CCI [redacted] 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 Atopic Dermatitis

Interleukin-18 (IL-18) is a pleiotropic cytokine which acts as a modulator of the innate and adaptive immune response in a context dependent manner with potential to amplify pathways important in AtD [Saikiran, 2013; Lee, 2015]. Increased IL-18 levels were observed in the skin and plasma of patients with AtD and correlated with disease severity [Inoue, 2011]. In preclinical models, overexpression of IL-18 induces skin inflammation, while 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 study and exploratory studies in T2DM and DGF following renal transplantation [Mistry, 2014; McKie, 2016; Wlodek, 2021]. A phase 1b study 215253 which enrolled participants with moderate to severe AtD has been completed. Adults who have participated in study 215253 are not eligible for the LTE.

A study exploring CCI [redacted] safety, PK, and PD was conducted in healthy participants of Caucasians, Japanese and Chinese ancestry [GSK Document No.: RPS-CLIN-052602].

Study 220723 in Atopic Dermatitis

The aim of this study is to determine the long-term safety and efficacy of a range of doses of GSK1070806 CCI [redacted] in participants with moderate to severe AtD who have completed the qualifying Ph2 parent GSK AtD studies.

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). This is 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] of GSK1070806, respectively [GSK Document No.: RPS-CLIN-052602].

In addition, a Ph1b study 215253 in which a single dose of GSK1070806 (2 mg/kg) 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 a single dose of GSK1070806 2 mg/kg 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 [GSK Document No.: RPS-CLIN-052602]

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 CCI 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 studies. No causal association has been established.	**Monitoring:** • Serious infections and opportunistic infections are categorized as AESIs. • TB testing will be performed per SoA. • 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. **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 CCI [redacted] or SC injection.	**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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical Data: GSK1070806 has been administered to humans via CCI and no serious hypersensitivity reactions have been reported in completed clinical studies.	• Participants will be monitored for approximately 2 hours post dose at CCI. Thereafter, post dose monitoring duration will be at Investigator's discretion. • Monitor for serious hypersensitivity reactions throughout the study. • 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.
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 CCI 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 CCI, and no CCI site reactions were observed in completed studies.	**Monitoring:** • ISRs are categorized as AESIs. • Participants will be monitored for approximately 2 hours post dose at CCI. Thereafter, post dose monitoring duration will be at the Investigator's discretion. • 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 4 weekly [redacted] administrations at doses up to [redacted]. In a SC 26-week toxicology study in monkeys, ADAs were noted in monkeys who received GSK1070806 at [redacted]. 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 anti-GSK1070806 antibodies post dosing (Study A18110040). Two of 32 healthy participants (6%) of Asian or European/Caucasian ancestry who received GSK1070806 had anti-GSK1070806 antibodies post dosing (Study 218841). There was no apparent change in the individual PK or safety profile of GSK1070806. No anti-GSK1070806 antibodies 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.
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.	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 [redacted] 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	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). **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 single CCI dose nonclinical safety pharmacology study and a 4- week toxicology study in monkeys (CCI administered weekly for 4 weeks). **Clinical Data:** Events of hypertension have been reported in completed studies. No causal association has been established.	**Monitoring:** Vital signs are routinely monitored in the study according to the SoA.
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.	**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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical Data: No pregnancies were reported in completed studies. The effect of GSK1070806 on human pregnancy is unknown.	**Monitoring:** • A WOCBP must have a negative urine pregnancy test (or serum as required by local regulations) before each dose of study intervention 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.
Study Procedures		
Blood draws	Venous access in some participants may be problematic and the needles used may cause bruising (ecchymosis) around the access site.	• 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. Whole blood samples will be collected by site personnel experienced in phlebotomy.

2.3.2. Benefit assessment

Participants may or may not experience benefit in improved symptoms of AtD and clinical presentation following administration of GSK1070806. Participants, that in opinion of the Investigator may benefit from GSK1070806 by enrolling in this study, 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.

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

Objective(s)	Endpoint(s)
Primary	
To describe long term safety of a range of doses and dosing regimens of GSK1070806 in participants with moderate to severe AtD	Incidence of: • Adverse events (AEs) and discontinuation from study treatment due to AEs. • Serious adverse events (SAEs) and adverse events of special interest (AESI).
Secondary	
To evaluate the long-term efficacy of a range of doses and dosing regimens of GSK1070806 in participants with moderate to severe AtD	Achieving a response (for binary endpoints) at Weeks 16, 32, 48 and every 48 weeks thereafter: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline* • PP-NRS Reduction of ≥4 points Achieving a maintained response (for binary endpoints) for at least 16/32/48 and every 48 weeks thereafter after first response in: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline* PCFB in the EASI (continuous endpoint) at weeks 16, 32, 48 and every 48 weeks thereafter.

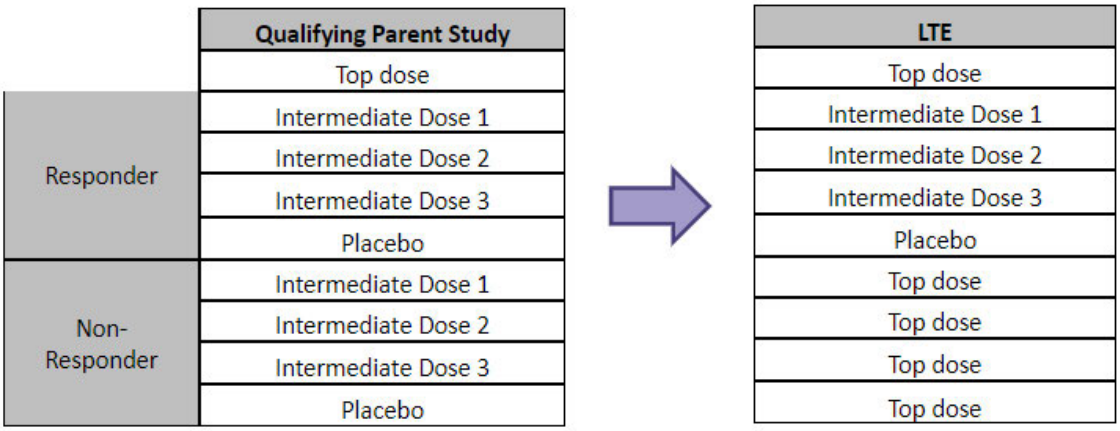
Objective(s)	Endpoint(s)
Exploratory	
CCI [redacted]	
To evaluate the efficacy of a range of doses and dosing regimens of GSK1070806 on Health Related-Quality of Life (HR-QoL) as assessed by a range of PROs in adults with moderate to severe AtD.	CFB to Weeks 16, 32, 48 and every 48 weeks thereafter in: • DLQI • POEM • WPAI-AD • HADS • PROMIS-Sleep Disturbance 8b • PP-NRS CFB to Week 16 in: • SP-NRS At Week 16,32, 48 and every 48 weeks thereafter achieving: • PP-NRS Reduction of ≥3 points • PP-NRS score of 0
CCI [redacted]	

*Please refer to Section 9.3.1 for baseline definitions.

3.2. Estimands

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

Both safety/efficacy estimands and their strategy will be applied to the safety/efficacy objectives which will be analyzed by treatment arms defined by the treatment received in the qualifying Ph2 parent study and the treatment received in the LTE:



3.2.1. Estimand Strategy for the Safety Objective

Estimand 1 for the primary safety objective	
Clinical question of interest	What is the long-term safety of a range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments in participants with moderate to severe AtD as measured by occurrence of AEs, SAEs, AESI, discontinuation from study treatment due to AEs that happen to participants while on treatment [i.e., within the 5 half-lives CCI [redacted] post last dose]? Rationale: The study is designed to evaluate the long-term safety of a range of doses and regimens of GSK1070806 with or without use of non-medicated background treatments. It is important to evaluate the risk-benefit of GSK1070806 while participants are on treatment so this estimand addresses the scenario in which only safety events attributable to treatment are included. All ICEs will be handled using the While on Treatment strategy defined as 5 half-lives CCI [redacted] post last dose. The safety estimand applies only for data collected in the LTE (i.e., does not include the time in the qualifying Ph2 parent study).
Treatment Condition	A range of doses and regimens of SC GSK1070806 and placebo with or without use of non-medicated background treatments.
Endpoint	Incidence of: • AEs • SAEs. • AESI. • Discontinuation from study treatment due to AE.

Estimand 1 for the primary safety objective	
Population	Participants with moderate to severe AtD who have previously been treated with medicated topical treatments only or 1 biologic therapy (in addition to GSK1070806 if the participant received active treatment in their qualifying Ph2 parent study).
Strategy for ICEs	ICEs: • Permanent treatment discontinuation for any reason **Strategy: While on treatment;** any safety events which occur post ICE which are not classified as treatment emergent (i.e., happening outside of the 5 half-lives CCI timeframe) will be excluded • Use of rescue therapy for AtD **Strategy: While on treatment;** any safety events which occur post ICE which are not classified as treatment emergent (i.e., happening outside of the 5 half-lives CCI timeframe) will be excluded • 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 study medication) **Strategy: While on treatment;** any safety events which occur post ICE which are not classified as treatment emergent (i.e., happening outside of the 5 half-lives CCI timeframe) will be excluded
Population-level summary	Number and percentage of participants in each treatment condition.

An additional estimand #1 for the safety objectives is defined below. The key difference to the primary estimand is in the strategy for handling all the ICEs. Following the additional estimand #1, all the ICEs will be handled using the treatment policy. Summaries will include all safety events regardless whether the ICE happened within the 5 half-lives CCI post last dose or outside of the 5 half-lives timeframe and all the safety events will be attributable to treatment (as opposed to the primary estimand where only events that happen within the 5 half-lives CCI post last dose will be attributable to treatment due to while on treatment strategy).

Additional estimand #1 for the primary safety objective	
Clinical question of interest	What is the long-term safety of a range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments in participants with moderate to severe AtD as measured by occurrence of AEs, SAEs, AESI, discontinuation from study treatment due to AEs; regardless of discontinuation of investigational treatment or use of rescue therapy? Rationale: The study is designed to evaluate the long-term safety of a range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments. It is important to evaluate the risk-benefit of GSK1070806 irrespective of permanent treatment discontinuation or use of rescue therapy. 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	A range of doses and dosing regimens of GSK1070806 and placebo with or without use of non-medicated background treatments.
Endpoint	Incidence of: • AEs • SAEs. • AESI. • Discontinuation from study treatment due to AE.
Population	Participants with moderate to severe AtD who have previously been treated with medicated topical treatments only or 1 biologic therapy (in addition to GSK1070806 if the participant received active treatment in their qualifying Ph2 parent study).
Strategy for ICEs	ICEs: • Permanent treatment discontinuation **Strategy: Treatment policy;** all data collected after the ICE (i.e., any safety events which occur post ICE) will be included in summaries • Use of rescue therapy for AtD **Strategy: Treatment policy;** all data collected after the ICE (i.e., any safety events which occur post ICE) will be included in summaries • 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 study medication) **Strategy: Treatment policy (in line with the strategy for the ICE of treatment discontinuation);** all data collected after the ICE (i.e., any safety events which occur post ICE) will be included in summaries. Summaries will include all safety events regardless whether the ICE happened within the 5 half-lives CCI post last dose or outside of the 5 half-lives timeframe.
Population-level summary	Number and percentage of participants in each treatment condition.

3.2.2. Estimand Strategy for the Efficacy Objectives

Estimand for the binary and continuous secondary efficacy objectives	
Clinical question of interest	What is the long-term efficacy of range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments in participants with moderate to severe AtD, irrespective of permanent treatment discontinuation or use of rescue therapy for AtD? Rationale: The study is designed to evaluate the long-term efficacy of range of doses and dosing regimens of GSK1070806 with or without use of non-medicated background treatments. This estimand provides evidence of efficacy regardless of whether the participants took the drug as per the protocol and is most closely reflective of usual clinical practice.
Treatment Condition	A range of doses and regimens of SC GSK1070806 and placebo with or without use of non-medicated background treatments regardless of permanent treatment discontinuation or use of rescue therapy for AtD (treatment policy strategy).
Endpoints	Achieving a response (for binary endpoints) at Weeks 16, 32, 48 and every 48 weeks thereafter: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline* • PP-NRS Reduction of ≥4 points Achieving a maintained response (for binary endpoints) for at least 16/32/48 and every 48 weeks thereafter after first response in: • IGA score of 0 or 1 • EASI Reduction of ≥75% from Baseline* PCFB in the EASI (continuous endpoint) at weeks 16, 32, 48 and every 48 weeks thereafter.
Population	Participants with moderate to severe AtD who have previously been treated with medicated topical treatments only or 1 biologic therapy (in addition to GSK1070806 if the participant received active treatment in their qualifying Ph2 parent study).
Strategy for ICEs	ICEs: • Permanent treatment discontinuation for any reason **Strategy: Treatment policy (for both continuous and categorical endpoints)**; all data collected after the ICE will be included in summaries. • Use of rescue therapy for AtD **Strategy: Treatment policy (for both continuous and categorical endpoints)**; all data collected after the ICE will be included in summaries. • 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 study medication) **Strategy: Hypothetical (for both continuous and categorical endpoints)**; data collected after the ICE will not be included in summaries, and outcomes will be assumed to be similar to participants who did not experience the ICE.
Population-level summary	• Number and percentage of participants in each treatment condition achieving an endpoint (for binary endpoints: IGA score of 0 or 1, EASI Reduction of ≥75% from Baseline, PP-NRS Reduction of ≥4 points) • Mean and 95% CIs (for continuous endpoints: PCFB EASI).

Additional estimands for efficacy may be defined and implemented with further details documented in the SAP.

4. STUDY DESIGN

4.1. Overall design

Please refer to the study design schema in Section 1.2.

This is a Phase 2b, LTE study to evaluate the safety and efficacy of a range of doses of GSK1070806 CCI [redacted] in eligible participants, with moderate to severe AtD who have completed qualifying Ph2 parent GSK AtD clinical studies that in the opinion of the investigator may benefit from treatment, and have provided consent to the LTE.

CCI [redacted]

The study will have maximum CCI [redacted] and a CCI [redacted] safety follow up period. Subject to regulatory approval, the study treatment duration may be increased if necessary to align with revised commercial availability, or reduced, if an alternative early access (or equivalent) program is started, or if development of GSK1070806 in AtD is stopped. Participants who prematurely withdraw from the treatment period will be followed up for at least CCI [redacted] post last dose.

Treatment allocation at Day 1 of LTE for participants coming from qualifying Ph2 parent studies:

Responders from the qualifying Ph2 parent studies, defined as participants achieving IGA 0/1 or EASI 75 response at primary analysis time-point, will maintain the same treatment during the LTE, to better understand long-term maintenance of response.

Non-responders from the qualifying Ph2 parent studies, will be allocated to the top dose to increase the probability of achieving responder status.

Medicated topical treatments (such as low and moderate TCS) will be permitted as concomitant treatment for AtD symptoms during this study.

All injections of the study medication will be administered in the clinic. The study treatment will be administered in the abdomen or thigh. Participants will remain in the clinic for safety monitoring for approximately 2 hours for the first 2 doses of the study. For subsequent doses, duration of post dose monitoring will remain at Investigator's discretion. Participants will be observed for AEs including systemic reaction (i.e., allergic [type 1 hypersensitivity] reaction and other systemic reactions) and local injection site reactions.

To maintain the blinding to dose and frequency from qualifying Ph2 parent study, all participants will receive CCI SC injections until their qualifying Ph2 parent study has been analyzed or reported. Participants on CCI frequency from the qualifying Ph2 parent study will receive GSK1070806 CCI alternating with a placebo injection CCI to maintain the blind. After their qualifying Ph2 parent study has been analyzed or reported, placebo injections will be discontinued.

The primary endpoint of Incidence of AEs, discontinuation from study treatment due to AEs, SAEs, and AESIs will be measured throughout the duration of the study. In addition, efficacy will be measured throughout the duration of the study via the assessment of EASI, IGA, PP-NRS, SP-NRS. Quality of life and impact of disease will be assessed using the POEM, DLQI, PROMIS-Sleep Disturbance 8b and HADS, and WPAI-AD measures.

Safety will also be assessed by monitoring adverse events, ECGs, serum chemistry, hematology and urinalysis laboratory testing, physical examination, pulse, and blood pressure. Serum and blood samples will be collected for pharmacokinetic and pharmacodynamics analysis and immunogenicity.

The study will appoint an iDRC, independent to the study team, that will review accumulated safety and efficacy data, at interim analyses periodically throughout the study to determine appropriate recommendations for study conduct.

4.2. Scientific rationale for study design

The study is designed to evaluate the long-term safety and efficacy of a range of doses of GSK1070806 CCI in participants with moderate-to severe atopic dermatitis, who participated in previous GSK1070806 atopic dermatitis studies. This study includes a blinded initial treatment period, based on responders/non-responders' status in the qualifying Ph2 parent study, to ensure there will be no unblinding related bias until qualifying Ph2 parent study has been analyzed or reported.

By enrolling participants from qualifying Ph2 parent studies, who the investigator believes would derive benefit from receiving GSK1070806, this study represents a population analogous to one that would be treated in clinical practice. The use of low and moderate TCS will be allowed during the study.

GSK1070806 is an experimental drug, the long-term study will provide appropriate safety and efficacy monitoring based on the phase of development. The study will have maximum 5-year treatment period (264 weeks) and a CCI safety follow up period, which is anticipated to enable participants to receive treatment with GSK1070806 until it is expected to become commercially available. The CCI follow up period was established according to the half-life of the study drug. Subject to regulatory approval, the study treatment duration may be increased if necessary to align with revised commercial availability, or reduced, if an alternative early access (or equivalent) program is started, or if development of GSK1070806 in AtD is stopped. Participants who prematurely withdraw from the treatment period will be followed up for at least CCI post last dose.

4.2.1. Participant input into design

Patient engagement surveys were conducted for the Ph2b parent study and outcome of these surveys was considered for the LTE study.

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 parent Ph2b study 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).

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

CCI [redacted]

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 (W280).

The end of the study (EoS) is defined as the date of the last visit of the last participant related to primary and secondary endpoints. If EoS is not equal to LSLV, it must be achieved no later than 8 months after LSLV.

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 of the following criteria apply:

- Participant must sign and date an informed consent. INC#1
- Participant must be 18 years of age inclusive, or older at the time of signing the informed consent. For country specific age criteria refer to Appendix 6 (Section 10.6). INC#2
- Participants with a diagnosis of moderate to severe AtD who have completed the qualifying Ph2 parent GSK AtD studies, who, in the opinion of the investigator, may benefit from treatment with GSK1070806. INC#3
- 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). INC#4
- 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. The investigator should evaluate potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention. INC#5
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) 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. INC#6

5.2. Exclusion criteria

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

5.2.1. Medical Conditions

- Had study intervention permanently discontinued at any time during a qualifying Ph2 parent GSK AtD clinical study, or developed a medical condition that would preclude participation as per qualifying Ph2 parent GSK AtD clinical study protocol. EXC#1
- Participants who, during their participation in qualifying Ph2 parent GSK AtD clinical study, developed an AE or an SAE based on laboratory parameters, physical examination, vital signs, ECG, medical history, which in the opinion of the Investigator could indicate that continued treatment with IMP may present an unreasonable risk for the participant. EXC#2

5.2.2. Prior/Concomitant Therapy

- Use of medicated topical treatment for AtD, within 1 week prior to Day 1 visit, such as: TCI/TCS, PDE-4 and topical JAKi
  - 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. EXC#3
- Any participant who received prohibited systemic therapies, including systemic therapy used as rescue medication for AtD, from the time of screening for the qualifying Ph2 parent GSK AtD clinical study to the start of the LTE protocol will not be eligible. EXC#4
- 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). EXC#5

5.2.3. Prior/Concurrent Clinical Study Experience

- Participants taking part in any other clinical study, other than qualifying Ph2 GSK parent studies. EXC#6

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.

5.3.3. Activity

No specific restrictions.

5.3.4. Other restrictions

Not specific restrictions.

5.4. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned 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, and any SAE.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

The below study interventions can be administered in the LTE, depending on the study interventions applicable in the qualifying Ph2 parent study.

Details on which interventions will be applicable for the participants will be provided in the pharmacy manual.

Table 3 Study Intervention Administered

Study intervention name:	GSK1070806 Injection, 100 mg/mL	GSK1070806 Injection, 100 mg/mL	GSK1070806 Injection, 100 mg/mL	GSK1070806 Injection, 100 mg/mL	Placebo 0.9% sodium chloride injection
Dose levels	CCI				CCI
Dose volume					Matching active intervention
Dose Regimen					CCI to maintain the blind of qualifying Ph2 parent study for the CCI regimen (*)
Formulation	CCI				
Presentation	Study Intervention will be provided centrally by the sponsor in CCI Each CCI will be labelled as required per country requirement.	Study Intervention will be provided centrally by the sponsor in CCI Each CCI will be labelled as required per country requirement.	Study Intervention will be provided centrally by the sponsor in CCI Each CCI will be labelled as required per country requirement.	Study Intervention will be provided centrally by the sponsor in CCI Each CCI will be labelled as required per country requirement.	Study intervention will be purchased locally, commercially and used in its commercial container closure systems
Type (study intervention or control)	Study intervention	Study intervention	Study intervention	Study intervention	Control

(*) Placebo injections intended to maintain the blinding until their qualifying Ph2 parent study has been analyzed or reported.

6.2. Preparation, handling, storage, and accountability

- Placebo (0.9% normal saline) will not be supplied by the sponsor. It will be purchased commercially by the study site, subsidiary, or designee and used in its commercial container closure system as single-dose product. The manufacture's drug label instructions and/or packet insert should be followed for handling, dose preparation, and administration. Sites should use the most up to date version of packet insert.
- 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 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 with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study 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 Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Assignment to study intervention

Study using RTSM	All participants will be allocated to study intervention using RTSM RAMOS NG, based on their responder/non-responder status in the qualifying Ph2 parent study and the study intervention they received in the qualifying Ph2 parent study. Details on the allocation algorithm will be provided in the pharmacy manual. In order to avoid unblinding related bias before analysis in qualifying Ph2 parent study, intervention allocation and administration will be blinded for the participants and the site staff (except for the unblinded pharmacist or delegate), until their qualifying Ph2 parent study has been analyzed or reported. Before the study is initiated, the log-in information and directions for the RTSM will be provided to each site. A unique participant number (different from the one received in the qualifying Ph2 parent study) will be assigned to any participant who has at least 1 procedure performed, other than informed consent. The unique participant number will be used to identify individual participants during the course of the study. Once a participant number have been assigned to a participant, they will not be reassigned to any other participant in the study. Study intervention will be dispensed at the study visits as summarized in the SoA. Returned study intervention should not be re-dispensed to the participants.

RTSM = Randomization and Trial Supply Management; SoA = Schedule of activities.

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.	Until their qualifying Ph2 parent study has been analyzed or reported, investigators will remain blinded to each participant's assigned study intervention. To maintain this blind, unblinded authorized staff will be responsible for the preparation and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense. 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 study allocation/dispensing has been conducted accurately.
Emergency unblinding	Until their qualifying Ph2 parent study has been analyzed or reported this is a double-blind study in which participants, investigators and blinded site staff are blinded to study intervention. The RTSM 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 RTSM, 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 performing [redacted] development using [redacted] unblinded datasets, including baseline demographic characteristics.

CRF = Case report form; GSK = GlaxoSmithKline Biologicals SA; [redacted] RTSM = Randomization and Trial Supply Management.

A participant may continue in the study if that participant's intervention assignment is unblinded. 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 safety report be sent to one or more regulatory agencies, a copy of the report identifying the participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Study intervention compliance

When participants are dosed at the site, they will receive study intervention directly from the authorized unblinded site staff under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

The dose of study intervention and study participant identification will be confirmed at the time of dosing by the authorized unblinded site staff on specific unblinded forms.

6.6. Dose modification

Dose justification and stopping criteria are detailed in Section 4.3 and Section 7.1, respectively. This protocol allows some alteration from the currently outlined dosing schedule, but the maximum dose will not exceed [redacted].

Dose modification is possible only as described in Section 6.9.3.

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

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:

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate.
- Document the quantity of the excess dose in the eCRF.

6.9. Prior and concomitant therapy

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- the name of medication, vaccine, or therapy
- the reason for use
- dates of administration, including start and end dates
- route, and
- dosage information including dose and frequency for concomitant therapy.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Permitted Concomitant Therapies

The use of concomitant medications for other medical conditions, for example, hypertension, diabetes, or acute infections, is permitted during this study.

Use of topical treatments

Medicated topical treatments (such as low and moderate TCS) will be permitted throughout the study.

Non-medicated moisturizers

Participants should apply a stable regimen of non-medicated topical moisturizer daily throughout the study. The participants may continue their current over-the-counter moisturizer regimen, if approved by the investigator.

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.

Concomitant therapy regimens

All participants should maintain their usual medication regimens for concomitant conditions or diseases throughout the study, unless those medications are specifically excluded in the protocol.

Participants taking concomitant medications should be on stable dosages at the time of rollover and should remain at stable dosages throughout the study, unless changes need to be made because of AEs.

Changing concomitant therapy

Participants should consult with authorized study personnel before taking any new medications or supplements during the study. Authorized study personnel should consult the sponsor’s medical monitor if there are any questions about concomitant therapies during the study.

6.9.2. Prohibited medications

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

- Systemic treatments (oral or injectable):
  - Immunosuppressants:
    - Corticosteroids (e.g., prednisolone, budesonide) (unless used as `rescue` aligned with the guidance described in Section 6.9.3)
    - Calcineurin inhibitors (e.g., tacrolimus, cyclosporin) (unless used as `rescue` aligned with the guidance described in Section 6.9.3)
    - 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 study.

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 medicine

During this study, rescue therapy may be needed if the participant experiences clinical worsening of symptoms that are intolerable.

Allowed rescue medication

The use of rescue medications should be consistent with local guidelines.

The investigator should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose as shown in the SoA.

At any point in the study, rescue treatment for AtD (high potency topical therapies) may be provided to participants during the study. Investigators will be required to perform an IGA assessment prior to starting rescue treatment and initiate rescue treatment only in participants who either have an IGA score = 4 or have intolerable symptoms.

In participants who do not improve sufficiently, with the medicated topical treatments (such as low and moderate TCS) after at least 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, this will lead to discontinuation of study drug, except for a short-term use of oral corticosteroids (≤10 days).

From Week 8 of the LTE, the participants on rescue therapy that start losing response* will have the opportunity to receive the top dose.

*Loss of response: participants unable to maintain the IGA 0/1 or EASI 75 response after **having at least 2 weeks of TCS high potency treatment**.

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 and safety information (e.g., telephone contact, retrieval of vital status information through medical records). See the SoA (Section 1.3) 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 8.3.5
- 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 stopping criteria
Physician decision
Pregnancy
Protocol deviation
Site terminated by sponsor
Study terminated by sponsor
Withdrawal by participant
Other
Death

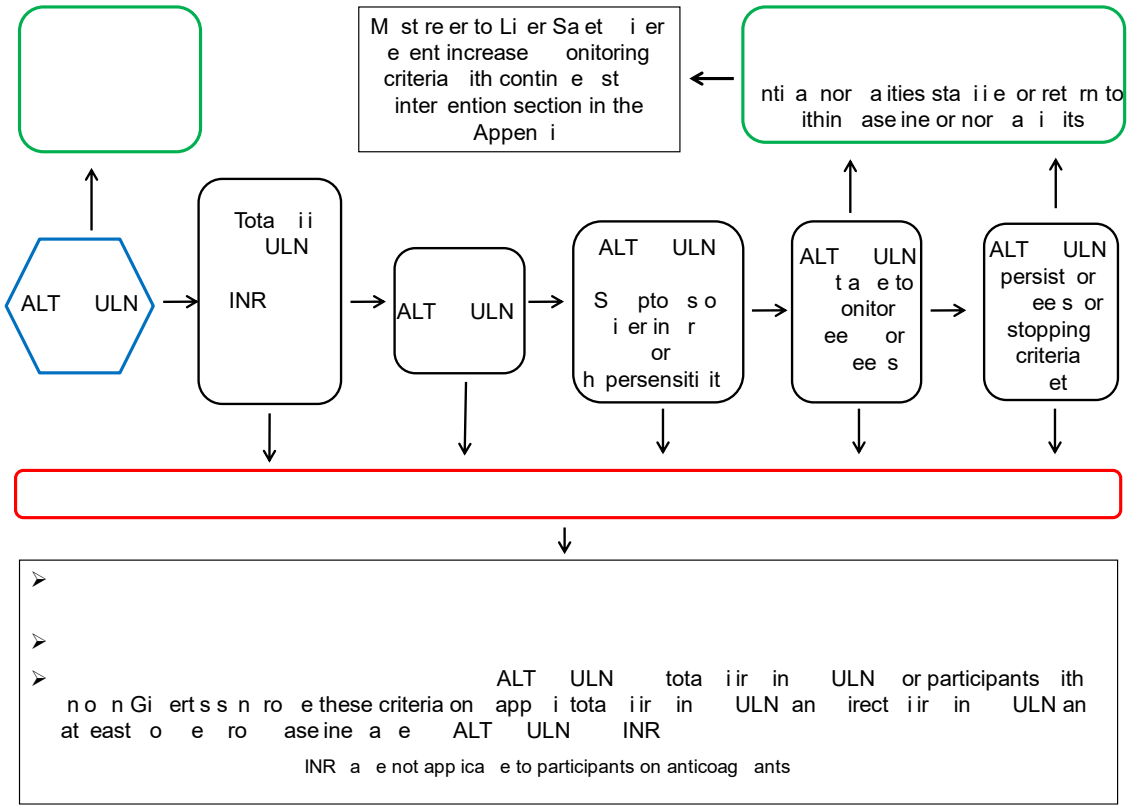
7.1.1. Liver event stopping criteria

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 1 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 the best interest of the participant.

Figure 2 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 10.5.1 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 10.5.2 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 QT interval corrected using 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

QTc = QT interval corrected.

7.1.3. Temporary discontinuation

If a serious infection, opportunistic infection, or suspected TB develops, temporarily delay administration of the 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 in this study are not allowed.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

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

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

At the time of withdrawing from the study, if possible, an EW visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study withdrawal 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 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 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, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, 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.
- While on site, study procedures should be conducted preferably in the following order:
  - Participant reported outcomes
  - Physician reported-outcomes
  - SAEs/AEs and concomitant medications recording
  - ECG, physical examination, vital signs
  - Blood and urine sampling. All PK, PD and immunogenicity sampling must be done before dosing.
  - Dosing
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All relevant 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'.
- Signed informed consent for the LTE study will be collected preferably the visit before, but no later than the End of Study (EOS) visit in the qualifying Ph2 parent study.
- In case a TCS 7-day wash-out is to be initiated at EoS visit in qualifying Ph2 parent study, Day 1 visit is to be performed at the latest 9 days after EoS visit of qualifying Ph2 parent study. In such case, all efficacy assessments (IGA, EASI, PROs) are to be conducted again at Day 1 visit. If no TCS wash-out is needed or if the TCS wash-out is completed at EoS visit of qualifying Ph2 parent study, this EoS visit can also be Day 1 visit of the LTE (all D1 assessments and samplings will be from the EoS visit from qualifying Ph2 parent study) and the Day 1 dosing can take place.
- Should the participant not be able to stay for Day 1 dosing and the post-dose safety monitoring period of 2 h, then Day 1 visit needs to take place within 3 days after EoS visit of Ph2 parent study. If Day 1 visit is later than 3 days after EoS visit of qualifying Ph2 parent, then efficacy assessments (IGA, EASI, PROs) will have to be repeated.
- 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.
- On the visits where blood sampling will be performed, the collected blood volume depending on the scheduled analyses is provided in 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 date/year of birth, sex, race, and ethnicity the participant's eCRF if allowed per local regulation.

Collection of sex, race and ethnicity data (if allowed per local regulation) is necessary to assess and monitor the diversity of the study participants, and to determine if the study 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 records. Record pre-existing conditions, signs and/or symptoms present prior to study start in the eCRF.

8.2. Efficacy assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. 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 and certified 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.

The IGA must be conducted prior to conducting the EASI assessment.

Assessors must be trained and certified 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.

8.2.2. Patient Reported Outcomes (PROs)

Refer to SoA Section 1.3 for the scheduling of PROs. The PROs will be administered to participants in different regions in their respective local languages.

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 up to Week 16. 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.

After Week 16, the frequency of administration will be reduced from daily assessments to assessments only at specific site visits as per SoA (Section 1.3).

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 up to Week 16 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 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.

8.2.2.4. 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.

8.2.2.5. 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.

8.2.2.6. 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.

8.2.2.7. 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.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA Section 1.3. 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, assessments of the skin, CV, respiratory, gastrointestinal, and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen (liver and spleen).
- 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, weight, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests). Weight will only be collected at EoS and EW Visits.
- Blood pressure, pulse measurements and respiratory rate is recommended to be preceded by a few 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 but before lung function testing 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 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 for the list of clinical safety laboratory tests to be performed in accordance with laboratory 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 or after the last dose of study intervention should be repeated 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 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.
- 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.

8.4. 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 study procedures, 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 legally authorized representative).

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

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

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 Section 8.4.1.

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, per the local country requirements. 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. AESIs

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, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	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 reports 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 CCI 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 10.3.3 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 eCRF. Instructions for the collection, processing, storage, and shipment of the samples will be described in the laboratory 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 study.

8.6. Pharmacodynamics (Target engagement)

Serum samples will be collected for the measurement of Total IL-18 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 eCRF. Instructions for the collection, processing, storage and shipment of the samples will be described in the laboratory 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 study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Immunogenicity samples will be collected at the time points specified in the SoA table. Details for immunogenicity blood sample collection, processing, storage, and shipping will be provided in the laboratory manual. Additionally, samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

The timing and number of planned immunogenicity/PK/PD samples may be altered during the course of the study, based on newly available data to ensure appropriate safety monitoring or event-driven testing.

The detection and characterization of antibodies to GSK1070806 may be performed using an ADA assay applied in a tiered testing strategy. Additional analyses may be performed to further characterize the antibodies for their ability to neutralize the activity of GSK1070806 if required. Samples may be used for immunogenicity assay life-cycle management if necessary.

Samples may be stored for a maximum of 20 years (or according to local regulations) following the last participant’s last visit for the study at a facility selected by the sponsor to allow for scientific research and further analysis of immune responses to GSK1070806.

8.10. Health economics or medical resource utilization and health economics

Health economics OR Medical resource utilization and health economics parameters are not evaluated in this study.

8.11. SPFQ- Study Participant Feedback Questionnaire (optional)

This study will include an option for participantss to complete an anonymized questionnaire, SPFQ, to provide feedback on their clinical study experience. Individual participant level responses will not be reviewed by investigators. Responses would be used by the sponsor to understand where improvements can be made in the clinical study process. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect or AEs and therefore would not be study data. Please refer to SOA for exact timepoints.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

There are no formal statistical hypotheses to be tested: this study is designed to describe the long-term safety and efficacy of GSK1070806.

9.2. Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	All participants who signed the ICF and entered the study.	Study Population
Assigned	All participants who were assigned to study intervention in the study.	Study Population
Safety	All assigned participants who receive at least 1 dose of study intervention in this LTE study. Participants will be analyzed according to the intervention they actually received.	Study Population Safety Efficacy PROs
PD	All participants in the Safety analysis set who had at least 1 non-missing PD assessment. Data will be reported according to the actual study intervention.	PD
PK	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (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

9.3. Statistical analyses

9.3.1. General Considerations

No formal statistical hypotheses will be tested as this study is designed to describe the long-term safety and efficacy of GSK1070806.

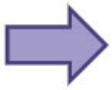
The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any changes to the original planned analysis 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 will be expressed as n (%), and continuous variables will be presented as mean with standard deviation or as median with interquartile range, depending on distribution.

For safety and efficacy analyses, qualifying Ph2 parent study baseline will be used for all the treatment arms in the LTE.

Data will be summarized descriptively by treatment arms defined by the treatment received in the Ph2 parent study and the treatment received in the LTE:

	Qualifying Parent Study
Responder	Top dose
	Intermediate Dose 1
	Intermediate Dose 2
	Intermediate Dose 3
	Placebo
Non-Responder	Intermediate Dose 1
	Intermediate Dose 2
	Intermediate Dose 3
	Placebo



LTE
Top dose
Intermediate Dose 1
Intermediate Dose 2
Intermediate Dose 3
Placebo
Top dose
Top dose
Top dose
Top dose

From Week 8 of the LTE, participants on rescue therapy that start losing response will have the opportunity to receive the top dose for the rest of the study (as described in Section 6.9.3). The participants who switched treatment during the study may be pooled together and presented as a separate group for the descriptive statistics (i.e., in addition to treatment arms specified above). Some of the above treatment arms may be pooled together for the purpose of reporting the study if appropriate, further details will be provided in the SAP.

9.3.2. Primary Analyses

9.3.2.1. Primary endpoint analyses

The primary objective of this study is to assess long-term safety. Please refer to Section 3.1 for primary endpoints and Section 3.2 for estimands and Section 9.3.1 for definition of baseline for safety.

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
All safety	All analyses will be descriptive in nature. Data will be summarized using frequency counts, proportions, summary statistics, graphs, and listings. Incidence rates and exposure-adjusted incidence rates will be calculated for AEs, SAEs, and AESIs.

Data will be summarized using frequency counts, proportions, summary statistics, graphs. Incidence rates and exposure-adjusted incidence rates will be calculated for AEs, SAEs, and AESIs. Laboratory data, immunogenicity data, ECG and vital signs will be presented in tabular and/or graphical format and summarized descriptively according to GSK standards.

9.3.3. Secondary endpoint analyses

The secondary objective of this study is to evaluate long-term efficacy of GSK1070806 in participants with moderate to severe atopic dermatitis. Please refer to Section 3.1 for secondary endpoints, Section 3.2 for estimands and Section 9.3.1 for definition of baseline for efficacy.

The following summaries will be provided in treatment arms defined by the treatment received in the qualifying Ph2 parent study and the treatment received in the LTE:

- For binary endpoints: number and percentage of participants in each treatment condition achieving an endpoint. Missing data in binary endpoints will be imputed as non-response.
- For continuous endpoints: mean and 95% CIs

All analyses will be descriptive in nature.

Endpoint	Statistical Analysis Methods
All clinical efficacy assessments	Data will be summarized using summary statistics, frequency counts, proportions, graphs, and listings.

Full details of all data analyses will be provided in the SAP.

9.3.4. Exploratory Analyses

CCI [redacted]. Details of this analysis and other exploratory endpoint analysis will be provided in the SAP.

9.4. Interim analyses

Unblinded analyses may be conducted throughout the trial to support regulatory interactions, internal decision making and discussion about the development plans.

An iDRC will be utilized in this study to ensure ongoing objective medical and/or statistical review of safety and efficacy data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study.

Full details of any interim analyses will be prospectively described in the iDRC charter.

9.5. Pre-dose sample size determination

CCI

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 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 and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection (e.g., HIPAA and GDPR 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.
- 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 given sufficient time (approximately 1 week) to reflect between being informed and the signature of the consent.
- A physical copy of the ICF(s) must be provided to the participant.
- The participant must provide consent by signing an ICF, which summarizes the study, includes a consent statement and provides documentation that the participant agrees to continue participating in the study.

In case of unexpected pregnancy, participant must be informed that PI such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for collection of information about the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment strategy

As the participants will be rolling-over from a qualifying Ph2 parent study and that no new participants will be enrolled in the study, no recruitment strategy will be defined.

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 must be informed that 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, that data will be used as described in the informed consent.
- The participant must be informed that 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

In line with routine pharmacovigiliance, an 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.

An iDRC will be appointed for this study. The iDRC review interim data periodically throughout the study 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 iDRC Charter.

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 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 layperson summary of results 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 treatment allocation at the time of the treatment unblinding in the qualifying Ph2 parent study 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 patient 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 eCRFs 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 non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plans.
- 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 a minimum period of 15 years from the issue of the final CSR/ equivalent summary or in accordance with Applicable Law, whichever is longer. 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 source data are sent for external assessment or adjudication (e.g., endpoint adjudication committee; expert reader), source data 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/eDiaries and/or DCT Platform or entered in the eCRF/eDiaries and/or DCT Platform 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 guidelines.

- 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.

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

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

- 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 6 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[1]	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[2]	Gamma-Glutamyl Transferase (GGT)	Albumin
	Sodium			
	Estimated Creatinine Clearance/glomerular filtration rate (CKD-EPI[3])			

Laboratory Assessments	Parameters
Coagulation Profile	• International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT), Fibrinogen
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 Assessments	• 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 and 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[4]

ULN = Upper limit of normal; WBC = White blood cell; WONCBP = Woman of nonchildbearing potential.

Note: Full CTCAE descriptions and grades can be found in the U.S Department of Health and Human Services, [CTCAE, 2017] Version 5.0.

1. Details of liver event stopping criteria and required actions and follow-up are given in Section 7.1.1 Liver event stopping criteria and Section 10.5 Liver safety requirements and guidelines. All events of ALT ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to GSK within 24 hours (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. 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.
4. Should be performed as described in the SoA.

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. • Significant failure of an expected pharmacologic or biological action. • 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 one 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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
– 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 one of the other outcomes listed in the above definition. These events should usually be considered serious. o 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 CV events

CV 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.

CV definition:
• 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, AESI and SAE 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 a SAE follow-up report with the updated causality assessment.
- The causality assessment is one 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 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, pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious 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 or until the participant is lost to follow-up.

Follow-up during the study

AEs, SAEs or 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 product that is not part of the study design, 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 one 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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study 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 Clinical Trial Facilitation Group (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).

10.5. Appendix 5: Liver safety requirements and guidelines

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

Table 7 Required actions, monitoring, and follow-up to assess causality of liver event

Liver event study intervention stopping criteria	
ALT-absolute	ALT ≥5xULN
ALT Increase	Unable to monitor weekly for 4 weeks: ALT ≥3xULN Able to monitor weekly: 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.
Bilirubin[1, 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)
INR[2]	ALT ≥3xULN and INR>1.5
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required actions, monitoring and follow-up to assess causality of liver event	
Actions and monitoring	**Follow-up to assess causality of liver event**
• **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-to assess liver event causality within 24 hours. • Monitor participant 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. **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/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.	• 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 (where available), 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. **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.

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

Table 8 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.

10.6. Appendix 6: Country-specific requirements

10.6.1. 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.

Participants from Japan are not eligible if positive for HBsAb, negative for HBV DNA, HBV vaccination history is not clear.

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.

10.6.2. 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.

10.6.3. 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.

10.6.4. 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.

10.6.4.1. " O O U O U O WITHDRAWAL CRIT "

The vulnerable subject populations mentioned in articles L1121-5, L1121-6, L1121-7, L1121-8 and L1122-1-2 of the public health code will be excluded from participating in the study.

A subject 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 subject is affiliated to or beneficiary of a social security category.

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

10.6.4.2. " U GOV O O "

- **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.

10.6.4.3. " G " 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).

10.6.4.4. 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.

10.6.4.5. 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).*

10.6.5. EU specific requirement

CCI

[redacted]

10.6.6. 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.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

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