TITLE PAGE

Protocol Title: A multicentre randomized, double-blind, placebo-controlled Phase 2 study to evaluate the safety, tolerability, efficacy, dose-response, pharmacokinetics and pharmacodynamics of repeat dosing of an anti-LAG3 cell depleting monoclonal antibody (GSK2831781) in patients with active ulcerative colitis.

Protocol Number: 204869/04

Compound Number: GSK2831781

Study Phase: Phase 2

Short Title: Safety, tolerability, efficacy and dose-response of GSK2831781 in ulcerative colitis.

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

Ruth Tarzi, BM BCh PhD FRCP Clinical Development Leader	**Date**

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Document Date**	**DNG Number**
Amendment 4	*12-NOV-2020*	*TMF-2197350*
Amendment 3	*03-SEP-2020*	*2017N337668_03*
Amendment 2	*10-SEP-2019*	*2017N337668_02*
Amendment 1	*17-JAN-2019*	*2017N337668_01*
Original Protocol	*15-OCT-2018*	*2017N337668_00*

Amendment 4: 12-NOV-2020

Overall Rationale for the Amendment:

The rationale for the amendment includes:

- Main changes: Response to Health Authority feedback following review of Protocol Amendment 3, regarding the first SC dose administration and post dose monitoring.
- Minor changes: clarification for investigators and administrative corrections.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis - Number of participants	Updated 'a complete week 10 Complete 4-domain Mayo score assessment' to '**an incomplete** week 10 Complete 4-domain Mayo score assessment'.	Correction to align mismatched text with Section 4.1.3.
Section 1.2 Schema	Removed the ambiguity for non-responders at Week 22: for these participants there are no remaining scheduled visits other than the Follow-up Visit.	Clarification for Investigators.
Section 1.3 Schedule of Activities (SoA): Double Blind Treatment	Repositioned/added table footnote superscripts (number 22) and updated text for footnotes 15, 20, 21, 22 and 28.	Clarification for Investigators.
Section 1.3 Schedule of Activities (SoA): Open Label Treatment	Repositioned/added table footnote superscripts (number 13) and updated text for footnotes 7, 8 and 13.	Clarification for Investigators.
Section 3 Objectives, Endpoints and Estimands	Updated the secondary endpoint 'Histological severity as determined by the Geboes Score at Week 10' to 'Histological severity as determined by the **Geboes Histological Index** at Week 10'.	Correction to align mismatched text with Section 1.1 (Synopsis).
Section 4.1.2 Open Label Treatment for	Added 'clinical response is calculated centrally in eCRF' and removed the	Clarification for Investigators.

Section # and Name	Description of Change	Brief Rationale
Non-Responders	ambiguity for non-responders at Week 22: for these participants there are no remaining scheduled visits other than the Follow-up Visit.	
Section 4.3.3. Open Label Treatment	Deleted a redundant sentence, as not relevant to the 'Dose Justification' section.	Clarification for Investigators.
Section 4.4 End of Study Definition	"Participants who withdraw from the study early should be encouraged to complete all visits **for that specific phase** as set out in the SoA (Section 1.3); however, if this is not possible at a minimum participants will be asked to complete all assessments at both the Early Withdrawal visit and a Follow-Up visit approximately 16 weeks after the last dose (Section 7.2) to ensure participant monitoring **following drug wash out**." • Added 'for that specific phase'. • Changed 'until drug washout is achieved' to 'following drug washout'.	Clarification for Investigators.
Section 6.2 Intervention Administration	Updated Table 1 and Table 2 to Increase the post dose monitoring period, for the first SC dose, from 30 mins to 2 hours.	Response to a request from a Health Authority, following Protocol Amendment 3 review.
	Updated Table 1 and Table 2 to include the flush time for the 3rd and 4th IV doses.	Clarification for Investigators: to be consistent with the 1st and 2nd IV dosing duration, which includes the flush time.
Section 6.3 Preparation/Handling/ Storage/Accountability	Deleted 'from GSK' to clarify that a Material Safety Data Sheet (MSDS)/ equivalent is 'available upon request.'	Clarification for Investigators.
Section 7.1 Discontinuation of Study Intervention	Updated to reflect that participants discontinuing study treatment will be requested to attend the remaining visits for the treatment phase they are in, and that an Early Withdrawal visit is only needed for participants that do not wish to attend these remaining visits.	Clarification for Investigators.
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Updated to reflect that participants discontinuing study treatment will be requested to attend the remaining visits for the treatment phase they are in, and that an Early Withdrawal visit is only needed for participants that do not wish to attend these remaining visits	Clarification for Investigators.
Section 8.7.1 Time Period and	Removed a redundant sentence and clarified that all SAEs are to be collected	Clarification for Investigators.

Section # and Name	Description of Change	Brief Rationale
Frequency for Collecting AE and SAE Information.	from the signing of the informed consent form.	
Section 10.10 Appendix 10 Home Healthcare	Removed 'Week 14' from 'Double-blind Responders' and 'Week 26' from 'Open Label Responders' as visits where home health care may be permitted. Added 'first SC dosing' to the first bullet under 'exceptions to the option for home healthcare include:'.	Response to a request from a Health Authority, following review of Protocol Amendment 3.
Section 10.12 Appendix 12 Abbreviations and Trademarks	Removed duplicate listing of abbreviations: 'ETP' and 'ECG'	Correction of errors.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A multicentre randomized, double-blind, placebo-controlled Phase 2 study to evaluate the safety, tolerability, efficacy, dose-response, pharmacokinetics and pharmacodynamics of repeat dosing of an anti-LAG3 cell depleting monoclonal antibody (GSK2831781) in patients with active ulcerative colitis.

Short Title: Safety, tolerability, efficacy and dose-response of GSK2831781 in ulcerative colitis.

Rationale:

T cells are integral to the pathogenesis of ulcerative colitis (UC), and clinical experience with anti-integrin monoclonal antibodies has established the principle of T cell-targeted therapies in the disease. Lymphocyte Activation Gene-3 (LAG3) is expressed on recently activated T cells, and $LAG3^+$ T cells are present in only low numbers in the circulation and healthy tissues. They are, however, increased in the colon in active UC, where their numbers correlate with disease activity [Slevin, 2018]. GSK2831781 causes targeted depletion of $LAG3^+$ T cells and has shown preliminary evidence of clinical efficacy in plaque psoriasis (another T cell-mediated disease). It is therefore hypothesized that GSK2831781 will selectively deplete activated mucosal T cells in UC, but with relative sparing of resting T cells.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of repeat doses of GSK2831781 during the Double-Blind Induction Phase.	• Incidence of adverse events and serious adverse events during the Double-Blind Induction Phase. • Incidence of findings of potential clinical importance[1] during the Double-Blind Induction Phase for: o Vital signs o Clinical laboratory values (haematology, clinical chemistry and urinalysis). o QTc.
• To characterise the efficacy dose-response of GSK2831781 during the Double-Blind Induction Phase.	• Change from baseline in Complete 4-domain Mayo score[2] at Week 10.

Objectives	Endpoints
Secondary	
• To evaluate the safety and tolerability of repeat doses of GSK2831781 during the Double-Blind Extended Treatment Phase.	• Incidence of adverse events and serious adverse events in the Double-Blind Extended Treatment Phase. • Incidence of findings of potential clinical importance during the Double-Blind Extended Treatment Phase for: o Vital signs o Clinical laboratory values (haematology, clinical chemistry and urinalysis). o QTc.
• To investigate the effect of repeat doses of GSK2831781 on clinical efficacy including endoscopic mucosal healing during the Double-Blind Induction Phase.	• Adapted Mayo endoscopic score of 0 or 1 at Week 10. • Adapted Mayo clinical remission[3] at Week 10. • Adapted Mayo clinical response[3] at Week 10. • Symptomatic remission[4] over time. • Change from baseline in Partial Mayo score over time. • Change from baseline in Adapted Mayo endoscopic score and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) at Week 10.
• To investigate the effect of repeat doses of GSK2831781 on UC histologic disease activity during the Double-Blind Induction Phase.	• Histological severity as determined by the Robarts Histopathology Index at Week 10. • Histological severity as determined by the Nancy Histological Index at Week 10. • Histological severity as determined by the Geboes Histological Index at Week 10.
• To investigate the effect of repeat doses of GSK2831781 on biomarkers of UC disease activity during the Double-Blind Induction Phase.	• Change from baseline in serum C-reactive protein over time. • Change from baseline in faecal calprotectin over time.
• To investigate the pharmacokinetics of GSK2831781 following subcutaneous dosing.	• GSK2831781 PK parameters: AUC(0-tau), Cmax, tmax.

Objectives	Endpoints
• To investigate the immunogenicity of repeat doses of GSK2831781 during the Double-Blind Induction Phase.	• Incidence of anti-drug antibodies at each visit.
Safety	
• To evaluate the safety and tolerability of repeat doses of GSK2831781 in all trial phases.	• Adverse events, vital signs, clinical laboratory values (haematology, clinical chemistry, and urinalysis), 12-lead ECG.
• To investigate the immunogenicity of repeat doses of GSK2831781 in all trial phases.	• Incidence of anti-drug antibodies at each visit.

Footnotes:

1 Potential clinical importance is defined in the RAP for each relevant safety endpoint.
2 The Complete 4-domain Mayo score is used for the primary endpoint due to its wider dynamic range for assessment of dose-response compared to the Adapted Mayo score used for secondary and exploratory endpoints.
3 Clinical response and remission for the various iterations of the Mayo score are defined in Appendix 7, Section 10.7.
4 Symptomatic remission is defined as a rectal bleeding subscore of 0, and a stool frequency subscore of ≤1, with no worsening from baseline.

Overall Design:

This is a Phase 2, multicentre, randomized, double-blind, parallel group, placebo-controlled study to investigate safety, tolerability, efficacy and dose-response of GSK2831781 in participants with moderate to severe active UC as defined by a 4-domain (Complete) Mayo score of 6-12. The study will consist of five arms: GSK2831781 at 450 mg, 300 mg, 150 mg and 45 mg and a placebo group and will investigate the Induction (up to Week 10), and maintenance with an Extended Treatment Phase (Weeks 10-30), of the achievement and maintenance of clinical response, remission and mucosal healing.

In addition, Non-Responders identified following the Week 10 assessment will be moved to open label treatment consisting of Induction (Weeks 12 to 22), an Extended Treatment Phase (Weeks 22 to 52), and a Follow-Up to Week 54.

Disclosure Statement: This is a parallel group treatment study with five arms that is participant, Investigator and sponsor blinded.

Number of Participants:

Approximately 242 participants will be randomly assigned to study intervention under the assumption that a proportion will not receive all planned doses up to Week 10 and/or have an incomplete Week 10 Complete 4-domain Mayo score assessment. If the attrition rate is higher than planned for (e.g., 15% or more) then additional participants, up to a maximum of 320, may be recruited.

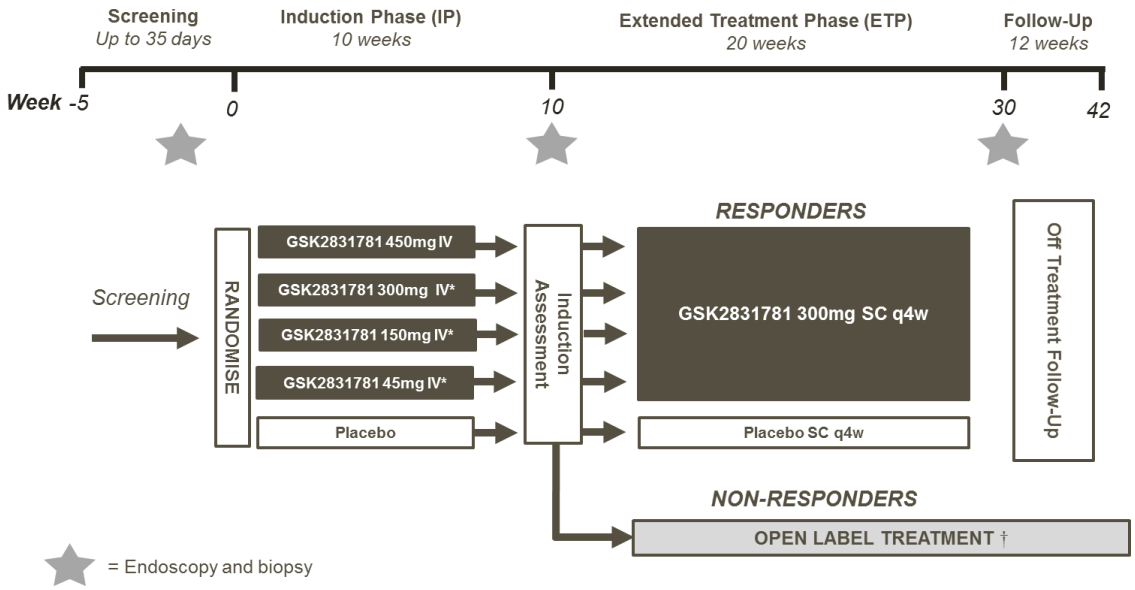
Intervention Groups and Duration:

Total duration for participants who respond to GSK2831781 will be approximately 47 weeks (see Section 1.2). The study consists of a 5-week screening window, 10-week Induction Phase (IP), 20-week Extended Treatment Phase (ETP), and a 12-week Follow-Up Phase. Non-Responders allocated to Open Label Treatment (GSK2831781 450 mg) who subsequently respond to treatment may spend up to 59 weeks in total on study. Intervention groups are shown in the schema below, Section 1.2.

Data Review Committee (DRC):

A DRC will be utilised in this study to review the interim analyses data in an unblinded manner. The DRC will be comprised of a predefined subset of project team members, senior GSK stakeholders and experts external to the project team to ensure that persons with the appropriate expertise and knowledge conduct and interpret interim reviews of data. No study personnel with direct contact with sites or site staff will be involved in the DRC (see Appendix 1, Section 10.1.5).

1.2. Schema



*Randomisation will initially be 2:1 to GSK2831781 450 mg or Placebo. When an appropriate number of participants have been randomised in these two arms for the interim analysis (Interim Analysis 3, see Section 9.5), randomisation to all dose regimens (GSK2831781 450 mg, 300 mg 150 mg, 45 mg or placebo) will be opened at a ratio of 2:3:3:3:2.. Dosing during the Double-Blind Induction Phase will be undertaken at Weeks 0 (Day 1), 2, 6 and 10. Responders at Week 10 (where Responder status is determined by a pre-specified algorithm in the eCRF) will continue into the Double-Blind ETP.

Participants originally randomised to GSK2831781 IV treatment arms (Induction) will receive subcutaneous doses of 300 mg GSK2831781 every 4 weeks at Weeks 14, 18, 22, and 26. Participants originally on placebo treatment arm, who attained response, will continue to receive blinded placebo through SC dosing at Weeks 14, 18, 22 and 26. The Double-Blind ETP ends at Week 30, with Follow-Up until Week 42 (16 weeks after the last dose).

[†]The open label patient journey is described fully in Section 4.1.2 and Figure 3. The Open Label ETP, for Non-Responders at Week 10, will constitute a full 10 weeks of induction dosing according to the same dosing schedule as GSK2831781 450 mg (IV doses at Weeks 12, 14, 18 and 22). The Open Label Induction Phase (OLIP) will start at Week 12 to allow turnaround of centrally determined responder status. Response following OLIP will be assessed at Week 22 in the Open Label ETP, and Responders will continue with doses of 300 mg GSK2831781 subcutaneously every 4 weeks from Week 26 to 38. Participants will then undertake a Follow-Up period of 12 weeks from Week 42 to Week 54. Participants in the Open Label ETP who are Non-Responders at Week 22 will discontinue study treatment and be managed according to physician standard of care but are still required to attend a Follow-Up visit approximately 16 weeks from the last dose event.

1.3. Schedule of Activities (SoA):

Double-Blind Treatment SoA

	Screening		Induction Phase						Extended Treatment Phase						Follow-Up[20]	Early Withdrawal Visit[21, 26]
WEEK			Pre-dose	Post-dose	2	4[26]	6	10	12[19]	14	18[26]	22[26]	26[26]	30	42[26]	
DAY	-35 to -7[23]	-14 to -7[14]	Day 1		15	29	43	71	85	99	127	155	183	211	295	
Window (days)					±2	±3	±3	±3	±5	±3	±3	±3	±3	±3	±7	
Study Population																
Informed Consent	X															
Inclusion/Exclusion Criteria	X															
Demography	X															
Weight	X							X		X				X	X	X
History[1] (Medical/Disease/ IBD Therapy)	X															
Extra-Intestinal Manifestations History	X															
Smoking status	X							X						X	X	X
Efficacy																
Determination of 'Normal' stool count for Mayo Score	X															
Endoscopy with Biopsy[2]		X						X						X		X[22]
Mayo (Complete or Partial)	P	C	P		P	P	P	C		P		P		C	P	C[22]/P
Steroid Taper									X							
Extra-Intestinal Manifestations Activity			X					X						X	X	X
Safety Assessments																
Vital Signs	X		X	X[16]	X[16]	X	X	X		X[16]	X[16]	X	X	X	X	X
12-lead ECG[3]	X		X	X[16]				X				X			X	X
Full/Brief Physical	F		B		B	B	B	B		B	B	B	B	B	F	F
Concomitant Medications	X		<----------												---------->	
AEs / SAEs[4]	<----------														---------->	
Haematology[5]	X		X		X	X	X	X		X	X	X	X	X	X	X
Clinical chemistry (incl. CRP)[5]	X		X		X	X	X	X		X	X	X	X	X	X	X
Pregnancy Test (WOCBP)[5, 6]	X		X			X	X	X		X	X	X	X	X	X	X

	Screening		Induction Phase						Extended Treatment Phase						Follow-Up[20]	Early Withdrawal Visit[21, 26]
WEEK			Pre-dose	Post-dose	2	4[26]	6	10	12[19]	14	18[26]	22[26]	26[26]	30	42[26]	
DAY	-35 to -7[23]	-14 to -7[14]	Day 1		15	29	43	71	85	99	127	155	183	211	295	
Window (days)					±2	±3	±3	±3	±5	±3	±3	±3	±3	±3	±7	
Urinalysis[5]	X		X		X	X	X	X		X	X	X	X	X	X	X
TB – QuantiFERON ± PPD[7]	X															
Serology (HIV, HBV, HCV, CMV, EBV and VZV)	X															
Clostridium difficile toxin	X															
FSH & oestradiol (if appropriate)[8]	X															
Dosing and PK/PD																
Randomization			X[27]													
IMP administration[9]			**IV**		**IV**		**IV**	**IV**		**SC**	**SC**	**SC**	**SC**			
PK[10, 11]			X	X[17]	X		X[18]	X		X	X	X	X	X	X	X
sLAG3[10, 11]			X	X[17]	X		X[18]	X		X	X	X	X	X	X	X
Blood proteomic signature[5]			X		X			X								
Blood transcriptomic signature[5]			X													
LAG3 Cell Depletion (by Flow Cytometry)[5,12]			X		X			X						X	X[28]	X[28]
Immunogenicity			X		X	X		X		X		X		X	X	X
4β-hydroxycholesterol (4βHC)[5]			X					X								
Faecal Calprotectin[24]			X		X		X	X				X		X	X	X
Serum Tryptase[5]			X				X	X				X		X	X	X
Patient Reported Outcomes																
IBDQ, FACIT-Fatigue and SF-36[13]			X				X	X				X		X	X	X
Bowel symptom eDiary	<----------															---------->
PGIC & PGIS[13]			X[15]					X						X	X	X
Exit Interview															X[25]	X[25]
Other																
PGx Sample	X															

Footnotes:

1 See SRM for requirements for data collection.
2 Endoscopy should be flexible sigmoidoscopy. However, colonoscopy can be performed at screening if required for assessment of dysplasia risk (see Section 5.1), and at any timepoint if clinically indicated.
3 ECG in triplicate at screening and single at all other time points. See Section 8.6.3, Electrocardiograms for further detail.
4 Collection of SAEs starts from screening whilst collection of AEs will commence from Day 1.
5 Unless specified otherwise, all samples will be taken prior to administration of study treatment.
6 Negative test required during screening and immediately prior to the first dose of study treatment. A serum pregnancy test is required at screening, after which a highly sensitive urine pregnancy test is adequate. If a urine test cannot be confirmed as negative, a serum pregnancy test is required.
7 A PPD test maybe performed following two indeterminate Quantiferon tests to determine TB status, see Section 5.2.
8 To confirm postmenopausal status, serum FSH and oestradiol testing will be performed for all postmenopausal females at the screening visit.
9 See Section 6.2 for details of dosing duration and monitoring period.
10 Unless stated, samples taken on a day of dosing must be pre-dose sample (up to 2 hr before the next dose).
11 Additional sampling will be required in a subset of participants to characterise SC pharmacokinetics. See Section 8.3, for schedule.
12 LAG3 depletion will only be undertaken in sites where shipping to central lab can be achieved in the required timeframe, see Section 8.4, and SRM.
13 IBDQ, FACIT-Fatigue, SF-36, PGIC and PGIS are to be performed before any other assessments on visit days.
14 A 7-day window enables turnaround of centrally read endoscopy score for inclusion to arrange Day 1 visit; however, endoscopy can be performed up to Day -3 if all other criteria for study eligibility have been met by this time and Robarts have agreed rapid turnaround of central endoscopy read.
15 PGIC not to be done on Day 1.
16 Vital signs to be taken every 30 minutes (±5 minutes) until completion of post dose monitoring period. A single ECG be taken within 4 hours of completion of dose administration. For participants who have discontinued treatment but remain on study, post-dose monitoring does not apply.
17 Samples to be taken immediately after end of IV infusion (preferably within 15 minutes).
18 Samples to be taken up to 2 hr before the next dose, and one sample immediately after end of IV infusion (within 15 minutes).
19 Week 12 visit scheduled to enable recall of Non-Responders to move to Open Label dosing at Week 12, see Open Label Treatment SoA below. Telephone call can be used to ensure Responders initiate steroid taper and cancel scheduled visit for Responders next due to undertake dosing at Week 14.
20 In case of Early treatment discontinuation, or study withdrawal, the investigator should undertake a Follow-Up visit approximately 16 weeks after the last dose event to allow safety monitoring following drug washout.
21 Participants who discontinue study treatment are encouraged to complete remaining scheduled visits for the treatment phase they are in. However, an Early withdrawal visit is only required for participants who prematurely discontinue study treatment and do not agree to complete the remaining scheduled visits for that phase.
22 Complete 4-domain Mayo Score (including Endoscopy) to be performed if withdrawal from study treatment occurs after Week 4 but prior to Week 10 (all participants) or between Week 18 and Week 30 for Responders. The endoscopy is to be performed either at the Early Withdrawal Visit (for participants who do not wish to complete remaining scheduled visits), or at Week 10 or Week 30 (for participants that agree to complete remaining scheduled visits after withdrawing from treatment).
23 The window for Screening Visit 1 can be extended to Day -45 where indeterminate test results are returned for assays requiring long central laboratory turnaround times (e.g., QuantiFERON and *C. difficile*). However, if haematology, clinical chemistry and (if applicable) serum pregnancy tests have been

performed outside of the Day -35 window they must be repeated and recorded as an unscheduled visit in the eCRF to confirm eligibility, even if performed at Screening Visit 2.

24 Faecal Calprotectin sample may be taken up to 48 hours prior to scheduled visit.

25 Exit interview, if applicable, to be undertaken either at Early Withdrawal or Follow-Up.

26 Home health care / telemedicine visits may be permitted where applicable country and local regulations and infrastructure allow.

27 Randomisation may be performed on Day -1. Randomisation may only proceed when all information pertaining to patient eligibility has been confirmed, including eCRF Mayo score eligibility calculation.

28 Samples only to be taken for participants that achieved a responder status at Week 10 and subsequently withdraw from treatment.

- Safety, pharmacokinetic, pharmacodynamic/biomarker or other assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.
- For details on home healthcare and telemedicine approaches, please refer to Appendix 10.

Open Label Treatment SoA

	Open Label Induction Phase				Open Label Extended Treatment Phase						Open Label Follow up[7]	Open Label Early Withdrawal Visit[8, 12]
WEEK	**12**	**14**	**18**	**22**	**24**	**26**	**30[12]**	**34[12]**	**38[12]**	**42[12]**	**54[12]**	
DAY	**85**	**99**	**127**	**155**	**169**	**183**	**211**	**239**	**267**	**295**	**379**	
Window (days)	**±5**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	
Endoscopy with Biopsy				X								X
Mayo (Complete or Partial)	P	P	P	C			P		P	P	P	C[13]/P
Extra-Intestinal Manifestations Activity				X						X	X	X[13]
Steroid Taper					X							
Weight				X						X		
Safety Assessments												
Vital Signs	X[5]	X[5]	X	X		X[5]	X[5]	X	X	X	X	X
12-lead ECG	X[9]			X							X	X
Full/Brief Physical	B	B	B	B		B	B	B	B	B	F	F
Concomitant Medications	<----------											---------->
AEs / SAEs	<----------											---------->
Haematology[1]	X	X	X	X		X	X	X	X	X	X	X
Clinical chemistry (incl. CRP)[1]	X	X	X	X		X	X	X	X	X	X	X
Pregnancy Test (WOCBP)[1, 2]		X	X	X		X	X	X	X	X	X	X
Urinalysis[1]	X	X	X	X		X	X	X	X	X	X	X
Dosing and PK/PD												
IMP administration[3]	**IV**	**IV**	**IV**	**IV**		**SC**	**SC**	**SC**	**SC**			
PK[1]	X[6]			X[6]						X	X	X
sLAG3[1]	X[6]			X[6]						X	X	X
Immunogenicity[1]	X	X		X			X		X	X	X	X
Faecal Calprotectin[10]	X		X	X					X	X	X	X
Patient Reported Outcomes												
IBDQ, FACIT-Fatigue and SF-36[4]			X	X					X	X	X	X
Bowel symptom eDiary	<----------											---------->
PGIC & PGIS[4]				X						X	X	X
Exit Interview											X[11]	X[11]

Footnotes:

1 Unless specified otherwise, all samples will be taken prior to administration of study treatment.
2 A highly sensitive urine pregnancy test is adequate. If a urine test cannot be confirmed as negative, a serum pregnancy test is required.
3 See Section 6.2, for details of dosing durations and monitoring periods.
4 IBDQ, FACIT-Fatigue, SF-36, PGIC and PGIS are to be performed before any other assessments on visit days.
5 Vital signs to be taken every 30 minutes (±5 minutes) until completion of post dose monitoring period. For participants who have discontinued treatment but remain on study, post-dose monitoring does not apply.
6 Additional PK sample immediately after end of IV infusion (preferably within 15 minutes of end of IV infusion).
7 In case of Early treatment discontinuation, or study withdrawal, the investigator should undertake a Follow-Up visit approximately16 weeks after the last dose event to allow safety monitoring following drug washout.
8 Participants who discontinue study treatment are encouraged to complete remaining scheduled visits for the treatment phase they are in. However, an Early withdrawal visit is only required for participants who prematurely discontinue study treatment and do not agree to complete the remaining scheduled visits for that phase.
9 A single ECG to be taken any time within post-dose monitoring period
10 Faecal Calprotectin sample may be taken up to 48 hours prior to scheduled visit.
11 Exit interview, if applicable, to be undertaken either at Early Withdrawal or Follow-Up.
12 Home health care / telemedicine visits may be permitted where applicable country and local regulations and infrastructure allow.
13 Complete 4-domain Mayo Score (including Endoscopy) to be performed if withdrawal from study treatment occurs after Week 16 but prior to Week 22 (all participants). The endoscopy is to be performed either at the Early Withdrawal Visit (for participants who do not wish to complete remaining scheduled visits), or at Week 22 (for participants that agree to complete remaining scheduled visits after withdrawing from treatment).

- Safety, pharmacokinetic, pharmacodynamic/biomarker and/or other assessments may be altered during the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.
- For details on home healthcare and telemedicine approaches, please refer to Appendix 10.

2. INTRODUCTION

2.1. Study Rationale

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD) characterized by chronic relapsing and remitting inflammation of the colon and rectum. There remains a high unmet need for novel treatments that achieve a higher rate of efficacy in resolving disease symptoms, and inducing and maintaining mucosal healing to achieve long-term corticosteroid-free remission.

This study is the first experience in patients with active moderate to severe UC with GSK2831781, a humanised Antibody-Dependent Cell Cytotoxicity (ADCC)-enhanced monoclonal antibody that is specific to the Lymphocyte Activation Gene-3 (LAG3) protein. LAG3 is not expressed by resting T cells, but is upregulated after T cell activation [Workman, 2002]. Furthermore, as only 0.5 to 5% of T cells in blood and secondary lymphoid organs express LAG3, GSK2831781 should spare $LAG3^-$ resting memory and naïve T cells, as well as the majority of natural regulatory T cells that are responsible for normal immune homeostasis. Therefore, the key attribute of LAG3 is its relatively selective expression profile for activated T cells.

T cells are integral to the pathogenesis of UC, and clinical experience with anti-integrin monoclonal antibodies such as Vedolizumab establishes the principle of T cell modulation in treatment. $LAG3^+$ cell numbers are increased in the colon in active UC, correlate with disease activity, and reduce after successful treatment with established biologic therapies but not in non-responders [Slevin, 2018]. By rapid and potent depletion of $LAG3^+$ T cells in diseased tissues, there is the potential to achieve fast and long-term disease remission. Given the highly selective nature of depletion, there may be improved safety and tolerability compared to current standard of care, and by targeting both intestinal and extra-intestinal activated T cells, GSK2831781 may have additional positive impacts on extra-intestinal manifestations of disease, such as arthropathy.

The primary objectives of this Phase 2 study are to assess the safety and tolerability of repeat doses of GSK2831781, and characterise the dose-response of GSK2831781 in change from baseline in Mayo score at Week 10. Key secondary endpoints include endoscopic mucosal healing and Mayo remission at Week 10, following which there will be an Extended Treatment Phase until Week 30 to gain insights into maintenance of remission.

2.2. Background

Ulcerative colitis is a chronic, relapsing-remitting inflammatory disorder with a prevalence estimated to be 70-500 cases per 100,000 [Ng, 2018]. Symptoms vary depending on the severity of inflammation and extent of disease, but patients typically experience recurrent episodes of rectal bleeding and diarrhoea, often associated with crampy abdominal pain and tenesmus. Severe or refractory colitis can necessitate surgical colectomy, and patients with longstanding UC are at increased risk of colorectal cancer. There are currently no medical therapies that are curative, and surgery is associated with significant morbidity (including recurrent pouchitis in up to 25% of patients, faecal incontinence, and female

infertility). With existing pharmacological treatments, many patients either fail to respond or respond incompletely (i.e. have residual symptoms or ongoing mucosal inflammation), lose response over time, or experience treatment-limiting side-effects. Only a minority attain and maintain steroid-free remission in the long-term, and consequently other treatments are required to fulfil these unmet needs.

Clinical experience with GSK2831781 to date comes from a single IV ascending dose study (NCT02195349, GSK Study 200630) in healthy volunteers (up to 0.15 mg/kg) and patients with mild to moderate plaque psoriasis (0.5-5 mg/kg). No safety or tolerability concerns were identified. Proof of mechanism was achieved, with dose-dependent depletion of $LAG3^+$ cells in blood and skin, positive effects on psoriatic skin disease activity markers such as CD3 and pro-inflammatory messenger ribonucleic acid (mRNA) transcripts, and preliminary evidence of clinical efficacy in ameliorating psoriasis plaques [see GSK2831781 Investigator Brochure (IB)].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks of GSK2831781 may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk Refer to GSK2831781 IB for details	Mitigation Strategy
Investigational Product (IP) [GSK 2831781]		
Neutropaenia	**Non-clinical:** In the 1-month GLP toxicology study, clinically significant decreases in neutrophil count, which were considered adverse, were observed in 2/12 monkeys which were administered 100 mg/kg/week subcutaneously (SC) or intravenously (IV). Including separate single and repeat dose pharmacology studies, decreases in neutrophil count of a similar magnitude occurred in 2/15 animals at 30 mg/kg, but not in 7 animals administered at 3 mg/kg. In the 26-week GLP toxicology study a transient decrease in neutrophil counts was observed at ≥30 mg/kg/week from Day 14 in females and Day 21/29 in males. The neutrophil count increased to or close to pre-study levels by the end of treatment (except in 1 male, which had immune complex disease). These changes were not considered adverse. **Clinical:** No neutropaenia, or trends towards reduced neutrophil counts, were observed in the FTIH study (200630) in healthy volunteers or patients with plaque psoriasis, up	Exclusion criteria for low neutrophil counts ($<1.5x10^9$/L) at baseline. Neutrophil count and adverse events (AE)/serious adverse events (SAEs) related to neutropaenia will be monitored. Haematological temporary withholding and stopping criteria. Investigators should manage participants as clinically indicated if neutropaenia is seen.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk Refer to GSK2831781 IB for details	Mitigation Strategy
	to a maximum single dose of 5 mg/kg, or in the Phase 1 study (207823), at single doses of 150 mg or 450 mg.	
Infection	**Non-clinical:** No specific studies have been conducted in nonclinical species to investigate the effect of GSK2831781 on response to viral or bacterial infection. In the 26-week study, natural killer cells were lower (down to 0.3 or 0.1X pre-study) in 4 of the 8 monkeys dosed at 100 mg/kg/week from Day 29, although levels were at or near the normal range. A significant proportion of newly activated T cells express LAG3, and therefore T cell proliferation upon encounter with an infectious agent may be inhibited by GSK2831781 if exposure is at the same time. However, it has been demonstrated that in healthy volunteers only a small proportion of central memory T cells express LAG3, so there is low risk of eliminating central memory of anti-infectious immune response against future encounter. **Clinical:** No clinical concerns regarding infections were identified in the Phase 1 studies (200630 and 207823).	Appropriate exclusion criteria for history of e.g. tuberculosis (screening for latent infection included) or other relevant chronic infectious disease (e.g. Hepatitis B and C, HIV). In addition, participants with a recent infection or evidence of significant active infection will be excluded from the study. Participants will not be allowed to receive live vaccines within the 4 weeks prior to Day 1 or during the study until the end of Follow-Up. Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus. If indicated, non-live vaccines may be administered while receiving GSK2831781 based on a treating physician assessment of the benefit:risk (e.g., risk of theoretical decreased responsiveness). Close monitoring of participants for infections will be continued up to the Follow-Up visit, and supportive therapy (including anti-infectives) provided as clinically indicated.
Infusion reaction/hypersensitivity	**Non-clinical:** No evidence to date.	IV investigational medicinal product (IMP) will be administered by clinical staff at clinical sites with appropriate staff training and facilities for the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk Refer to GSK2831781 IB for details	Mitigation Strategy
	Clinical: No infusion reactions or hypersensitivity were observed in the Phase 1 studies (200630 and 207823).	emergency management of hypersensitivity, angioedema and anaphylaxis. Participants with be monitored as per the monitoring schedules outlined in Section 6.2. SC dosing may be undertaken, either at clinical sites, or where applicable country and local regulations and infrastructure allow, at participants' homes. For home administration, this will only be conducted by clinical staff with advanced cardiovascular life support (ACLS) training. Participants will not be eligible for home drug administration if they have previously experienced an infusion or hypersensitivity reaction during IV dosing of study treatment, if the participant's home is more than 30 minutes away from an emergency medical facility with capability to manage a severe hypersensitivity reaction, or in any other situation where the Investigator considers dosing at the clinical site to be in the participant's best interests for safety. Individual safety stopping criteria and appropriate treatment for hypersensitivity reactions.
Local injection site reaction	**Non-clinical:** Mononuclear cell perivascular infiltration was observed at SC injection sites of monkeys given ≥30 mg/kg/week in the 26-week study. Partial recovery	Injection sites will be monitored visually following SC administrations as per the monitoring schedules outlined in Section 6.2, and any adverse reactions managed appropriately and monitored until

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk Refer to GSK2831781 IB for details	Mitigation Strategy
	in females and full recovery in males at 30 mg/kg/week was observed after 17 weeks off-dose. Not seen with IV administration. **Clinical:** No reactions were observed following IV administration in the FTIH study (200630). No reactions were observed following SC dosing in the Phase 1 study 207823.	resolution. If a reaction is observed, Investigators and home nurses are advised to rotate sites in the affected individual to help mitigate further risk. Participants in whom no reaction is observed following the first two SC administrations will be advised to report any reactions that subsequently occur to the clinical Investigators, who will arrange management as appropriate and monitor until resolution.
Immunogenicity	**Non-clinical:** A single dose of 3 mg/kg GSK2831781 in a cynomolgus monkey PK study led to a significant anti-drug antibody (ADA) response in all monkeys. In the 4-week and 26-week GLP toxicology studies ADAs were also seen in four monkeys at 30 mg/kg and in one at 100 mg/kg post dose. These findings were not associated with adverse effects. In one male neutrophil counts remained low for the duration of treatment. This animal also had a number of nonspecific changes including reduced body weight, increased heart rate, decreased serum albumin, increased serum protein, alkaline phosphatase, total bilirubin and cholesterol, proteinuria, increased reticulocytes and decreased platelet count. These changes, considered to be immune complex mediated, were transient and of minimal magnitude. In general, the relevance of such	Safety and tolerability is being assessed in participants (including clinical chemistry, haematology, adverse events, hypersensitivity reactions). Immunogenicity and the impact, if any, on pharmacokinetic and safety parameters will be monitored.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk Refer to GSK2831781 IB for details	Mitigation Strategy
	preclinical findings is not thought to predict ADA formation in man. **Clinical:** Pre-existing ADAs and post-dosing ADA have been identified in humans. No adverse reactions or alterations in PK associated with immunogenicity were observed in the FTIH study 200630. No immunogenicity was observed in the Phase 1 study 207823.	
Cytokine release syndrome (CRS)	**Non-clinical:** Hyper-immune activation leading to activation of the innate immune system is only a theoretical safety concern, as there is no *in vitro* and *in vivo* evidence of cytokine release associated with $LAG3^+$ and the T cell depletion mechanism. As GSK2831781 is expected to induce ADCC, this may lead to cytokine release due to cell lysis. However, a low proportion of T cells express LAG3, therefore the risk of this is expected to be lower than less targeted depleting monoclonal antibodies (mAbs). **Clinical:** No cytokine release syndrome was observed in the Phase 1 studies 200630 and 207823. In study 200630 there were minor transient increases in serum TNF-α concentrations between 6-48 hours after dosing at all	Appropriate monitoring for clinical symptoms associated with cytokine release such as fever, nausea, chills, hypotension, tachycardia, asthenia, headache, rash, tongue and throat swelling, and dyspnoea, during and for an appropriate period after dosing. Participants will be informed in the ICF to seek prompt medical advice should any of these symptoms occur, particularly within 72 hours of dosing. Staff administering and monitoring IMP administration will be trained in emergency care and resuscitation. All IV doses will be administered at clinical sites. SC administration may take place at clinical sites, or where applicable country and local regulations and infrastructure allow, at the participant's home; for home administration, staff

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk Refer to GSK2831781 IB for details	Mitigation Strategy
	dose levels, but no dose-response relationship, and the magnitude of these rises was not clinically relevant. There were no meaningful changes to serum IL-6, IL-8, IFN-γ or G-CSF.	must be ACLS trained, with access to an emergency medical facility no more than 30 minutes away.
Autoimmune-like reactions	A small percentage of regulatory T cells express LAG3. The clinical relevance of this minority subset of T cells in the pathogenesis of autoimmune reactions is unknown. In the 4-week study minimally increased percentages of subpopulations of regulatory T cells were noted on Day 29 at 100 mg/kg/week IV, which was not observed in monkeys administered 100 mg/kg/week SC. No changes in regulatory T cells were observed in the 26-week study, from Day 25 to Week 29. Increases in anti-KLH IgM and IgG responses were noted after each KLH injection (administered during Weeks 16 and 19) in monkeys given 30 or 100 mg/kg/week for 26-weeks, which persisted in the 30 mg/kg/week group at 12-weeks off-dose. **Clinical:** No autoimmune phenomena were observed in the FTIH study 200630. In patients who received GSK2831781, clinical activity scores for psoriasis (a T cell-mediated disease) tended to improve over the time course of exposure to IMP. In the Phase 1 study	Appropriate exclusion criteria for participants (e.g. exclusions for acute severe colitis), to exclude patients most at risk in the event of disease worsening. Participants will undergo regular clinical examination and AEs that could be related to autoimmunity, including worsening of underlying disease, will be monitored. Given the increases in anti-KLH IgM and IgG responses observed in cynomolgus monkeys, there is a theoretical potential for an enhanced response to vaccination, which has not yet been evaluated in clinical studies. The implications of this are not known but are not considered high risk.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk Refer to GSK2831781 IB for details	Mitigation Strategy
	207823, GSK2831781 did not reduce the numbers of circulating regulatory T cells in peripheral blood compared to placebo.	
Drug-drug interactions	Formal drug interaction studies have not been performed with GSK2831781; however, during inflammation, enzymes such as cytochrome P450 (CYP) can be down-regulated leading to instances of reduced clearance and increased plasma concentrations of administered drugs. As GSK2831781 depletes activated T cells, this could result in a reduction in proinflammatory cytokines systemically, which might exert an indirect effect on drug metabolizing enzyme (DME) expression and activity. Reports of clinical effects with other drugs suggest that the magnitude and impact of such drug interactions are generally small (<2-fold) and clinically significant only for drugs that have a narrow therapeutic range.	Participants who are co-administered drugs with a narrow therapeutic index should be monitored for clinical evidence of changes in exposure, and therapeutic drug monitoring performed as clinically indicated.
Reproductive Toxicity	**Non-clinical:** Whereas there are no data for the drug class or mode of action pointing to a known pregnancy hazard, no animal reproduction testing has been conducted. Therefore, there is the potential for unidentified risks to the embryo-foetus or pregnancy. Doses up to 100 mg/kg/week for 26-weeks did not result in pathology in the reproductive organs of mature monkeys or effects on spermatogenesis staging.	Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate. WOCBP will be required to have established, proper use of a highly effective method for avoiding pregnancy (see Appendix 4, Section 10.4.2) at screening to ensure there is a minimum of 1 month of effective contraception prior to first dose, and to utilize one form of highly effective

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk Refer to GSK2831781 IB for details	Mitigation Strategy
	Clinical: WOCBP were included in the psoriasis cohorts of study 200630, with appropriate pregnancy testing and contraceptive requirements. No pregnancies have been observed. The IMP level of mAb in human semen is expected to be too low to be of concern.	contraception throughout the study until after the Follow-Up visit. Pregnancy testing will be performed at screening and prior to the first dose, at least monthly during the dosing period, and at regular intervals until Follow-Up, as documented in the clinical protocol. WOCBP who are partners of male subjects in the study will not be required to be protected from seminal fluid exposure or need to use a condom plus highly effective method of contraception.
Study Procedures		
Endoscopy with biopsy	Whilst endoscopic examination of the gut is generally well tolerated, potential risks of the procedure include discomfort, bleeding or perforation (1/5000 for sigmoidoscopy and 1/3000 for colonoscopy).	Sigmoidoscopy rather than colonoscopy (unless a colonoscopy is clinically indicated, for example for malignancy/dysplasia screening at baseline) will be used to reduce risk of endoscopy-related complications. Endoscopy will be performed by experienced and trained staff only. Participants will be informed of expected post-procedure bleeding and will be instructed to contact the clinical site should they experience any adverse events after the procedure.

2.3.2. Benefit Assessment

There are additional, but limited, treatment options available for participants who have an inadequate response to current therapies for UC. It is hypothesised that GSK2831781 will deplete potentially pathogenic, recently activated LAG3$^+$ T cells, which are enriched at the disease site in T cell-driven immunoinflammatory disorders such as inflammatory bowel disease (IBD), leading to a reduction of disease activity. There will be some direct benefit to the participant through their contribution to the process of developing new therapies in an area of unmet need, including more frequent contact and assessment by clinicians expert in managing UC.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures to minimise risks, the potential risks of participation in this study of GSK2831781 are justified by the anticipated benefits that may be afforded to participants with UC.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of repeat doses of GSK2831781 during the Double-Blind Induction Phase.	• Incidence of adverse events and serious adverse events during the Double-Blind Induction Phase. • Incidence of findings of potential clinical importance[1] during the Double-Blind Induction Phase for: o Vital signs. o Clinical laboratory values (haematology, clinical chemistry and urinalysis). o QTc.
• To characterise the efficacy dose-response of GSK2831781 during the Double-Blind Induction Phase.	• Change from baseline in Complete 4-domain Mayo score[2] at Week 10.
Secondary	
• To evaluate the safety and tolerability of repeat doses of GSK2831781 during the Double-Blind Extended Treatment Phase.	• Incidence of adverse events and serious adverse events in the Double-Blind Extended Treatment Phase. • Incidence of findings of potential clinical importance[5] during the Double-Blind Extended Treatment Phase for: o Vital signs.

Objectives	Endpoints
	○ Clinical laboratory values (haematology, clinical chemistry and urinalysis). ○ QTc.
• To investigate the effect of repeat doses of GSK2831781 on clinical efficacy including endoscopic mucosal healing during the Double-Blind Induction Phase.	• Adapted Mayo endoscopic score of 0 or 1 at Week 10. • Adapted Mayo clinical remission[3] at Week 10. • Adapted Mayo clinical response[3] at Week 10. • Symptomatic remission[4] over time. • Change from baseline in partial Mayo score over time. • Change from baseline in Adapted Mayo endoscopic score and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) at Week 10.
• To investigate the effect of repeat doses of GSK2831781 on UC histologic disease activity during the Double-Blind Induction Phase.	• Histological severity as determined by the Robarts Histopathology Index at Week 10. • Histological severity as determined by the Nancy Histological Index at Week 10. • Histological severity as determined by the Geboes Histological Index at Week 10.
• To investigate the effect of repeat doses of GSK2831781 on biomarkers of UC disease activity during the Double-Blind Induction Phase.	• Change from baseline in serum C-reactive protein over time. • Change from baseline in faecal calprotectin over time.
• To investigate the pharmacokinetics of GSK2831781 following subcutaneous dosing.	• GSK2831781 PK parameters: AUC(0-tau), Cmax, tmax.
• To investigate the immunogenicity of repeat doses of GSK2831781 during the Double-Blind Induction Phase.	• Incidence of anti-drug antibodies at each visit.
Safety	
• To evaluate the safety and tolerability of repeat doses of GSK2831781 in all trial phases.	• Adverse events, vital signs, clinical laboratory values (haematology, clinical chemistry, and urinalysis), 12-lead ECG.

Objectives	Endpoints
• To investigate the immunogenicity of repeat doses of GSK2831781 in all trial phases.	• Incidence of anti-drug antibodies at each visit.
Exploratory	
• To investigate the effect of repeat doses of GSK2831781 on patient-reported outcomes in all trial phases.	• Change from baseline in daily e-Symptom Diary, FACIT-Fatigue, Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36, and PGIS. • PGIC at Week 10 and Week 30.
• To investigate the effect of repeat doses of GSK2831781 on clinical efficacy during the Double-Blind Extended Treatment Phase.	• Change from baseline in Adapted Mayo score between Week 10, and Week 30. • Adapted Mayo endoscopic score of 0 or 1 at Week 30. • Adapted Mayo clinical remission[3] at Week 30. • Adapted Mayo clinical response[3] at Week 30. • Change from baseline in Adapted Mayo endoscopic score and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) at Week 30. • Symptomatic remission[4] over time. • Change from baseline in Partial Mayo score over time. • Change from baseline in histological severity as determined by the Robarts Histopathology Index, Nancy Histological Index and Geboes Score at Week 30. • Clinical response[3] at Week 10, maintained at Week 30. • Clinical remission[3] at Week 10, maintained at Week 30.
• To investigate the effect of repeat doses of GSK2831781 on oral corticosteroid use for participants using corticosteroids at baseline.	• Corticosteroid-free Adapted Mayo clinical remission at Week 30 (with at least 28 consecutive days corticosteroid-free, including Weeks 26 to 30).

Objectives	Endpoints
	• Change from baseline daily corticosteroid dose to average daily corticosteroid dose during the taper period[5].
• To investigate the effect of repeat doses of GSK2831781 on biomarkers of disease activity in patients moderate to severe active UC during the Double-Blind Extended Treatment Phase and Open Label Treatment Phases.	• Change from baseline in serum C-reactive protein over time. • Change from baseline in faecal calprotectin over time.
• To investigate the effect of repeat doses of GSK2831781 on colon biopsy tissue and blood biomarkers in patients with moderate to severe active UC in all Treatment Phases.	• Change from baseline in colon biopsy tissue biomarkers at Week 10 and Week 30, which may include but not be limited to: o Number of $LAG3^+$ and $CD3^+$ cells by IHC. o Composition of immune cell populations, including but not limited to $CD3^+$ cells by epigenetic counting or T cell receptor sequencing. o Transcriptomic profiles, including but not limited to LAG3. • Change from baseline in blood biomarkers, which may include but not be limited to: o Number of $LAG3^+$ cells at Week 10 and Week 30. o 4β-hydroxycholesterol:cholesterol ratio. o Serum tryptase. o Proteomic profiles.
• To investigate the effect of repeat doses of GSK2831781 on plasma sLAG3 in patients with moderate to severe active UC in all Treatment Phases.	• Soluble LAG3 (sLAG3) concentrations.
• To evaluate the concentration-time profiles of GSK2831781 after repeat intravenous and	• GSK2831781 PK concentrations.

Objectives	Endpoints
subcutaneous dosing in all Treatment Phases.	
• To investigate the effect of repeat doses of GSK2831781 on clinical efficacy in Non-Responder patients during Open Label Induction and Extended Treatment Phases.	• Change from baseline in Adapted Mayo score between Week 10, and Week 22. • Adapted Mayo endoscopic score of 0 or 1 at Week 22. • Adapted Mayo clinical remission[3] at Week 22. • Adapted Mayo clinical response[3] at Week 22. • Change from baseline in Adapted Mayo endoscopic score and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) at Week 22. • Change from baseline in histological severity as determined by the Robarts Histopathology Index, Nancy Histological Index and Geboes Score at Week 22. • Clinical response based on partial Mayo score[3] at Week 22, maintained at Week 42. • Clinical remission based on partial Mayo score[3] at Week 22, maintained at Week 42. • Symptomatic remission[4] over time. • Change from baseline in partial Mayo score over time.
• To investigate the effect of repeat doses of GSK2831781 on extraintestinal manifestations in all Treatment Phases.	• Incidence of extraintestinal manifestations over time.

Footnotes:

1 Potential clinical importance is defined in the research analysis plan (RAP) for each relevant safety endpoint.
2 The Complete 4-domain Mayo score is used for the primary endpoint due to its wider dynamic range for assessment of dose-response compared to the Adapted Mayo score used for secondary and exploratory endpoints.
3 Clinical response and remission for the various iterations of Mayo score are defined in Appendix 7, Section 10.7.
4 Symptomatic remission is defined as a rectal bleeding subscore of 0, and a stool frequency subscore of ≤1, with no worsening from baseline.
5 Taper period is defined from the start of the taper (Weeks 12 or 24, respectively, for the Double-Blind and Open Label Extended Treatment Phases) to completion of the respective Extended Treatment Phases.

Primary estimand for dose-response: "Treatment policy"	
Objective:	To characterise the efficacy dose-response of GSK2831781 during the Double-Blind Induction Phase.
Estimand:	**<u>Primary efficacy estimand</u>** <u>Description</u> Mean change from baseline to Week 10 in Complete 4-domain Mayo score for each dose level and placebo in patients with moderate to severe, active Ulcerative Colitis and in the absence of IP discontinuation due to the COVID-19 pandemic. <u>Attributes</u> • **Treatment**: Placebo and four doses of GSK2831781 IV: 450 mg, 300 mg, 150 mg and 45 mg in addition to background therapy and stable dose of corticosteroid where relevant. • **Population:** Patients with moderate to severe, active Ulcerative Colitis as per inclusion/exclusion criteria. • **Outcome measure:** Change from baseline to Week 10 in Complete 4-domain Mayo score. • **Intercurrent events and strategy:** o *Intercurrent event (ICE): Discontinuations due to the COVID-19 pandemic* • Strategy: handled as though discontinuation had not occurred (hypothetical strategy, setting assessments to missing with missing at Random [MAR] assumption). o *ICE: Discontinuations not due to the COVID-19 pandemic* • Strategy: treatment policy. • **Population-level summary:** Mean change from baseline.

Additional estimand for dose-response: "Hypothetical"	
Objective:	To characterise the efficacy dose-response of GSK2831781 during the Double-Blind Induction Phase.
Estimand:	**<u>Additional estimand for primary efficacy objective and endpoint</u>** <u>Description</u> Mean change from baseline to Week 10 in Complete 4-domain Mayo score for each dose level and placebo in patients with moderate to severe, active Ulcerative Colitis and in the absence of the listed inter-current

	events which include IP discontinuation and specified important protocol deviations. Attributes • **Treatment:** Placebo and four doses of GSK2831781 IV: 450 mg, 300 mg, 150 mg and 45 mg in addition to background therapy and stable dose of corticosteroid where relevant. • **Population:** Patients with moderate to severe, active Ulcerative Colitis as per inclusion/exclusion criteria. • **Outcome measure:** Change from baseline to Week 10 in Complete 4-domain Mayo score. • **Intercurrent events and strategy:** o Discontinuation from IP (for any reason). o Excluded medication administered. o Wrong study treatment dosed (including protocol deviation subcategory of "study treatment not administered per protocol" which covers missed doses). o Unblinding of participant's treatment allocation for site and/or participant. o For all of these ICEs a 'hypothetical' strategy will be used that assumes that the specified intercurrent event did not occur. The assessments will be set to missing with MAR assumption. • **Population-level summary:** Mean change from baseline.

Key secondary estimand for decision making: "Composite"	
Objective:	To investigate the effect of repeat doses of GSK2831781 on clinical efficacy including endoscopic mucosal healing during the Double-Blind Induction Phase.
Estimand:	*Description* Difference in response rates between active doses of GSK2831781 and Placebo when added to background therapy in patients with moderate to severe, active, Ulcerative Colitis. *Attributes* • **Treatment:** Placebo and active doses of GSK2831781 in addition to background therapy and stable dose of corticosteroid where relevant. • **Population:** Patients with moderate to severe, active Ulcerative Colitis as per inclusion/exclusion criteria. • **Outcome measure:** Endoscopic Mucosal Healing at Week 10 assessment, where success is defined as: o Achieving a score on the endoscopic component of the Adapted Mayo score of 0 or 1, and

	○ Not discontinuing IP due to reasons unrelated to the COVID-19 pandemic, and ○ Not taking medications excluded by the protocol or increasing dose of corticosteroid. • **Intercurrent events and strategy:** ○ *ICE: discontinuation from IP, unrelated to COVID-19 pandemic.* ▪ Strategy: included in outcome via composite strategy (setting response status as non-responder). ○ *ICE: discontinuation from IP due to COVID-19 pandemic.* ▪ Strategy: handled as though discontinuation had not occurred (hypothetical strategy, setting response status to missing with MAR assumption). ○ *ICE: valid endoscopy result not available due to COVID-19 pandemic.* ▪ Strategy: handled as though missing assessment had not occurred (hypothetical strategy, setting response status to missing with MAR assumption). ○ *ICE: valid endoscopy result not available for technical reasons.* ▪ Strategy: handled as though missing assessment had not occurred (hypothetical strategy, setting response status to missing with MAR assumption). • **Population-level summary:** Difference in proportion of participants who achieve response between placebo and relevant active doses.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multicentre, randomized, double-blind, parallel group, placebo-controlled study of GSK2831781 in participants with moderate to severe active UC. This study will investigate the safety and tolerability, efficacy, dose-response, PK and PD of GSK2831781. In addition, the study will investigate SC dosing during the Extended Treatment Phase.

Following the Induction Phase (up to Week 10), participants who respond will enter a double-blind Extended Treatment Phase until Week 30, with Follow-Up to Week 42. Non-

Responders identified following the Week 10 assessment will move to Open Label Treatment, consisting of Induction (Weeks 12 to 22) an Open Label Extended Treatment Phase (Weeks 22 to 42) and a Follow-Up to Week 54 (see Section 4.1.2).

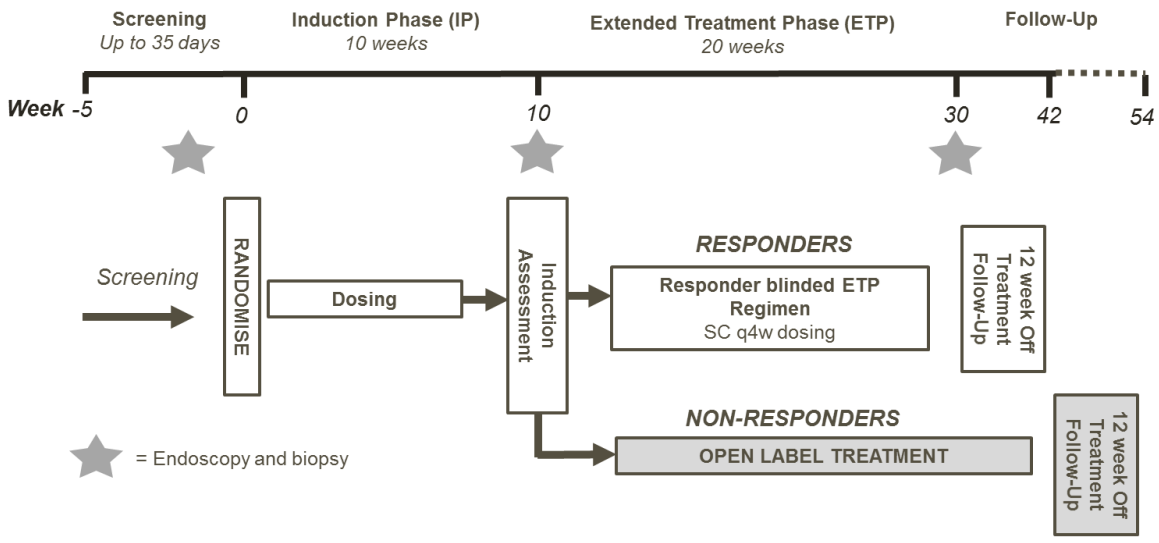
At the start of the study, participants will be randomised to GSK2831781 450 mg or placebo in a 2:1 ratio. When an appropriate number of participants have been randomised in these two arms for the futility interim analysis (Interim Analysis 3, See Section 9.5), randomisation to all dose regimens (GSK2831781 450 mg, 300 mg 150 mg, 45 mg or placebo) will be opened in a 2:3:3:3:2 ratio. No pause in recruitment is planned, although study recruitment may be paused for internal decision making at the Sponsor's discretion.

A number of interim analyses will be performed during the study, where the DRC will review unblinded data for decision-making purposes (see Section 9.5 for further details).

In line with routine pharmacovigilance, an internal GSK Safety Review Team (SRT) (which will include a subset of the 204869 study team) will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

An overview of the patient journey for the study is shown in Figure 1 and described below.

Figure 1 Participant journey



4.1.1. Double-Blind Treatment

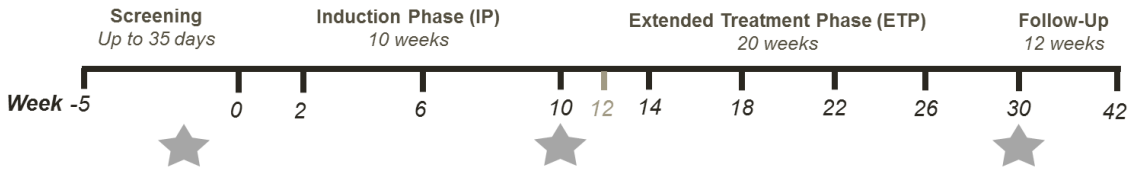
Following informed consent, the screening period for participants is 35 days. Eligible participants, determined by entry criteria including the baseline centrally read endoscopy (endoscopy to be completed no earlier than Day -14), will be randomised on either Day 1 or Day -1, and commence 10 weeks of blinded treatment in the Double Blind Induction Phase (IP).

At Week 10, all participants will undergo an Induction Assessment, including centrally read endoscopy. Following the endoscopy, the Responder status (see Appendix 7, Section 10.7), as identified by the results of the central assessment of clinical response and implemented in the eCRF, will be communicated to sites prior to the Week 12 visit.

Participants identified as Responders who received GSK2831781 during Induction will then receive 300 mg GSK2831781 subcutaneously (SC) every four weeks during the double-blind Extended Treatment Phase (ETP), from Week 14 until Week 26. Responders in the placebo group during Induction will continue to receive placebo SC every four weeks in the double-blind ETP (Figure 2). A mandatory corticosteroid taper (if applicable) will begin at Week 12, described in Section 6.6.1.1.

At Week 30, all participants in the Double-Blind ETP will undergo an Assessment, including centrally read endoscopy. Subsequently, all participants will remain in study, but off treatment, to Week 42 in the 12-week Follow-Up phase.

Figure 2 Double-blind ETP dosing regimen (for Responders only)



Induction Phase IV treatment at Week 0, 2, 6 and 10	Extended Treatment Phase SC treatment at Week 14, then q4w thereafter to Week 26
GSK2831781 450 mg IV	GSK2831781 300mg SC q4w
GSK2831781 300 mg IV	
GSK2831781 150 mg IV	
GSK2831781 45 mg IV	
Placebo IV	Placebo SC q4w

= Endoscopy and biopsy

4.1.2. Open Label Treatment for Non-Responders

Participants who have not attained clinical response, determined following a centrally read endoscopy at Week 10 (calculated centrally through the eCRF), will be assigned to Open Label Treatment. This offers the opportunity to characterise participants who may respond slower to treatment, as well as providing participants who have not responded on their randomized dose regimen the opportunity to receive GSK2831781 at the highest dose. The total duration of open label treatment will be up to an additional 30 weeks of treatment

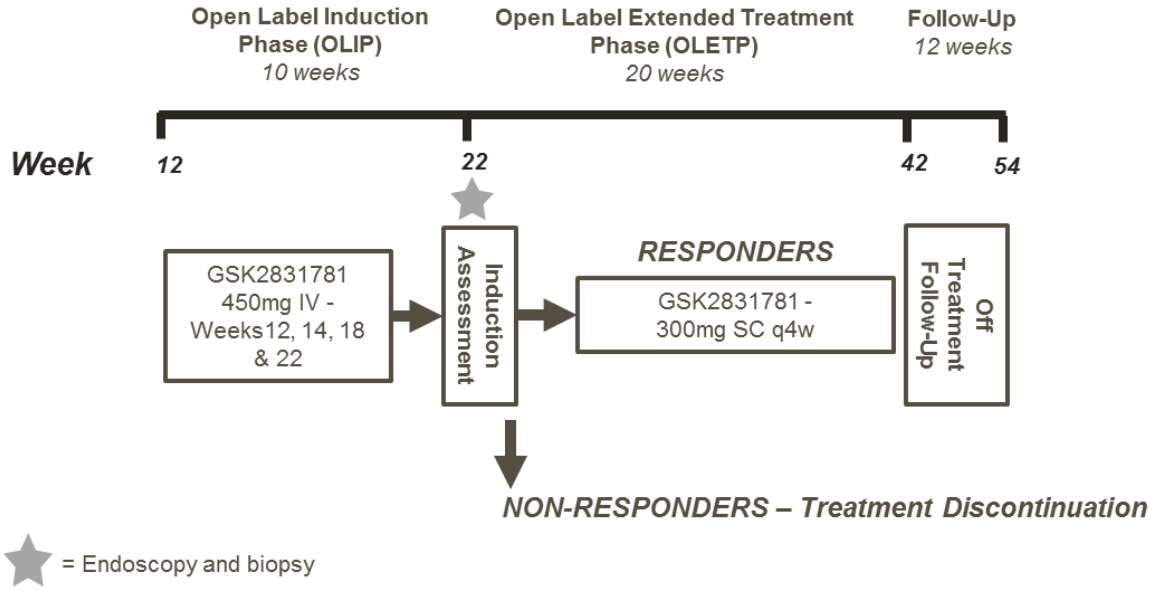
(Week 12 to Week 42) and a 12-week Follow-Up (Figure 3).

Participants who have not attained clinical response, determined following a centrally read endoscopy at Week 22 (calculated centrally through the eCRF), will discontinue study treatment and are still required to attend a Follow-Up visit approximately 16 weeks from the last dose event.

Participants identified as Responders will then receive 300 mg GSK2831781 SC every four weeks during the Open Label Extended Treatment Phase from Week 22 until Week 42. A mandatory corticosteroid taper (if applicable) will begin at Week 24, described in Section 6.6.1.1.

Subsequent to Week 42, all Open Label Extended Treatment Phase participants will remain in study, but off treatment, to Week 54 in a 12-week Follow-Up phase.

Figure 3 Open Label Treatment for Non-Responders at Week 10



4.1.3. Type and number of participants

Participants with moderate to severe active UC as defined by a 4-domain (Complete) Mayo score of 6-12 at screening, including a centrally read Mayo endoscopic score of ≥2 within 14 days of randomization (Day 1), will be randomised into the study (see Section 5, for full list of inclusion/exclusion criteria). Participants will be stratified first by ethnicity (Japanese or non-Japanese). Non-Japanese participants will then be further stratified according to prior treatment (advanced therapy naïve, experienced a single class of advanced therapy, or experienced multiple classes of advanced therapies [advanced

therapies include anti-TNF therapies, anti-integrin therapies, anti-IL-12/23 monoclonal antibodies, and JAK inhibitors]).

Approximately 242 participants will be randomly assigned to study intervention under the assumption that a proportion will not receive all planned doses up to Week 10 and/or have an incomplete Week 10 Complete 4-domain Mayo score assessment. If the attrition rate is higher than planned for (e.g., 15% or more) then additional participants, up to a maximum of 320, may be recruited. At the start of the study, participants will be randomised to GSK2831781 450 mg and Placebo in a 2:1 ratio. When an appropriate number of participants have been randomised in these two arms for the interim analysis (Interim Analysis 3, See Section 9.5), randomisation to all dose regimens (GSK2831781 450 mg, 300 mg, 150 mg, 45 mg or Placebo) will be opened. See Section 6.4 for the randomisation ratios.

No pause in recruitment to the study is planned whilst interim analyses are conducted, although recruitment into the study may be paused for internal decision making at the Sponsor's discretion. At appropriate interim analyses a sample size re-estimation may be conducted, to ensure that sufficient participants are recruited. The randomisation will be stratified to ensure participants will be appropriately represented across the dose regimens and placebo. The maximum number of randomized participants will be 320 (see Section 9.2.2 for further details).

The proposed SoA for the study, including the Open Label Treatment, can be seen in Section 1.3.

4.2. Scientific Rationale for Study Design

This is the first study of GSK2831781 in participants with moderate to severe active UC, and the first repeat dose study. There are two primary objectives, the first of which is to evaluate the safety and tolerability of repeat doses GSK2831781. The second primary objective is to characterise the efficacy dose-response in the Induction Phase of GSK2831781 in patients with moderate to severe active UC.

The placebo group is required for a valid evaluation of adverse events attributable to GSK2831781 treatment versus those independent of GSK2831781 treatment. The placebo participants will also serve as controls for the biomarker and efficacy assessments. Participants randomised to receive placebo during the Induction Phase who have not responded by the Induction Assessment (Week 10) will have opportunity to access Open Label treatment with GSK2831781 450 mg IV.

The endpoint chosen for primary characterisation of the dose-response is the change from baseline in Mayo score (See Appendix 7, Section 10.7) at Week 10. This will be evaluated alongside the key secondary endpoint of endoscopic mucosal healing. Longitudinal data demonstrate that patients who attain mucosal healing have a superior long-term prognosis, including lower risk of future surgery and hospitalisation, need for systemic steroids, and development of colorectal cancer [Rutter, 2004]. Patient-reported outcomes are also included in the secondary and exploratory analyses.

In addition to endoscopic and symptomatic assessments, other key endpoints contributing to an understanding of whether GSK2831781 successfully ameliorates mucosal inflammation are being undertaken, including: histological, immunohistochemical and transcriptomic assessment of gut biopsies; levels of faecal calprotectin; and C-reactive protein (CRP) concentrations in blood. Further exploratory endpoints include characterisation of PK and efficacy with a single dose level of subcutaneous GSK2831781 in the Extended Treatment Phase, to determine applicability of this dosing route in future studies.

Participants will be followed for 16 weeks after the last administration of GSK2831781. Due to the non-linear nature of the PK and limited number of observations in the final phase, the terminal half-life could not be determined in the FTIH study 200630. However, the data from this study show that after dosing at 5 mg/kg IV (470 mg on average), the mean plasma concentration of GSK2831781 at Day 85 (i.e. 12 weeks after dosing) had dropped to 0.5 µg/mL, from a mean Cmax of 162 µg/mL, and in 2 out of 6 participants the concentration had dropped below the limit of quantification (10 ng/mL). At Day 121 (i.e. 17 weeks after dosing; next time point for PK), the concentrations in all participants who had received 5 mg/kg had dropped below the limit of quantification. Since only very limited accumulation is expected for monoclonal antibodies in general and, based on population PK modelling of the data from study 200630, a wash out period of 16 weeks after the last administration has been selected as a sufficient time for washout and determination of repletion of $LAG3^+$ cells.

A key feature of the study is that there will be a number of interim analyses that may be performed, which will include the assessment of PK and an assessment of futility (see Section 9.5 for further details).

4.3. Justification for Dose

4.3.1. Double-Blind Induction Phase

The top dose will be 450 mg IV at Day 1 (Week 0), Day 15 (Week 2), Day 43 (Week 6) and Day 71 (Week 10). Simulations using a PK/PD model that was developed using PK and cell depletion data in blood from the FTIH study (Study 200630), and $LAG3^+$ cell numbers from colon [Slevin, 2018] show that at a dosing interval of 4 weeks, this dose is predicted to reduce $LAG3^+$ T cells (memory compartment) in blood to ~5%, and in colon to 5-20%, of baseline levels as measured in patients with active UC.

The dosing interval is 4-weekly, except for the first 2 doses, which will be 2 weeks apart. This is predicted to achieve the maximum reduction in $LAG3^+$ T cells faster, particularly in colon.

The maximum dose in the FTIH study was 5 mg/kg. Since the average weight of the participants was 94.38 kg in that treatment group (range of 85.3-108, N=6), on average the administered dose was 470 mg, which is similar to the proposed top dose of 450 mg IV. The population PK model predicts an average Cmax of 204 µg/mL and AUC(0-4wks) of 37 mg.hr/mL at Week 10. In the FTIH study, Cmax ranged between 120-230 µg/mL and AUC(0-t) ranged between 33-59 mg.hr/mL. Therefore, it is expected that the exposure at

the top dose in the current study will be similar to the observed exposure in FTIH study at 5 mg/kg single dose IV. Additionally, the proposed starting dose of 450 mg (~6.4 mg/kg for 70 kg participant) is 15.6x lower than the NOAEL (100 mg/kg/week, highest dose tested) from the 26-week GLP toxicity study in monkey, and the predicted mean Cmax and AUC are 15.2x and 12.1x lower, respectively.

For characterising the dose-response relationship, three further dose levels are included: 300 mg, 150 mg and 45 mg, all administered at the same time points as 450 mg. At the lowest dose of 45 mg, PK/PD modelling predicts only limited depletion of $LAG3^+$ T cells in colon, and in blood to about 25-50%.

4.3.2. Double-Blind Extended Treatment Phase (ETP)

All participants who responded during the double-blind Induction Phase (see Section 4.1) will be dosed during the ETP via the subcutaneous route. It is anticipated in the longer term that SC administration will be preferable, and lower doses may be required to maintain target depletion. This is based on clinical experience with other mAbs in UC (for example, Infliximab and Vedolizumab), and the biology of the disease (after successful induction treatment, the elevated levels of $LAG3^+$ cells in the colon are expected to be reduced). Therefore, the dose during the double-blind ETP will be 300 mg SC every 4 weeks. For participants in the 45 mg or 150 mg cohorts who respond in the Induction Phase, this may represent a dose escalation; however, this is still considered justified to explore the potential to achieve even more clinically meaningful responses and deep remission.

4.3.3. Open Label Treatment

All participants who did not respond during the double-blind Induction Phase will receive 450 mg IV at Weeks 12, 14, 18 and 22 (Open Label Induction Phase), followed by 300 mg SC every 4 weeks from Week 26-38 (Open Label Extended Treatment Phase). Since only minimal (further) accumulation of GSK2831781 is expected, continuing treatment at 450 mg IV for Non-Responders who might have received this dose during the double-blind Induction Phase as well will result in only limited, if any, increases in exposure.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled assessment shown in the SoA (Section 1.3).

Participants who withdraw from the study early should be encouraged to complete all visits for that specific phase as set out in the SoA (Section 1.3); however, if this is not possible at a minimum participants will be asked to complete all assessments at both the Early Withdrawal visit and a Follow-Up visit approximately 16 weeks after the last dose (Section 7.2) to ensure participant monitoring following drug wash out.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

AGE and WEIGHT
1. Participant must be 18 years of age or older and >40kg at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
Participants who have a: 2. Diagnosis of ulcerative colitis, established at least 3 months prior to screening, as documented by diagnostic sigmoidoscopy or colonoscopy, and biopsy. 3. Complete 4-domain Mayo Score of 6 to 12, with disease extending ≥15cm from the anal verge, with a centrally read endoscopic subscore of ≥2 at screening endoscopy, and a rectal bleeding subscore ≥1. 4. A history of *at least* <u>one</u> of the following: • Inadequate response to, loss of response to, or intolerance to azathioprine or mercaptopurine (including thiopurine methyltransferase (TPMT) and *NUDT15* genetic mutations precluding use), ciclosporin, tacrolimus or methotrexate. • Inadequate response to, loss of response to, intolerance to, or demonstrated dependence on oral corticosteroids. • Inadequate response to, loss of response to, or intolerance to at least one approved advanced therapy for UC, including anti-TNF therapies, anti-integrin therapies, anti-IL-12/23 monoclonal antibodies or JAK inhibitors. 5. Surveillance colonoscopy (performed according to local standards) within 12 months of screening (or during screening, if required) for participants with: • Pancolitis of >8 years duration; or • Patients with left-sided colitis of >12 years duration; or • For patients for whom this criterion does not apply, colorectal cancer surveillance should be undertaken according to local or national guidelines for patients with age ≥50, or with other known risk factors for colorectal cancer.

SEX
6. Male and Female participants: Both male and female participants are eligible to participate. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: • Not a woman of childbearing potential (WOCBP), see Section 10.4.1. OR • A WOCBP who agrees to use a highly effective contraceptive method for at least 4 weeks prior to dosing, until the Follow-Up visit. See Section 10.4.2.

INFORMED CONSENT
7. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. Participants with a current diagnosis of indeterminate colitis, inflammatory bowel disease-unclassified, Crohn's disease, infectious colitis, or ischaemic colitis. 2. Participants with fulminant ulcerative colitis (as defined by 6 bloody stools daily AND 1 or more of: i) body temperature ≥100.4°F (or 38°C) or ii) heart rate >90 beats per minute), or toxic megacolon. 3. Prior extensive colonic resection, subtotal or total colectomy, or proctocolectomy, or planned surgery for UC. 4. Participants with any uncontrolled medical conditions, other than active UC, that in the opinion of the Investigator put the participant at unacceptable risk or interfere with study assessments or integrity of the data. Other medical conditions should be stable at the time of screening and be expected to remain stable for the duration of the study. 5. Unstable lifestyle factors, such as alcohol use to excess or recreational drug use, to the extent that in the opinion of the Investigator they would interfere with the ability of a participant to complete the study. 6. An active infection or a history of serious infections as follows:

- Use of antimicrobials (antibacterials, antivirals, antifungals or antiparasitic agents) for an infection within 30 days before first dose (topical treatments may be allowed at the Medical Monitor's discretion).
- A history of opportunistic infections within 1 year of screening (e.g. *Pneumocystis jirovecii*, aspergillosis or CMV colitis). This does not include infections that may occur in immunocompetent individuals, such as fungal nail infections or vaginal candidiasis, unless it is of an unusual severity or recurrent nature.
- Recurrent or chronic infection or other active infection that, in the opinion of the Investigator, might cause this study to be detrimental to the patient.
- Symptomatic herpes zoster within 3 months prior to screening.
- History of tuberculosis (active or latent), irrespective of treatment status.
- A positive diagnostic TB test at screening (defined as a positive QuantiFERON test). In cases where the QuantiFERON test is indeterminate, the participant may have the test repeated once and if their second test is negative they will be eligible. In the event a second test is also indeterminate, the Investigator has the option to undertake PPD testing. If the PPD reaction is <5 mm, then the participant is eligible. If the reaction is ≥5 mm, or PPD testing is not undertaken, the participant is not eligible.
- Positive *Clostridium difficile* toxin test during screening. However, rescreening can be undertaken following successful treatment.

7. Current or history of chronic liver or biliary disease (with the exception of Gilbert's syndrome, asymptomatic gallstones or uncomplicated fatty liver disease).
8. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency (unless the participant has a documented history of selective IgA deficiency).
9. A major organ transplant (e.g. heart, lung, kidney, liver, pancreas) or haematopoietic stem cell/marrow transplant.
10. Any planned major surgical procedure during the study.
11. A history of malignant neoplasm within the last 5 years, except for adequately treated non-metastatic basal or squamous cell cancers of the skin (within 1 year) or carcinoma in situ of the uterine cervix (within 3 years) that has been fully treated and shows no evidence of recurrence.

PRIOR/CONCOMITANT THERAPY

12. A change in dose of oral sulfasalazine or aminosalicylate within 2 weeks prior to baseline endoscopy.
13. Greater than 20 mg/day oral prednisolone (or equivalent, see SRM), or a change in dose of corticosteroid within 2 weeks prior to baseline endoscopy, or anticipated

inability to maintain a stable dose of corticosteroids (≤20 mg oral prednisolone or equivalent, see SRM) until Week 12.

14. Topical (rectal) corticosteroids or topical (rectal) aminosalicylate within 2 weeks prior to baseline endoscopy.
15. Initiation or a change in dose of mercaptopurine or azathioprine (including initiation or discontinuation of allopurinol) or methotrexate within 8 weeks prior to baseline endoscopy.
16. Treatment with ciclosporin, tacrolimus or thalidomide within 4 weeks prior to baseline endoscopy.
17. Treatment with an anti-TNF biologic within 8 weeks prior to baseline endoscopy, anti-integrin or anti-IL-12/23 biologics within 12 weeks prior to baseline endoscopy, or a JAK inhibitor within 4 weeks prior to baseline endoscopy.
18. A history of inadequate response, loss of response, or intolerance to more than three classes of approved advanced therapies for UC (including anti-TNF therapies, anti-integrin therapies, anti-IL-12/23 monoclonal antibodies, or JAK inhibitors; but excluding exposure within a clinical trial setting), of which participants must not have had inadequate response (primary non-response) to more than two classes.
19. Received faecal microbiota transplantation within 4 weeks prior to baseline endoscopy.
20. Received live vaccination within 4 weeks of Day 1 or plan to receive during the study until Follow-Up.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

21. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the screening endoscopy day in the current study:
    a. Biologics: 3 months, 5 half-lives, or twice the duration of the biological effect of the investigational product (whichever is longer);
    b. New Chemical Entities (NCEs): 30 days, 5 half-lives or twice the duration of the biological effect (whichever is longer).

DIAGNOSTIC ASSESSMENTS*

22. Absolute neutrophil count $<1.5x10^9$/L or a haemoglobin <80 g/L or lymphocyte count $<0.8x10^9$/L.
23. Estimated glomerular filtration rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) calculation <60 ml/min/1.73m^2 at screening.
24. ALT >2x ULN and bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.

25. Other clinically significant abnormalities of laboratory assessments, as judged by the Investigator and/or GSK Medical Monitor, that could affect the safety of the participant, or the interpretation of the data from the study.
26. Presence of hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb), or positive hepatitis C antibody result at screening (NB. participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA test is obtained).
27. Positive serology for HIV at screening.
28. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months.
29. QTc >450 msec or QTc >480 msec for participants with bundle branch block at screening and Day 1. The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or over read.**

* Retesting, in the case of potentially spurious results or sample handling errors, is allowed during the screening period.

** Same correction to be used throughout the study.

OTHER EXCLUSION CRITERIA
30. Participants with hypersensitivity to GSK2831781 or any excipients in the clinical formulation of GSK2831781 (See GSK2831781 Investigator Brochure).

5.3. Lifestyle Considerations

5.3.1. Tobacco and Caffeine

Smoking and caffeine can have an influence on the severity of ulcerative colitis disease symptoms. For that reason, participants should keep their smoking habits and caffeine intake broadly constant throughout the study. Use of nicotine replacement therapy should be recorded as concomitant medication.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice in future at the discretion of the Investigator, in discussion with the

Medical Monitor as needed. Rescreened individuals will be assigned a new participant number.

Screening assessments that yield aberrant results (e.g., safety laboratory samples) may be repeated once within the screening window by the Investigator based upon judgement. Retested participants should be assigned the same participant number as for the initial screening.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

Intervention Name	**GSK2831781**	**Placebo**
Type	Biologic	N/A
Dose Formulation	CCI [redacted]	Commercial saline solution (0.9% (w/v) Sodium Chloride)
Unit Dose Strength(s)	150 mg/mL	N/A
Dosage Level(s)	IV: 45 mg, 150 mg, 300 mg and 450 mg SC: 300 mg	N/A
Route(s) of Administration	IV infusion and SC injection	IV infusion & SC injection
IMP and NIMP	IMP	NIMP
Sourcing	Provided centrally by the Sponsor or designee	Supplied by site
Packaging and Labelling	Study intervention will be provided in vial. Each vial will be labelled as required per country requirement.	N/A
[Current/Former Name(s) or Alias(es)]	aLAG3, anti-LAG3	N/A

6.2. Intervention Administration

GSK2831781 is a fully humanized monoclonal antibody and all formulation ingredients have been previously used in the clinic. The intervention administration timings and monitoring periods as shown in Table 1 (Responders) and Table 2 (Open Label) must be undertaken for each participant.

Table 1 Intervention Duration and Monitoring Schedule (Double-Blind Induction and Double-Blind Extended Treatment Phase)

Dose	Dosing Duration*	Monitoring period
IV (Week 0, Day 1)	2 hr	2 hr
IV (Week 2)	2 hr	2 hr
IV (Week 6)	32 min	1 hr
IV (Week 10)	32 min	30 min
SC (Week 14)	n/a	2 hr
SC (Week 18)	n/a	30 min
SC (Week 22)	n/a	n/a
SC (Week 26)	n/a	n/a
* Including flush, see Study Reference Manual for details.		

Table 2 Intervention Duration and Monitoring Schedule (Open Label Induction and Open Label Extended Treatment Phase)

Dose	Dosing Duration*	Monitoring period
IV (Week 12)	2 hr	2 hr
IV (Week 14)	2 hr	2 hr
IV (Week 18)	32 min	1 hr
IV (Week 22)	32 min	30 min
SC (Week 26)	n/a	2 hr
SC (Week 30)	n/a	30 min
SC (Week 34)	n/a	n/a
SC (Week 38)	n/a	n/a
* Including flush, see Study Reference Manual for details.		

6.3. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. 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).
4. Further guidance and information for the final disposition of unused study intervention are provided in the SRM.

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.

6.4. Measures to Minimize Bias: Randomization and Blinding

6.4.1. Method of Treatment Assignment

At Screening a unique Participant Number (case report form (CRF) number) will be assigned to any participant who has at least one Screening procedure performed, other than informed consent. The unique Participant Number will be used to identify individual participants during the study.

Participants who meet the screening eligibility criteria will be randomised to a treatment group through RAMOS NG. RAMOS NG will confirm the participant's CRF number (Participant number) and provide the randomisation number, where a randomisation number will be assigned from a randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Once assigned, this number must not be reassigned to any other participant in the study.

Therefore, the randomisation is centrally controlled by RAMOS NG.

Randomisation of participants must be undertaken prior to dosing, preferably on Day 1, but may be conducted on Day -1 if required to allow the site pharmacist to prepare the dose. Randomisation may only occur if all information pertaining to patient eligibility has been confirmed, including eCRF Mayo score eligibility calculation.

The total number of participants recruited to the study will be up to a maximum of 320. At the start of the study, participants will be randomised in a 2:1 ratio to GSK2831781 450 mg and Placebo. When an appropriate number of participants have been randomised in these two arms for the interim analysis (Interim Analysis 3, see Section 9.5), randomisation to all dose regimens (GSK2831781 450 mg, 300 mg 150 mg, 45 mg or Placebo) will be opened in the ratio 2:3:3:3:2.

Randomisation will first be stratified by ethnicity (Japanese or non-Japanese participant). For the purposes of stratification, a Japanese participant must be living in Japan at the time of randomisation. Non-Japanese participants will be further stratified according to prior treatment (advanced therapy naïve, experienced a single class of advanced therapy, or experienced multiple classes of advanced therapies).

To ensure balance across the doses within Japanese participants, recruitment to GSK2831781 450 mg or placebo in a 2:1 ratio may continue after all dose regimens have been opened. When an appropriate number of Japanese participants have been dosed to GSK2831781 450 mg or placebo in a 2:1 ratio, recruitment to the remaining doses will continue using the same ratio as the rest of the participants. Due to number of expected Japanese participants, randomisation within this group will not be stratified according to prior treatment.

The treatment codes are as follows:

Treatment Code	**Treatment Description**
A	GSK2831781 450 mg
B	GSK2831781 300 mg
C	GSK2831781 150 mg
D	GSK2831781 45 mg
P	Placebo

Following the double-blind Induction Phase of the study, participants will be allocated to the next treatment phase according to their Responder status:

Responder status at Week 10	**Treatment Phase**
GSK2831781 Responder	Double-blind Extended Treatment Phase • GSK2831781 300 mg SC every four weeks
Placebo Responder	Double-blind Extended Treatment Phase • Placebo SC every four weeks
Non-Responder	Initiate Open Label Induction Phase followed by Open Label Extended Treatment Phase

6.4.2. Blinding

This will be a double-blind study with respect to allocation of GSK2831781 or placebo to participants (excluding Open Label Treatment). All site staff will be blinded with the exception of unblinded pharmacists or delegates. The following will apply:

- RAMOS NG will be programmed with blind-breaking instructions. The Investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the Investigator.
- It is preferred (but not required) that the Investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK within 24 hours of breaking the blind, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.
- A participant may continue in the study if the participant's treatment code is unblinded by the Investigator or treating physician. If the participant discontinues the date and primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to Investigators in accordance with local regulations and/or GSK policy.
- The DRC committee, consisting of a restricted set of key project team personnel with no contact with sites, senior stakeholders and external experts will review unblinded study data. No one external to the DRC committee will see unblinded study data. Further details of how the blind will be protected in the committee are included in the DRC charter.

6.5. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- GSK2831781 will be intravenously and subcutaneously (if Responders) administered to participants at the site. Administration will be documented in the source documents and reported in the CRF.
- All efforts should be made to administer GSK2831781 according to the SoA (Section 1.3), but if a dose is missed, it should be administered as soon as possible. However, two consecutive doses, whether IV or SC, should never be given less than 7 days apart. The Medical Monitor should be contacted if there are any questions regarding missed doses.

6.6. Concomitant Therapy

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

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. Participants will be questioned about concomitant medication at each study visit.

6.6.1. Permitted Concomitant Medications

Investigators are expected to comply with all local standard of care practices and product labelling for listed permitted concomitant medications including prophylactic therapies, contraception requirements, laboratory testing, follow-up care and other precautions and contraindications should continue to be followed throughout the study.

6.6.1.1. Corticosteroids

Oral corticosteroids are allowed up to a maximum dose of 20 mg/day prednisolone (or equivalent, as detailed in the SRM) on entry to the study, providing they have not been commenced, or the dose altered, within two weeks prior to the baseline endoscopy. The dose of corticosteroids should not change between the baseline endoscopy and Week 12. A dose increase as rescue therapy for UC constitutes an individual stopping criterion (see Section 7.1.1). If the dose of corticosteroid needs to be reduced due to a safety concern, this should be documented appropriately.

A corticosteroid taper is mandatory from Week 12 for participants who are Responders at the Induction Assessment. Non-Responders at Induction who commence Open Label treatment and subsequently attain response (determined following a centrally read endoscopy at Week 22) will undergo corticosteroid taper from Week 24. For Responders, corticosteroids should be tapered according to the following regimen:

- For prednisolone doses >10 mg/day (or equivalent), the dose should be reduced from Week 12 at a rate of 5 mg/week (or equivalent) until a 10 mg/day dose is reached.

- For prednisolone doses ≤10 mg/day (or equivalent), or once a 10 mg/day dose (or equivalent) is achieved by tapering, the dose should be reduced at a rate of 2.5 mg/week (or equivalent) until discontinuation.

- Where the initial steroid dose is such that tapering by the above regimen would be challenging because of medicine formulation, it is acceptable for the first step of the taper to be down to a dose that subsequently allows a taper by the above parameters. However, this initial reduction should be by no more than 5 mg prednisolone

equivalent (if initial prednisolone equivalent dose is >10mg/day) or by 2.5 mg (if initial prednisolone equivalent dose is ≤10 mg/day).

- For participants who cannot tolerate the corticosteroid taper without recurrence or exacerbation of clinical symptoms, corticosteroids may be increased up to a maximum of the original dose at the start of the Induction Phase (but should not exceed the baseline dose). In such cases, the tapering regimen above must be reinitiated within 2 weeks of the dose increase. Following two unsuccessful attempts at corticosteroid taper, the patient may re-escalate doses of corticosteroid up to the baseline level.

6.6.1.2. Other therapies

The therapies for UC specified in Table 3 are allowed providing the dosages are stable for the specified period of time prior to baseline endoscopy and throughout the study until Follow-Up. Decreases in dosing for safety reasons are allowed if required, but the reasons for the change, date and time of the change, as well as the name and dosage regimen adopted must be recorded. The dose should not be subsequently increased:

Table 3 Permitted concomitant medications

Medication	Stable Dose Period Requirement
Oral 5-ASA or sulfasalazine.	For 2 weeks prior to baseline endoscopy until after the Follow-Up visit.
Azathioprine or mercaptopurine.	For 8 weeks prior to baseline endoscopy until after the Follow-Up visit (including initiation or discontinuation of allopurinol).
Oral methotrexate.	For 8 weeks prior to baseline endoscopy until after the Follow-Up visit.
Oral corticosteroids.	See Section 6.6.1.1.

6.6.2. Prohibited Concomitant Medications

The following medications are prohibited for the time period prior to baseline endoscopy until after the last endoscopy or Follow-Up visit (as detailed in Table 4). Participants who initiate prohibited medications must be discussed with the Medical Monitor and may be asked to discontinue study treatment if there is a safety concern. Details of any medication received must be recorded as described above (Section 6.6.1). Table 4 below lists the prohibited medications.

Table 4 Prohibited Medications

Medication	Time period of Prohibition
Topical (rectal) or intravenous corticosteroids, or topical (rectal) 5-ASA.	Within 2 weeks prior to baseline endoscopy until after the last endoscopy.
Ciclosporin, tacrolimus, mycophenolate mofetil or thalidomide.	Within 4 weeks prior to baseline endoscopy until after the Follow-Up visit.
Anti-TNF therapy (e.g. infliximab, adalimumab, golimumab, or biosimilars).	8 weeks prior to baseline endoscopy until after the Follow-Up visit.
Anti-integrin or anti-IL-12/23 biologics	12 weeks prior to baseline endoscopy until after the Follow-Up visit.
Tofacitinib.	Within 4 weeks prior to baseline endoscopy until after the Follow-Up visit.
Rituximab.	Within 1 year prior to baseline endoscopy until after the Follow-Up visit.
Any other biologic therapy for the treatment of UC not listed above.	Within 3 months, 5 half-lives or twice the duration of the biological effect (whichever is longer) prior to baseline endoscopy until after the Follow-Up visit.
Any other small molecule agent for the treatment of UC not listed above.	Within 30 days, 5 half-lives or twice the duration of the biological effect (whichever is longer) prior to baseline endoscopy until after the Follow-Up visit.
Treatment with any other form of systemic immunosuppressive medication not mentioned elsewhere in this table or in Section 6.6.1.	Prohibited during the study and until after the Follow-Up visit.
Leukocyte apheresis.	Within 4 weeks prior to baseline endoscopy until after the Follow-Up visit.
Faecal microbiota transplantation.	Within 4 weeks prior to baseline endoscopy until after the Follow-Up visit.
Live vaccination.	Within 4 weeks of Day 1 until after the Follow-Up visit.

6.6.3. Rescue Therapy

If a participant requires rescue therapy for UC (including treatments specified in Section 6.6.2, and/or surgical intervention), or a dose increase of background UC medication is required, he/she should discontinue study Intervention, and the appropriate treatment should be given at the discretion of the Investigator. Doses of permitted concomitant medication for UC should not otherwise be increased for the duration of the study, although if a corticosteroid taper has occurred, prescribed corticosteroid doses may be increased up to, but not beyond, the dose prescribed at baseline (see Section 6.6.1.1). The date and time of rescue intervention, as well as the name and dosage regimen of the rescue medication, must be recorded. Following intervention discontinuation participants should undertake an Early Withdrawal visit and a Follow-Up visit approximately 16 weeks after the last dose

at a minimum. However, it is encouraged that participants undertake all remaining scheduled visits set out in the SoA, Section 1.3.

6.6.4. Potential for drug-drug interactions

No formal drug-drug interaction studies have been performed with GSK2831781. However, during inflammation, enzymes such as cytochrome P450 can sometimes be down-regulated, leading to reported instances of reduced clearance and increased plasma concentrations of administered drugs. If inflammation related to ulcerative colitis changes over the course of the study, this might have an indirect effect on drug metabolising enzyme expression and activity, although the magnitude and impact of such interactions are generally small.

Participants who are co-administered drugs that are metabolised by cytochrome P450 and have a narrow therapeutic index should be monitored for clinical evidence of changes in exposure (e.g. evidence of reductions in drug efficacy, or of increased effect or toxicity). Therapeutic drug monitoring should be performed as clinically indicated.

6.7. Dose Modification

Dose regimens (levels and/or frequencies) of GSK2831781 as described in Section 4.3 may be modified up or down based on ongoing review of the unblinded safety, pharmacokinetic, pharmacodynamic, biomarker and efficacy data by the DRC. However, exposure levels will not exceed those of the GSK2831781 450 mg dose regimen.

6.8. Intervention after the End of the Study

Study intervention will cease at the end of a participant's Follow-Up period. GSK2831781 will not be made available to participants after the end of the study due to the early stage of development, and because other treatments are available. The Investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An SRT will oversee the safety of participants in this study. The SRT will review blinded safety data at regular intervals during the study and ad hoc as required, and have oversight of any emerging safety data related to GSK2831781, as described in the SRT charter. The DRC will review unblinded safety and efficacy data at defined intervals. Full details are included in the DRC Charter.

7.1. Discontinuation of Study Intervention

If study intervention is permanently discontinued, the participant should be encouraged to remain in the study and complete the planned visits and assessments for the treatment phase they are in at the time of treatment discontinuation, with a final Follow-Up visit

approximately 16 weeks from the last dose received, if possible. In the event of an early withdrawal from the study (See Section 7.2), participants should be encouraged to complete the early withdrawal visit and a Follow-Up visit approximately 16 weeks after the last dose event.

In addition, the Investigator should determine the primary reason for study intervention discontinuation. Withdrawal from study intervention due to an AE should be distinguished from withdrawal from study intervention due to insufficient response according to the definition of an adverse event.

7.1.1. Individual Safety Stopping Criteria

Study medication will be discontinued in the event of any of the following:

- The participant develops a serious or severe opportunistic or atypical infection.
- The participant experiences a serious or severe clinically significant hypersensitivity reaction following study investigational product administration, meeting the CTCAE criteria:
    - Anaphylaxis Grade 3 or 4.
    - Allergic reaction Grade 3 or 4.
    - Serum Sickness Grade 2-4.
- The participant experiences a serious clinically significant Cytokine Release Syndrome, defined as CTCAE Grade 2-4.
- The participant experiences an SAE where in the clinical judgement of the Investigator there is a reasonable possibility that the SAE may be caused by the investigational product.
- The participant becomes pregnant.
- The participant requires prohibited medications or an escalation of background medications above baseline for the treatment of ulcerative colitis (Section 6.6.2), including surgery.
- If the predetermined haematologic stopping criteria; liver chemistry stopping criteria; or QTc stopping criteria are met.

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

7.1.2. Haematologic Temporary Withholding and Stopping Criteria

7.1.2.1. Temporary withholding

Study treatment will be temporarily withheld for a participant if the absolute neutrophil count falls below $1.0x10^9$/L. Confirmatory re-testing should be undertaken within 3-5 days, and should be re-tested every 3-5 days until values have returned to above the haematological exclusion criteria threshold ($1.5x10^9$/L), at which point dosing can be resumed (however, two consecutive doses of GSK2831781, whether IV or SC, should never be given less than 7 days apart). If neutrophil counts do not return to normal/baseline

within a period of time judged reasonable by the Investigator, the aetiology should be identified, and the sponsor notified.

7.1.2.2. Permanent discontinuation

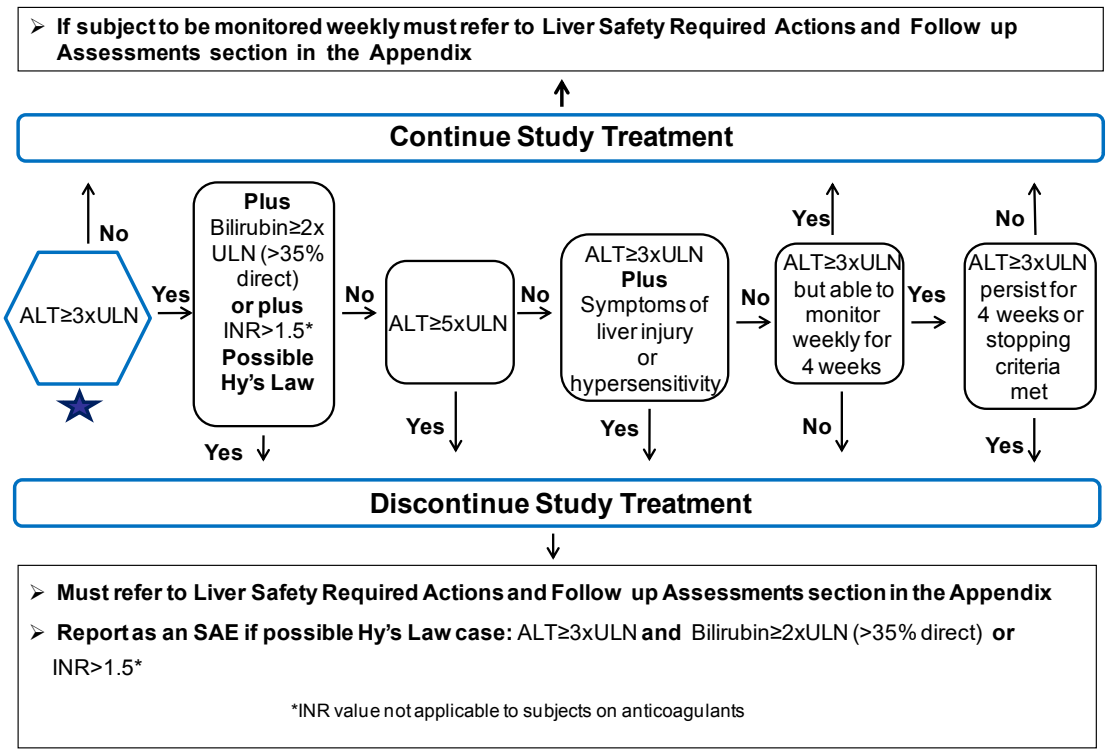
Study treatment will be discontinued for a participant if the following haematological stopping criteria are met:

- Absolute neutrophil count $<0.5x10^9$/L on any occasion (confirmed on repeat testing within 3-5 days).
- Absolute neutrophil count $<1.0x10^9$/L for 2 weeks.
- Grade 3 febrile neutropaenia (neutrophil count $<1.0x10^9$/L and fever ≥38.5 °C).

Treatment restart or re-challenge for these participants is not allowed. The Investigator must immediately inform the Medical Monitor of the event, and repeat testing must be conducted at an appropriate frequency until haematological laboratory values have returned to above the lower limit of normal.

7.1.3. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed (see algorithm below) to assure participant safety and evaluate liver event aetiology.



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.
Symptoms of liver injury or hypersensitivity include: fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia.

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6, Section 10.6.

7.1.4. QTc Stopping Criteria

A participant who meets the bulleted criteria based on the average of triplicate ECG readings will discontinue study treatment:

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

7.1.5. Group and Study Safety Stopping Criteria

In addition to the individual stopping criteria specified above, blinded data of AEs, SAEs, laboratory abnormalities, ECG abnormalities, and changes in vital signs occurring across all randomised participants will be regularly reviewed by the SRT to ensure appropriate participant safety.

Study stopping criteria have been set with respect to numbers of individual permanent discontinuations due to neutropaenia attributable to GSK2831781 (see Section 7.1.2.2):

- ≥2 participants, in up to 9 participants dosed in the study.
- ≥5 participants, in up to 60 participants dosed in the study.
- >10% of participants for the remainder of the study.

Rates meeting these thresholds will trigger an ad hoc DRC review, to determine whether neutropaenia is likely to be attributable to GSK2831781. Furthermore, the study may be terminated prematurely if there are new toxicological findings, SAEs or frequent AEs that invalidate the positive benefit-risk assessment. Any changes to the study due to safety reasons will be promptly communicated to the appropriate Regulatory Authorities.

7.1.6. Temporary withholding of IP

Temporary withholding of IP may occur in the event of:

- Meeting treatment withholding criteria for neutropaenia (see Section 7.1.2.1)
- In the event of a clinically significant infection that the Investigator believes may be related to, or exacerbated by, ongoing treatment with the study drug, and none of the permanent stopping rules have been met.
- In the event that the participant has a close household contact with a highly transmissible infection, the Investigator has discretion to delay dosing.

If the scheduled dose window is missed, re-initiation of study treatment intervention should be restarted as soon as possible but should not result in two consecutive doses, whether IV or SC, being given less than 7 days apart (see Section 6.5).

7.2. Participant Discontinuation/Withdrawal from the Study

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

At the time of discontinuing study treatment, participants should be encouraged to stay on schedule and attend all remaining visits set out in the SoA (Section 1.3) until the end of the current study phase. An Early withdrawal visit is only required for participants who prematurely discontinue study treatment and do not agree to complete the remaining scheduled visits for that phase. In both cases, all participants should undertake a Follow-Up visit approximately 16 weeks from the last dose received, where the participant will be permanently discontinued from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1, Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

- A signed, written informed consent form must be obtained from the participant prior to any study-specific procedures or assessments being performed.
- Study procedures and their timing are summarized in Section 1.3.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study is not expected to exceed 600 mL; however, repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For details on home healthcare and telemedicine approaches, please refer to Appendix 10.

8.1. Baseline Assessments

Baseline assessments will be captured to ensure characterisation of participants at baseline. The information to be captured is described fully in the SRM; however, in summary it includes but is not limited to:

- Extent of disease (proctosigmoiditis, left-sided or extensive/pancolitis).
- Duration of disease (date of diagnosis).
- Activity of disease.
- Previous treatment(s) for UC and reasons for discontinuation (if discontinued) – for each treatment.
- Smoking status.
- Extra-intestinal manifestations.
- Past medical history.
- Medication history.

8.2. Efficacy Assessments

8.2.1. Clinical Disease Assessments

8.2.1.1. Mayo Score

Clinical disease assessments will be undertaken using the Mayo Score. Multiple derivations will be calculated (described below) to enable characterisation of disease status, whilst also enabling comparison of disease remission and response with previous clinical studies in UC.

- The Complete 4-domain Mayo Score is a 12-point scoring system where disease is evaluated based on stool frequency, rectal bleeding, physician global assessment (PGA) and endoscopic appearance (with CCI associated with an endoscopic score of CCI).
- The Adapted Mayo Score is a 9-point scoring system where disease is evaluated based on stool frequency, rectal bleeding and endoscopic appearance (with any CCI associated with an endoscopic score of CCI or CCI).
- The Partial Mayo Score is a 9-point scoring system where disease is evaluated based on stool frequency, rectal bleeding and PGA, but no endoscopy component, and will be used to follow changes in these parameters over the course of the study.

The patient reported outcomes of Stool Frequency and Rectal Bleeding for Mayo scores will be calculated from participant eDiary data. To provide a participant's Mayo score status during study conduct, eDiary data will be transcribed into the eCRF for calculation of the Stool Frequency and Rectal Bleeding subscores. Identification of data to be used for calculation of the Mayo score will be based on:

- 3 consecutive days.
  - Where 3 consecutive days are not available, non-consecutive days may be used.
  - For determining eligibility in Screening, 3 days are mandatory. Exceptionally, for determining Responder status at Week 10 double blind and Week 22 Open Label, 2 days may be sufficient, the RAP details how these participants will be handled in the study analysis.
- Within 7 days prior to the endoscopy.
- As close to the date of endoscopy as possible.
- Excluding any days in which bowel preparations are administered.

For further guidance on which days to select in case of missed eDiary entries in any of the targeted days, see SRM for full details. Note that calculations must be made within eCRF to determine Eligibility (prior to Randomisation) and Responder status.

Complete and Adapted Mayo Scores will be calculated from eDiary data, site reported PGA scores and centrally read endoscopy scores at all time points indicated in the SoA (Section 1.3). Definitions of each of the Mayo Score systems, and associated response and remission definitions for each score, can be found in Appendix 7, Section 10.7.

To enable Mayo scoring of stool frequency it is necessary to determine baseline 'normal' number of stools per day through discussion between the patient and the Investigator. 'Normal' will be defined to the participant as "the number of stools in a 24 hour period when you are not experiencing a UC flare, or when you were in remission". If the patient reports that they have not attained remission, then the patient will be asked to identify the number of stools he or she had per day before the initial onset of signs and symptoms of UC. This will be used to inform subsequent Mayo scoring of stool frequency.

8.2.1.2. Ulcerative Colitis Endoscopic Index of Severity

The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) will be used as an additional tool to assess disease activity based on endoscopic vascular pattern, bleeding, erosions and ulcerations (see SRM for detail). It has been shown to accurately reflect overall assessment of endoscopic severity of UC and predict outcomes in severe disease [Xie, 2018]. Its broader range than the Mayo endoscopic score facilitates assessment of the dose-response relationship [Travis, 2012]. The UCEIS will be collected and scored centrally at all time points indicated in the SoA (see Section 1.3).

8.2.2. Histological Disease Assessments

Definitions of histological remission for histological disease assessments are included in the RAP. During the study, the Robarts Histopathology Index, Nancy Histological Index and Geboes Score will be assessed by central reading of gut pinch biopsies. Key domains for scoring of the indices include: chronic inflammatory infiltrate; neutrophils in the epithelium; lamina propria neutrophils (and eosinophils – Geboes Score); erosion and ulceration; and crypt destruction (Geboes Score).

8.2.3. Extraintestinal Manifestations

Extraintestinal manifestation (EIM) assessments are key clinical manifestations related to UC, and will be evaluated at screening and during the study (see SoA, Section 1.3). A number of EIMs will be assessed including but not limited to:

- Peripheral arthritis.
- Axial arthropathy.
- Dermatological manifestations.
- Uveitis.
- Primary sclerosing cholangitis.
- Oral aphthous ulceration.

If present, EIMs will be scored by the Investigator as detailed in the SRM.

8.2.4. Patient Reported Outcomes

All patient reported outcome (PRO) questionnaires will be completed on an electronic device. A Bowel Symptom Diary will be completed by participants daily at home, throughout the study. PRO measures for health outcomes assessment will be completed at

study visits, before any other study assessments, also on an electronic device. Sites will receive notification from the ePRO vendor when patients fail to complete the ePRO diary or other measures, and should follow-up with the patient to ensure completeness for all PRO questionnaires.

8.2.4.1. Participant Bowel Symptom Diary

Participants will be provided with a hand-held electronic device on which to record their bowel symptom data on a daily basis. The instructions will be provided to participants, to record the following information during the study:

Concepts covered:

- Absolute number of toilet visits for bowel movement.
- Frequency and description of blood in stools.
- Night time awakenings to go to the toilet for a stool.
- Bowel urgency.
- Tenesmus.

8.2.4.2. Patient Reported Outcomes (PRO) for Health Outcomes Assessment

The electronic device will be used to record various patient-reported outcomes (PRO) assessments on the specified study visit days before any other clinic assessments (refer to Section 1.3). The PROs used within this study will include but not be limited to:

- Inflammatory Bowel Disease Questionnaire (IBDQ).
- Short Form-36, version 2 (SF-36).
- FACIT-Fatigue.
- Patients' Global Impression of Change (PGIC) and Severity (PGIS).

8.2.4.2.1. Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ questionnaire is a psychometrically validated patient-reported outcome (PRO) instrument for measuring the disease-specific quality of life in participants with Inflammatory Bowel Disease, including UC. The IBDQ comprises 32 items, which are grouped into four dimensions: bowel function (10 items), systemic symptoms (5 items), social function (5 items), and emotional status (12 items). The four domains are scored as follows:

- Bowel symptoms: 10 to 70.
- Systemic symptoms: 5 to 35.
- Emotional function: 12 to 84.
- Social function 5 to 35.

The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better quality of life. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement. See SRM for the complete IBDQ.

8.2.4.2.2. Short Form-36, version 2 (SF-36)

The SF-36 is a widely used general health status questionnaire that assesses 8 domains of functional health and well-being: Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, Social Functioning, Mental Health, Role Limitations due to Emotional Problems, Vitality, and General Health Perceptions. A Physical health component summary score and Mental health component summary score are calculated from the 8 domain scores. The measure uses a recall period of one week. All questions are scored on a scale from 0 to 100, with 100 representing the highest level of functioning possible. The SF-36 is a psychometrically valid and reliable instrument that has been translated into many languages, and the scores have been shown to be responsive to change. Higher scores indicate better health-related quality of life.

On the specified study visit days, participants should complete the SF-36 on the electronic hand-held device, before other clinic assessments (refer to Section 1.3). The SF-36 should be checked for completeness by the study site staff. See SRM for the complete SF-36.

8.2.4.2.3. Patients Global Impression of Change (PGIC) and Severity (PGIS)

Patient Global Impression of Change is a subjective instrument commonly used to measure the perceived degree of change experienced by the patient. Patients will be asked to choose the response option that best describes the overall change in their UC symptoms since they started taking the study medication, on a 5-point Likert scale, at specific timepoints throughout the study (See Section 1.3). Response options range from “Much Better” to “Much Worse”. See SRM for the full PGIC.

Patient Global Impression of Severity is a subjective instrument commonly used to measure the degree of disease severity experienced by the patient. Patients will be asked to choose the response option that best describes the severity of their UC symptoms in the last 7 days, on a 5-point Likert scale, at specific timepoints throughout the study (see Section 1.3). Response options range from “None” to “Very Severe”. See SRM for the full PGIS.

8.2.4.2.4. FACIT Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) is a 13-item tool that measures an individual’s level of fatigue during their usual daily activities over the past week. Each question is rated on a scale of 0 (“CCI [redacted]”) to 4 (“CCI [redacted]”), with total scores ranging from 0 to 52, and lower scores representing greater fatigue.

On the specified study visit days, participants should complete the FACIT-Fatigue scale on the electronic hand-held device, before other clinic assessments (refer to Section 1.3). The FACIT-Fatigue should be checked for completeness by the study site staff. See SRM for the full FACIT-Fatigue.

8.2.5. Exit Interviews

A sub-group of participants will be invited to take part in qualitative, one-to-one interviews at the end of the study (see Section 1.3, and the SRM). Exit interviews will cover the following scope:

- Patient feedback on the daily Bowel Symptom Diary, including patient burden, comprehensiveness of symptoms covered, completion time, recall period, clarity of instructions, clarity of questions and supporting definitions and appropriateness of response options.
- Patient feedback on PRO measures for Health Outcomes Assessment (including IBDQ, SF-36, FACIT-Fatigue, PGIS and PGIC), including patient burden, ease of completion, comprehensiveness of symptoms and impacts covered by these instruments.
- Patient feedback on trial experience.

8.3. Pharmacokinetics

Blood samples for pharmacokinetic analysis of GSK2831781 will be collected at the time points indicated in Section 1.3, for all participants.

In order to properly characterise subcutaneous bioavailability and PK, additional subcutaneous PK and sLAG3 sampling will be performed on a subset of participants. The additional samples will be taken according to one of two schedules (Table 5 and Table 6), determined in discussion with the Sponsor or their representative and the study site. Once samples have been collected for a sufficient number of participants, this sampling may be discontinued, at the discretion of the Sponsor. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Collection, sample handling, processing, storage and shipping procedures are provided in the SRM or equivalent.

For details on home healthcare approaches, please refer to Appendix 10.

Table 5 SC PK and sLAG3 characterisation schedules for selected participants – Schedule 1

Week	**14**		**15**
Days since first SC dose	**1**	**3**	**7**
PK	X	X	X
sLAG3	X	X	X

Footnote: Samples can be taken at any time on the day

Table 6 SC PK and sLAG3 characterisation schedules for selected participants – Schedule 2

Week	**14**		**15**
Days since first SC dose	**2**	**5**	**10**
PK	X	X	X
sLAG3	X	X	X

Footnote: Samples can be taken at any time on the day

8.3.1. Soluble LAG3 (sLAG3)

Venous blood samples will be collected for measurement of soluble LAG3 (sLAG3) as specified in the Section 1.3, and in Table 5 and Table 6.

8.4. Pharmacodynamics

The pharmacodynamic (PD) effect of GSK2831781 on $LAG3^+$ cell depletion will be determined through analysis of blood, and gut pinch biopsies. Blood PD analysis will be undertaken in a subset of the patient population, at selected sites able to meet shipping requirements (within 48 hrs of testing labs) through flow cytometry. In addition, the PD of GSK2831781 will be determined in gut pinch biopsies through immunohistochemistry. Further detail on gut biopsy can be found in Section 8.4.1.3.

8.4.1. Biomarkers

Collection of samples for other biomarker research to explore UC disease processes and the impact of GSK2831781 is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SRM or equivalent:

- Blood.
- Faeces.

- Intestinal pinch biopsy.

8.4.1.1. Exploratory biomarkers in Blood

Serum samples for blood biomarkers will be collected at the time points indicated in the SoA (Section 1.3) to characterise systemic markers of UC and the impact of GSK2831781. Changes from baseline of markers of inflammation including but not limited to C-reactive protein (CRP) and cytokines will be explored. Proteomic and transcriptomic analysis may also be conducted on blood samples to investigate markers of disease activity, pathogenesis and potential stratifying markers of responsiveness.

8.4.1.2. Biomarkers in faeces

To further characterise biomarkers of UC and the impact of GSK2831781 on intestinal inflammation, faecal samples will be taken to enable measurement of markers including but not limited to faecal calprotectin, at the time points indicated in the SoA (Section 1.3). Information on sample processing is provided in the SRM or equivalent.

8.4.1.3. Tissue Biopsy

Tissue biopsies will be taken to assess the impact of GSK2831781 on mucosal healing, inflammation and target cell depletion. A target of nine 'adequate' biopsies for trial purposes (see SRM for detail) will be taken throughout the inflamed colon 15-25 cm from the anal verge during the endoscopy at baseline screening, Week 10 (all participants), and at Week 30 for Responders and Week 22 for Non-Responders on Open Label Treatment.

Details of biopsy sample collection processing, storage and shipping procedures are provided in the SRM or equivalent. Tissue samples will be divided accordingly for:

- Histology and immunohistochemistry assessments (approximately 3 biopsies). including but not restricted to numbers of $CD3^+$ $LAG3^+$ T cells.

- Gene expression analyses (approximately 3 biopsies) of markers of inflammation and tissue healing, including not limited to LAG3, IL-1β, IL-6 and IL-8.

- With the remaining biopsies (approximately 2, up to 3 biopsies), additional techniques including and not limited to epigenetic counting and T cell receptor (TCR) sequencing may be used to determine the effect of GSK2831781 on pathophysiological pathways in IBD.

8.5. Pharmacogenetics

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

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

See Appendix 5, Section 10.5 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SRM or equivalent.

8.6. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.6.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal, Endocrine and Neurological systems. Height (at baseline only) and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (including liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

For telemedicine visits, an evaluation of the participant will be performed by a physician through a video telemedicine format. If the Investigator feels an adequate clinical assessment has not been achieved, a clinic visit must be performed.

8.6.2. Vital Signs

Pre-dose vital signs are to be taken before blood collection for laboratory tests.

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

Blood pressure and pulse measurements will be with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.6.3. Electrocardiograms

- Triplicate (at screening) or single 12-lead ECG will be obtained as outlined in Section 1.3 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study, and this formula may not be changed or substituted once the participant has been screened.
- Where single ECG measurements are obtained, if the QTc measurement fulfils a QTc withdrawal criterion an additional two QTc readings will be obtained and the

average of these three measurements will be used. Refer to Section 7.1.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.6.4. Clinical Safety Laboratory Assessments

Refer to Appendix 2, Section 10.2 for the list of clinical laboratory tests to be performed and to Section 1.3 for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 16 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline, or are no longer considered significantly abnormal by the Investigator or Medical Monitor.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g. SAE or AE or dose modification), this must be documented in the eCRF.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the aetiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, Section 10.2, must be conducted in accordance with the SRM or equivalent and Section 1.3.

8.6.5. Immunogenicity Assessments

Antibodies to GSK2831781 will be evaluated in serum samples collected from all participants according to Section 1.3. Additionally, serum samples will also be collected at the Withdrawal visit from participants who discontinued study intervention or were withdrawn from the study. The detection and characterization of antibodies to GSK2831781 will be performed using a validated assay method by or under the supervision of the Sponsor.

Serum samples will be assessed for the presence of ADA using a tiered approach. Samples will first be screened for antibodies binding to GSK2831781. Samples with screening result above the screening cut point will be further assayed in an assay to confirm the specificity of the ADA. Samples testing positive in the confirmation assay will be further assayed through sequential dilution in order to report a titre value. The titre is the reciprocal of the last dilution at which the sample tests positive in the screening assay. Additional analysis may be performed on samples collected to monitor immunogenicity to assess the

presence of neutralizing antibodies to GSK2831781 and/or to further characterize the immunogenicity of GSK2831781.

8.6.6. Infusion-related Reactions, Hypersensitivity Reactions and Cytokine Release Syndrome.

As GSK2831781 is a fully humanized monoclonal antibody, it is considered unlikely that acute allergic reactions will occur in response to GSK2831781 exposure; however, all participants should be monitored carefully for evidence of allergic response. In the event of a suspected acute hypersensitivity reaction two blood samples should be taken for serum tryptase analysis:

- As soon as possible after the onset of symptoms, and
- Within 1-2 hours (but no later than 4 hours) from the onset of symptoms.

Participants should be instructed to report the development of rash, hives, pruritus, flushing, urticaria, vomiting, or other symptoms that may represent a hypersensitivity reaction to study intervention. In the case of a mild reaction, study intervention administration may be reinitiated (with appropriate pre-medication) at the discretion of the Investigator. Participants with a serious or severe clinically significant hypersensitivity reaction following study investigational product administration meeting the CTCAE criteria set out in Section 7.1.1 should discontinue study treatment.

If cytokine release syndrome (CRS) is suspected, in addition to assessment for infection, cytokine levels (including IL-6, IL-8, IFN-γ and TNF-α) and CRP should be measured approximately every other day until symptoms show improvement or an alternative diagnosis is confirmed.

8.6.7. Immunosuppression and Infections

Patients with signs and symptoms suggestive of infection should be treated as clinically indicated according to medical best practice. Blood, sputum, urine, and/or stool cultures will be obtained as appropriate for detection and diagnosis of infection. Blood samples for determination of viral serology ± measurement of viral load (CMV, EBV, VZV), as well as measurement of immunoglobulins, will be taken if the participant demonstrates clinical symptoms consistent with viral reactivation; serology samples for these viruses will also be tested at baseline.
If the infection fulfils the Individual Safety Stopping Criteria specified in Section 7.1.1, study treatment should be discontinued.

8.6.8. Autoimmunity

There are a small percentage of regulatory T cells that are $LAG3^+$ [Chung, 2013 Gagliani, 2013; Bornkamp, 2014; Camisaschi, 2010; and GSK internal data], and therefore Investigators should be alert for the development of autoimmunity. Any participant who reports symptoms suspicious for autoimmunity should be investigated and managed as clinically appropriate.

8.7. Adverse Events and Serious Adverse Events

The definitions of an AE and SAE can be found in Appendix 3, Section 10.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue GSK2831781 treatment (see Section 7).

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

All SAEs will be collected from the signing of the informed consent form until the Follow-Up visit at the time point specified in the SoA (Section 1.3).

All AEs will be collected from the start of intervention until the Follow-Up visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3, Section 10.3. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the sponsor.

8.7.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Section 10.3.

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

8.7.3. 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 AE/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined

in Section 7.3). Further information on follow-up procedures is given in Appendix 3, Section 10.3

8.7.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

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

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.7.5. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until the end of Follow-Up.

If a pregnancy is reported, the Investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4, Section 10.4.3.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.7.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3, Section 10.3.3 (Definition of Cardiovascular Events) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

8.8. Treatment of Overdose

For this study, any dose of GSK2831781 greater than the agreed dose level and frequency for a particular cohort will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event that an overdose is identified by unblinded staff, but is less than 450 mg in a 7 day period, this should be documented by the unblinded monitor (including the quantity and duration of the overdosing), but no additional action need be taken.

If the total dose administered has exceeded 450 mg in a 7 day period, the unblinded monitor should:

1. Contact the Medical Monitor immediately.
2. Ask the Medical Monitor to request that the Investigator closely monitors the participant for AE/SAE and laboratory abnormalities for at least 4 weeks from the date the overdose occurred, and thereafter as advised by the Medical Monitor.
3. If the overdose is identified within 21 days of its occurrence, request that the Medical Monitor advises the Investigator to obtain a plasma sample for PK analysis as soon as possible, and thereafter as advised by the Medical Monitor.
4. Document the quantity of the excess dose as well as the duration of the overdosing

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The first primary objective of this study is to assess the safety and tolerability of GSK2831781 in participants with moderate to severe UC. No formal hypotheses will be tested for this objective.

The second primary objective of this study is to evaluate the dose-response relationship in the change from baseline in the Complete 4-domain Mayo score, following 10 weeks of treatment with GSK2831781 or placebo. The dose response relationship will be characterised using the posterior probabilities of the parameters of an Emax model and by estimating the response at each dose level, using Bayesian methodologies, this will be the primary efficacy analysis. The primary efficacy analysis will therefore not use frequentist hypothesis testing, a characteristic of a well fitted model will be that the half width of the 95% credible interval for the change from baseline in Complete 4-domain Mayo response at ED90 is ≤ 1. The dose-response relationship will also be assessed for selected categorical secondary endpoints (Endoscopic Improvement, Clinical Response and Clinical Remission).

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

Approximately 242 participants will be randomly assigned to study intervention under the assumption that a proportion will not be able to provide a Week 10 Complete 4-domain Mayo score assessment under the additional (hypothetical) estimand. If the attrition rate is higher than planned for (e.g., 15% or more) then additional participants, up to a maximum of 320, may be recruited.

Primary Analysis: Dose-response change from baseline in Mayo score

At Week 10 the expected distribution of the change from baseline in the continuous Mayo score in the placebo group is a mean of -1 and a standard deviation of 1.5 (based on tofacitinib Phase II data [Sandborn, 2012]). Based on these assumptions the proposed sample size of 68 participants on the GSK2831781 450mg dose level, 42 participants on each of the GSK2831781 lower dose levels, and 48 participants on placebo are sufficient to characterise the dose-response curve. This is based on 5000 simulated trials where the following Emax model was fitted to simulated data:

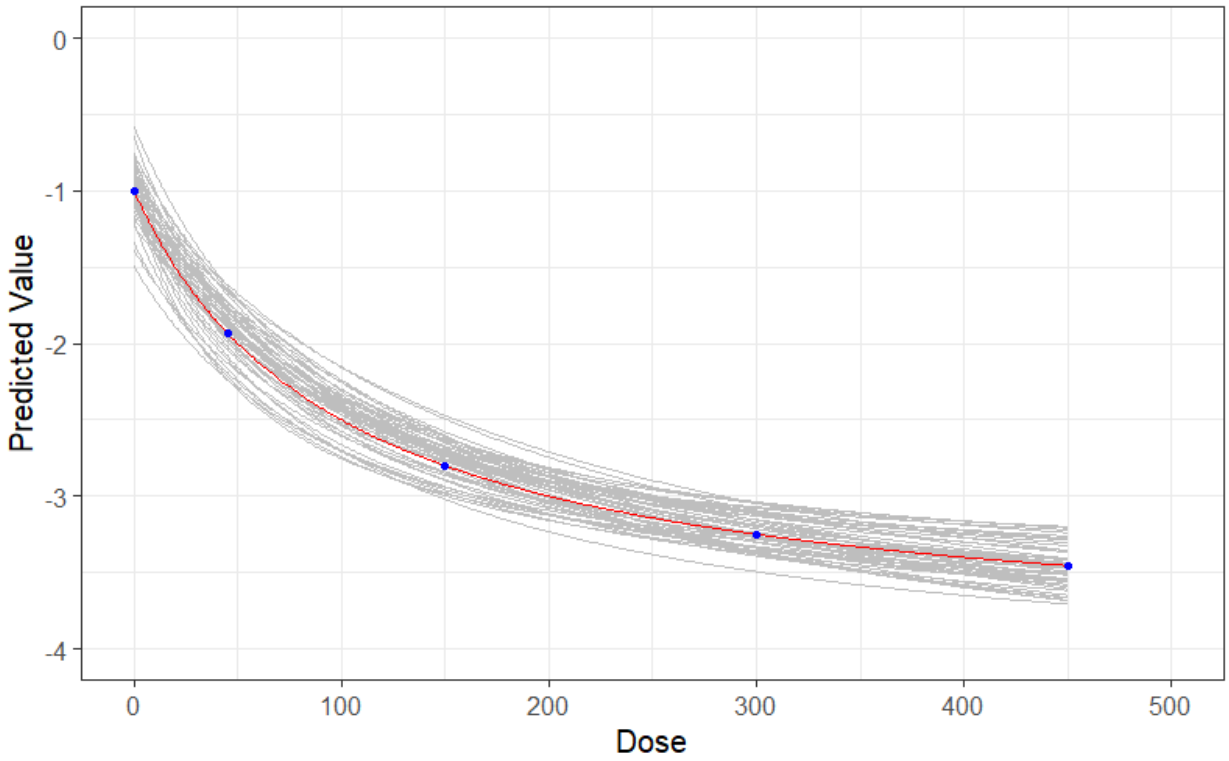
$$Y = E0 + Emax * (Di)^{\gamma} / \{ED50^{\gamma} + (Di)^{\gamma}\}$$

Where E0 is the minimum dose effect, Emax is the maximum achievable effect above placebo, ED50 is the dose at half Emax, Di are doses = 0, 45, 150, 300, 450 and γ is the slope parameter (shape of the potential dose response curve). Y is the change from baseline in the continuous Mayo score. E0 is the assumed effect with Dose=0 (placebo) which is -1, the Emax is taken as -3, $\gamma$is assumed to be 1 and ED50 is assumed to be 100.

For the E0 and Emax parameters a normal prior with mean 0 and standard deviation of 100 was used. For ED50 a beta(0.5, 5.2) was used scaled between 0 and 675 (1.5*top dose, as suggested by Bornkamp, 2014 as an approximation to the functional uniform prior). For the standard deviation a gamma (shape=2, rate=0.1) was used (Chung, 2013).

Figure 4 below illustrates a sample of fitted model curves. In these simulations the half width of the 95% credible interval for the Complete Mayo response at ED90 is ≤1 97% of the time:

Figure 4 Dose-response precision based on outlined assumptions



Note: True means from simulation marked in blue

To illustrate the properties of this sample size if it were to be analysed within a frequentist framework, the following sample size assessment is also provided:

Assuming normal distributions with a standard deviation of 1.5, there would be greater than 90% power for a pairwise comparison to detect a difference from placebo of 2 points on the change from baseline at Week 10 in Complete 4-domain Mayo score between 42 participants randomised to GSK2831781 at one of the three lower dose levels and 48 participants randomised to placebo at a 5% significance level.

Interim Analysis 3 (See Section 9.5)

The sample size for the Interim Analysis 3 is based on the change from baseline in the Complete 4-domain Mayo score. With 40 participants randomised to GSK2831781 450 mg and 20 randomised to placebo, assuming a placebo change from baseline of -1 and standard deviation of 1.5, there would be 90% power to detect a clinically meaningful difference of 2 points on the Complete 4-domain Mayo score between GSK2831781 and placebo at a 5% significance level.

Decision rules at Interim Analysis 3 and at primary completion are based on the proportion of participants who achieve endoscopic healing. At Interim Analysis 3, the predictive probability of success at the end of the study will be also calculated based on the endoscopic healing data observed at this interim analysis and the sample size was also evaluated through the assessment of operating characteristics of decision rules based on

this endpoint. The study would be stopped for futility if the probability of success was low. With this number of participants, assuming a placebo response of 20%, if there was no effect of GSK2831781 then there would be a >80% probability that the study would stop at this point.

The Bayesian decision criteria including the definition of end-of-study success are outlined in the DRC charter. Supportive frequentist analyses for pairwise treatment differences in change from baseline in the Complete 4-domain Mayo score will be provided.

9.2.2. Sample Size Re-estimation

At interim analyses 2, 3 and 4 (see Section 9.5) the sample size may be re-estimated based on emerging data. This will be based on the change from baseline in the continuous Mayo score. The sample size may need to be re-estimated if higher variability or differing placebo means are observed compared to those the study has been designed on. Therefore, any significant deviation from the assumptions used to power the study may result in changes to the study population including the number of participants to be randomized.

As part of this re-estimation if the distribution of the advanced therapy experience status (naïve or experienced) is unbalanced across the treatment groups then the recruitment strategy may be altered to establish a balance. A maximum of 320 participants could be randomized into the study following this sample size re-estimation.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF and were screened for eligibility.
Randomized	All participants who were randomly assigned to treatment in the study.
Safety	All randomized participants who receive at least 1 dose of study treatment.
PK	All participants in the Safety population who had at least 1 non-missing PK assessment (non-quantifiable values will be considered as non-missing values).
Intent to Treat Exposed (ITTE)	The ITTE population is defined as all participants who were randomised to treatment, who received at least one dose of study medication and who have at least one valid post dose assessment.

Population	Description
Per Protocol (PP)	The PP Population is defined as all participants who are included in the ITTE population and are not major protocol violators with regards to inclusion/exclusion criteria, investigational product compliance and concomitant medication instructions, as defined in the RAP. Participants to be excluded from the PP population will be identified prior to randomisation being unblinded or any data evaluation being performed.

9.4. Statistical Analyses

The Induction Phase and Extended Treatment Phase will be reported separately, where the primary and secondary analyses are based on the Weeks 0-10 of the Induction Phase.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary (efficacy)	• Bayesian dose-response analyses will be conducted for change from baseline in the Complete 4-domain Mayo score at Week 10. • The data will be initially analysed using an Emax model of the form: $Y = E0 + Emax * (Di)^{\gamma} / \{ ED50^{\gamma} + (Di)^{\gamma} \}$; where E0 is the minimum dose effect, Emax is the maximum achievable effect above placebo, ED50 is the dose at half Emax, Di are doses =0, 45, 150, 300, 450mg and γ is the slope parameter (shape of the potential sigmoid dose-response curve). Y is a measure of change from baseline in Mayo continuous score. • Initially, normal vague priors will be used for E0, γ and Emax: Normal(0, sd=100). A functional uniform prior will be used for ED50 and h (Bornkamp, 2014), where the prior density for the functional uniform prior is based on all the parameters in the model. The parameterisation of the priors used in the analysis will be reported in the clinical study report. • The primary dose-response model is the 4-parameter Emax model. Additional models will also be investigated: 3-parameter Emax model, power model, linear, quadratic, log-transformed dose. Each of the models will be fitted to the data and their fit compared using the Deviance Information Criterion (DIC). The model with the lowest DIC will be the primary model for inference if it shows a DIC difference from the 4-parameter Emax of at least 5. • A four parameter Emax dose-response model, once fitted, will be used to estimate the minimally effective dose and 95% credible interval of each dose level relative to placebo.

Endpoint	Statistical Analysis Methods
	• If the four parameter Emax model is not applicable then additional models will be investigated: three parameter Emax model, power model, linear, quadratic, log-transformed dose. Each of the models will be fitted to the data and their fit compared using the Deviance Information Criterion (DIC), where the model with the lowest DIC will be the primary model for inference. • Prior medication will be included as a stratification factor: advanced therapy naïve, experienced a single class of advanced therapy, or experienced multiple classes of advanced therapies. • Further details of the Emax model will be defined in the RAP. • The primary analysis will use the ITTE analysis population. • The primary estimand will use a treatment policy strategy for intercurrent events, with the exception of discontinuations due to COVID-19 pandemic which will use a hypothetical strategy. • Under the hypothetical strategy, data set to missing would be assumed to be missing at random (MAR).
Secondary	• Analyses of the secondary endpoints will be conducted using similar methodology as for the primary endpoint (with an appropriate link-function for binary endpoints). • The decision criteria at the interim analyses 3 and following completion of the primary analysis will primarily be based on the proportion of participants who achieve endoscopic healing. These are based on predictive probabilities based on the data available. Details are outlined in Section 9.5, and in the interim analysis charter and RAP.
Exploratory	• Will be described in the RAP.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary (safety)	• No formal statistical testing will be performed on safety data. • All safety evaluations will be based on the safety population. Clinical interpretation will be based upon review and displays of adverse events, laboratory values and vital signs. The principle consideration in this evaluation will be the Investigator-reported relationships of either adverse events or laboratory abnormalities to investigational product. • Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.4.3. Pharmacokinetic (PK) and Pharmacokinetic/Pharmacodynamic (PK/PD) analyses

All PK analyses (non-compartmental analysis and population PK analysis) will be performed on the PK population. All PK/PD analyses will be performed on the ITTE population.

Using standard non-compartmental analysis methods, the following PK parameters will be determined, as data permit, for each participant after SC dosing: Cmax, tmax and AUC(0-tau).

The population PK analysis and PK/PD analyses may be presented separately from the main clinical study report (CSR). The RAP will describe the planned analyses in greater detail.

9.4.4. Other Analyses

Pharmacodynamic and biomarker exploratory analyses will be described in the RAP.

9.5. Interim Analyses

In line with routine pharmacovigilance, an internal GSK SRT, which will include a subset of the 204869 study team, will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct.

At the interim analyses the data will be reviewed by the DRC. Further details of the DRC remit are provided in the DRC charter, and in Section 10.1.5. This charter outlines how the DRC will ensure data integrity and appropriate quality control of data prior to making decisions, as well as outlining membership of the DRC.

Up to four interim analyses may be conducted to assess the safety, pharmacokinetics and efficacy of GSK2831781 in this study. Recruitment will continue while the interim analyses are being conducted, except in the case of a safety concern. Interim analysis 3 incorporates a decision for futility.

Interim Analysis	**When**	**Objective**
1 (PK)	Approximately fifteen participants (across the highest dose and placebo) have completed their pharmacokinetic assessment at Week 2.	PK will be assessed to determine if the exposures in ulcerative colitis participants are similar to those predicted based on data observed in healthy volunteers and psoriasis patients.
2 (Early Efficacy) *Optional*	Up to a maximum of thirty-six participants (across the highest dose and placebo) have completed Week 10 assessments.	Assessment of the endoscopic mucosal healing response. Data will be reviewed by the DRC for internal decision making, where decision criteria are outlined in the DRC charter. An assessment of futility will not be made at this point. Additional data may be reviewed, including stool frequency and rectal bleeding.
3 (Efficacy futility)	Up to a maximum of sixty participants (across the highest dose and placebo) have completed Week 10 assessments.	Assess futility based on the proportion of participants who achieve endoscopic healing, based on the Mayo score. The predictive probability of success at the end of the study will be calculated based on the data observed at this interim analysis. The futility rule is outlined in the DRC charter and characteristics of which are included in the RAP. Additional data may be reviewed.

Interim Analysis	**When**	**Objective**
4 (Pharmacodynamic)	Approximately twenty participants per GSK2831781 dose level have completed Week 10 assessments.	Assessment of pharmacodynamic dose-response at Week 10. Data will be reviewed by the DRC for internal decision making, where decision criteria are outlined in the DRC charter. An assessment of futility will not be made at this point.

The DRC Charter and RAP will describe the planned interim analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 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 his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Safety Review Team (SRT)

In line with routine pharmacovigilance, an internal GSK SRT, which will include a limited number of 204869 study team members, will review blinded safety data, including clinical laboratory parameters and adverse events, at appropriate intervals during the period of study conduct. The SRT charter will outline the roles and responsibilities in more detail.

Data Review Committee (DRC)

A DRC will be utilised in this study to ensure objective medical and statistical review of safety and efficacy issues in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study via review of unblinded study data at interim analyses.

At the planned Interim Analyses unblinded study data will be reviewed by the DRC, and decisions made based on the criteria included in the DRC charter, which could include stopping the study for futility or altering the sample size based on sample size re-estimation, increasing up to the maximum of 320 participants.

The DRC will be composed of a limited number of people, who may be members of the 204869 study team, including the statistician, a senior safety representative, lead physician and where appropriate the pharmacokineticist. Detailed membership is outlined in the DRC charter. No members of the study team involved in the direct day to day conduct of the study or in the acquisition of data will take part in the DRC.

10.1.6. Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

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

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

The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan or contract.

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).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 15 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be

explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9. Study and Site Closure

GSK or its 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:

- 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 recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 7, will be performed by the central laboratory (Q2).

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.
- If an emergent result, condition or event warrants further investigation requiring tests not performed by the central laboratory (Q2).

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.

Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at intervals specified in the SoA (Section 1.3) during intervention. In the event of early study withdrawal, pregnancy testing (urine or serum) should be conducted at the end of the relevant systemic exposure plus an additional 30 days.

Table 7 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin

Laboratory Assessments	**Parameters**			
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein Albumin
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	C-Reactive Protein
Routine Urinalysis	• Specific gravity. • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. • Microscopic examination (if blood or protein is abnormal).			
Other Screening Tests	• Follicle-stimulating hormone and oestradiol (as needed in women of non-childbearing potential only). • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]. • Serology HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody, and hepatitis C virus antibody. • Serology CMV, EBV and VZV at baseline and in the event of possible viral reactivation.			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin), or ALT ≥3 × ULN and international normalized ratio (INR) >1.5 (if INR measured), which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Serum testing will be conducted for inclusion criteria. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC. A positive urine test will be confirmed by a serum test.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3. Appendix 3: Adverse Events: 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 <u>Meeting</u> 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 conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
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.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils 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.

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina.
- Congestive heart failure.
- Arrhythmias.
- Valvulopathy.
- Pulmonary hypertension.
- Cerebrovascular events/stroke and transient ischemic attack.
- Peripheral arterial thromboembolism.
- Deep venous thrombosis/pulmonary embolism.
- Revascularization.

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- 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 AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to GSK. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via eCRF Tool

- The primary mechanism for reporting SAE to GSK will be the eCRF.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The Investigator or medically-qualified sub-Investigator must show evidence within the eCRF (e.g. check review box, signature, etc.) of review and verification of the relationship of each SAE to GSK2831781/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the eCRF will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the eCRF has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF

- In rare circumstances and in the absence of email or 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 CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP

1. Premenarchal.
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.

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

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A blood sample with simultaneous follicle stimulating hormone and oestradiol falling into the central laboratory's postmenopausal reference range is confirmatory. In questionable cases for women <60 years of age.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance

HIGHLY EFFECTIVE CONTRACEPTIVE METHODS[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
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 *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use 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.

10.4.3. Collection of Pregnancy Information:

Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the Investigator, will be reported to GSK as described in Appendix 3. 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 will discontinue study intervention or be withdrawn from the study.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to GSK2831781 or IBD and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to GSK2831781, and/or IBD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analysed for epigenetic and T cell repertoire analysis. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK2831781 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2831781 (or study interventions of this class) or IBD continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

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

Phase II liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥3xULN and INR >1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention.
• Report the event to GSK within 24 hours.
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2].
• Perform liver chemistry event follow-up assessments.
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below).
• Do not restart/rechallenge participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted (see below).
• If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and continue</td><td>• Viral hepatitis serology[4].
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend.
• Obtain blood sample for pharmacokinetic (PK) analysis, as soon as possible, and at least within 7 days[5].
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin ≥2xULN.
• Obtain complete blood count with differential to assess eosinophilia.
• Record the appearance or worsening of clinical symptoms of liver injury, or</td></tr>
</table>

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

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin), or ALT ≥3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the threshold value stated will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; Hepatitis 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.
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study

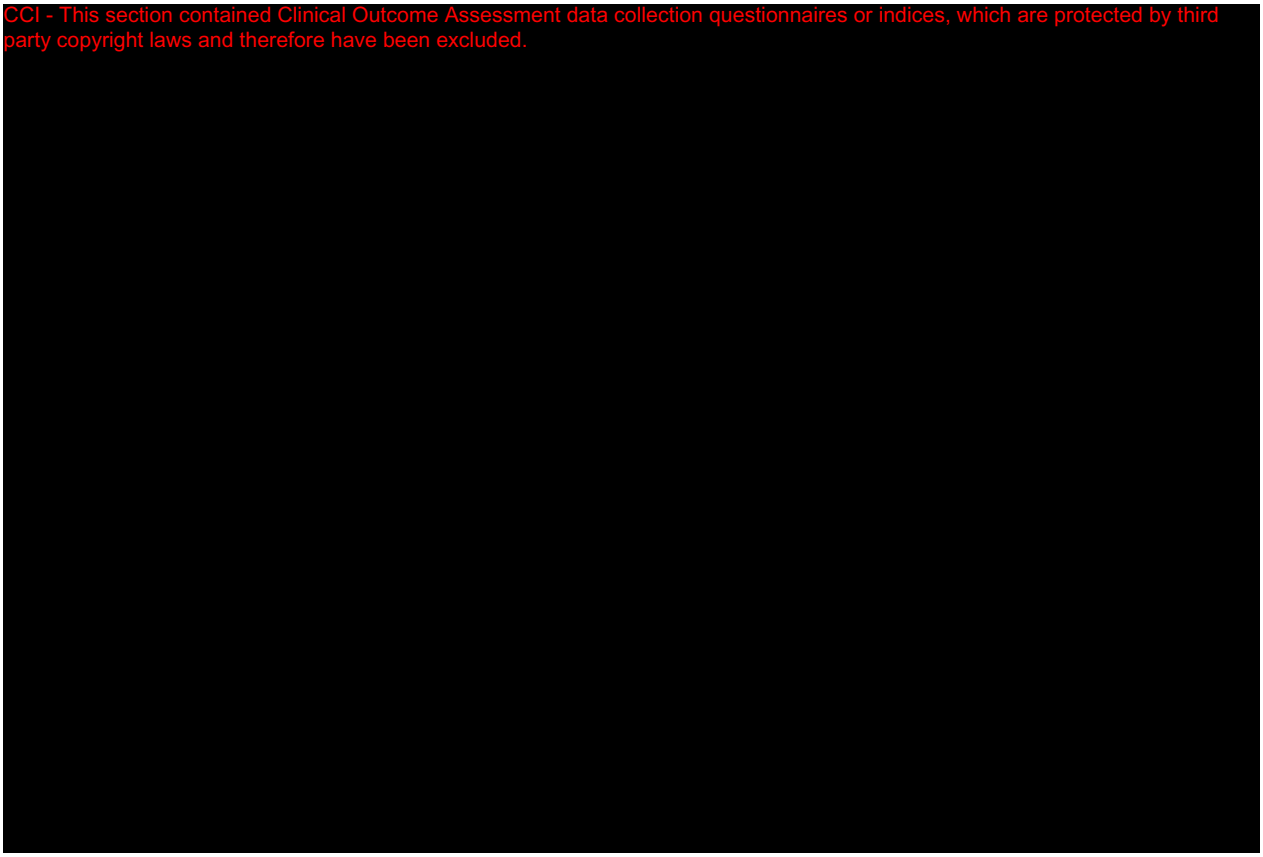
intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM. Not required for single-dose studies or equivalent.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, 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, bilirubin) until they resolve, stabilise or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

10.7. Appendix 7: Mayo Clinic Score Definitions

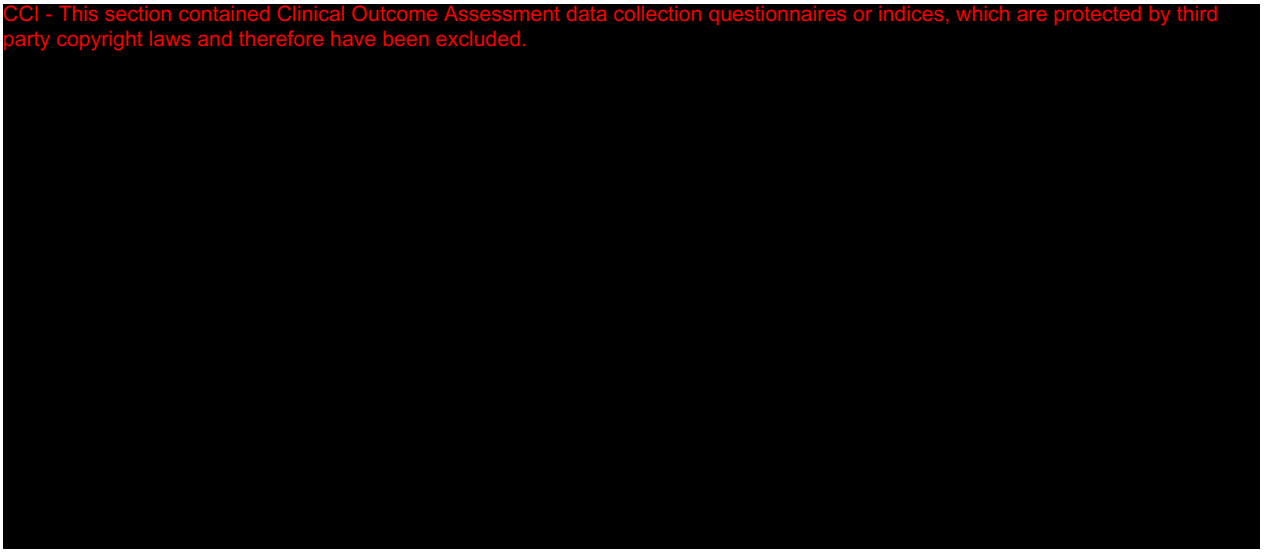
*Complete 4-domain Mayo Clinic Score (MCS)**



Clinical remission: Complete MCS ≤2, with no individual subscore >1.

Clinical response: Reduction in Complete MCS ≥3 points from baseline **AND** ≥30% from baseline **AND** decrease in the rectal bleeding subscore of ≥1 point from baseline (or a score of 0 or 1).

*Partial MCS**



CCI [redacted]

Clinical remission: Partial MCS ≤2, with no individual subscore >1.

Clinical response: Reduction in partial MCS ≥2 points from baseline **AND** ≥30% from baseline, **AND** a decrease in the rectal bleeding score of ≥ 1 point from baseline or a score of 0 or 1.

*Adapted 3-domain MCS**

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

[redacted]

Clinical remission: Adapted MCS of ≤2 with no individual subscore >1, a rectal bleeding subscore of 0, and stool frequency subscore ≤1 and not greater than baseline.

Clinical response: Reduction in adapted MCS ≥2 points from baseline **AND** ≥30% from baseline, **AND** a decrease in the rectal bleeding score of ≥ 1 point from baseline or a score of 0 or 1.

10.8. Appendix 8: Country-specific requirements

10.8.1. The Netherlands

Participants recruited from the Netherlands must fulfil the following inclusion criterion:

- Inadequate response to, loss of response to, or intolerance to at least one approved advanced therapy for UC, including anti-TNF therapies, anti-integrin therapies, anti-IL-12/23 monoclonal antibodies or JAK inhibitors.

10.9. Appendix 9: COVID-19

10.9.1. Overall Rationale for this Appendix

The COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or ancillary supplies, or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

10.9.2. Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit/risk when making enrollment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. However, where this is not possible, the following measures may be implemented for enrolled participants. Clinical Investigators should document in site files and in participant notes/Electronic Heath Records, as appropriate, how restrictions related to COVID-19 led to the changes in study conduct, the duration of those changes, and indicate which trial participants were impacted and how those trial participants were impacted (as per current local COVID-19 related regulatory guidance).

Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.9.3. Protocol Defined Procedures/Visits:

Where applicable country and local regulations and infrastructure for home healthcare allow, home nursing and telemedicine may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood, faeces and urine samples, measurement of vital signs and weight, and subcutaneous administration of study drug (at the discretion of the Investigator). It is the responsibility of the Investigator to inform GSK when this occurs and to document in source notes. For details on home healthcare approaches, please refer to Appendix 10.

The study Investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. In addition, home nurses may identify AEs as well and report them to the Investigator for evaluation.

10.9.4. Study Intervention(s)

- Staff at each clinical study center will be responsible for preparation of SC study intervention, according to procedures detailed in the Pharmacy Manual.
- The Principal Investigator assumes GCP responsibilities for IMP handling and the medical control for dispensing to patients. Site Staff should document the dispensing in the Dispensing/Accountability Logs adding a comment that this was a direct to patient (DTP) dispensing.
- For home healthcare, the home healthcare nurse assumes Good Clinical Practice (GCP) responsibilities for IMP handling from the point of dispensing to administration to patients.

10.9.5. Data Management/Monitoring:

If the eDiary device was provided to the participant, it must be returned to the site after the end of the relevant data collection period.

If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR), where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need (e.g., to assess participant safety or to ensure data integrity). In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.

Essential Document Sign-Off Process: If an Investigator is unable to print and sign essential documents such as a Protocol Amendment signature page then email approval can be accepted by replying to the relevant email that is sent by GSK or its delegate.

10.10. Appendix 10: Home Healthcare

The option for home healthcare, where applicable country and local regulations and infrastructure allow, may be permitted for the following visits (as per the SoA):

- All participants: Week 4.
- Additional SC PK analysis: All visits.
- Double-blind Responders: Weeks 18, 22 and 26.
- Open Label Responders: Weeks 30, 34, 38 and 42.
- All participants: Early Withdrawal, where endoscopy is not mandated or is refused.
- All participants: Follow-up.

Exceptions to the option for home healthcare include:

- All participants: Scheduled screening, IV dosing, first SC dosing and endoscopy visits.
- Anyone with any reaction (infusion reaction, hypersensitivity or CRS) following IV dosing of study treatment, irrespective of grade, during the Induction Phase (Double-Blind and Open Label).
- Anyone who, in the judgement of the Investigator, might have an issue accessing rapid emergency care should it be needed (including an anticipated time greater than 30 minutes transit to an emergency medical facility capable of managing a clinically significant hypersensitivity or anaphylactic reaction).
- Any other situation where the Investigator considers that dosing should be performed at the clinical site for participant safety.
- Any situation where the home nurse or participant may be put at risk of potential infection that cannot be adequately mitigated with available infection control precautions.
- The participant does not consent to home healthcare.

Home healthcare is defined as a remote visit that is performed at the participant's home by a nurse and an Investigator-led telemedicine call. The home nurse must have active certification for advanced cardiovascular life support as per local requirements, and at minimum within the preceding 4 years.

The participant must be informed of any potential risks associated with home healthcare and sign a revised Informed Consent Form, if required. IRB/Ethics committee should be informed and approve of this change in approach and the process documented in study files.

10.10.1. Home nursing

Activities that may be done as part of a home nurse visit must follow the schedule provided in the SoA (Section 1.3) and may include:

- Ensuring completion of PROs (IBDQ, FACIT-F, SF-36).
- Measurement of vital signs (BP, heart rate, body temperature) and weight.
- Facilitation of telemedicine call by PI or appropriately medically qualified designee.
- 12-lead ECG, using site-specific QT correction formula.
- Collection of all SoA mandated samples.
- Administration of study drug (subcutaneous delivery only, no infusions).
- Post-dose monitoring.
- Sending all collected samples to central labs.

10.10.2. Telemedicine

Telemedicine is defined as online (virtual) visits which will use a secure, video-enabled conference, web portal, or mobile application, as a way of communicating with and monitoring the participant's progress. Telemedicine visits are conducted by an Investigator or appropriately medically qualified designee, and should be undertaken in combination with visits from home nurses (see above).

Activities to be performed as part of a telemedicine visit must follow the schedule provided in the SoA (Section 1.3), and may include:

- Participant medical evaluation, and review of symptoms.
- Identification and reporting of concomitant medications.
- Daily eDiary review of compliance.
- Physician Global Assessment (PGA).
- EIM assessment.
- Identification, management, and reporting of AEs and SAEs.

Note: The Investigator or designee must ensure reporting of AEs and SAEs is completed in accordance with the protocol and applicable regulations, and that the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.

10.11. Appendix 11: References

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10.12. Appendix 12: Abbreviations and Trademarks

List of Abbreviations

ACLS	Advanced Cardiovascular Life Support
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AIC	Akaike's Information Criterion
ALT	Alanine transaminase
AUC	Area under the curve
BUN	Blood urea nitrogen
CMV	Cytomegalovirus
CRP	C-reactive protein
CYP	Cytochrome P450
DIC	Deviance Information Criterion
DoR	Delegation of Responsibilities
DME	Drug metabolizing enzyme
DRC	Data Review Committee
DTH	Delayed type hypersensitivity
DTP	Direct to Pharmacy
EBV	Epstein Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
EIM	Extra-intestinal manifestation
ePRO	Electronic Patient Reported Outcome
ETP	Extended treatment phase
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FSH	Follicle stimulating hormone
FTIH	First Time in Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HRQoL	Health-related quality of life
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
IEC	Independent Ethics Committee
ICE	Intercurrent Event
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IND	Investigational new drug
INR	International normalized ratio
IMP	Investigational medicinal product

IP	Induction phase
IRB	Institutional Review Boards
ITTE	Intent to Treat Exposed
IV	Intravenous
KLH	Keyhole limpet hemocyanin
LAG3	Lymphocyte activation gene-3
mAb	Monoclonal antibody
MAR	Missing at Random
MCH	Mean Corpuscular Haemoglobin
MCV	Mean corpuscular volume
MedRA	Medical Dictionary for Regulatory Activities Terminology
MHC	Major histocompatibility complex
mRNA	Messenger ribonucleic acid
NCE	New Chemical Entity
NIMP	Non-investigational medicinal product
NOAEL	No-observed-adverse-effect-level
OL	Open Label
OLETP	Open label extended treatment phase
OLIP	Open label induction phase
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically based pharmacokinetic
PD	Pharmacodynamic
PGA	Physician Global Assessment
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGx	Pharmacogenetic
PK	Pharmacokinetic
PRO	Patient-Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
RAP	Research Analysis Plan
RB	Rectal bleeding
SAE	Serious adverse event
SC	Subcutaneous
SDR	Source document review
SDV	Source data verification
SE	Standard error
SF	Stool frequency
SF-36	Short form health survey -36
sLAG3	Soluble lymphocyte activation gene-3
SoA	Schedule of activities
SRT	Safety Review Team
VZV	Varicella zoster virus
WOCBP	Women of child bearing potential
UC	Ulcerative colitis
UCEIS	Ulcerative colitis endoscopic index of severity
ULN	Upper limit of normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Chiron RIBA
SAS
WinNonlin

10.13. Appendix 13: Protocol Amendment History

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

10.13.1. Amendment 1: 17-JAN-2019

Overall Rationale for the Amendment:

- Changes requested by MHRA

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities	Footnote 6 of Double Blind Treatment SoA updated to include requirement for serum pregnancy test at screening.	Serum pregnancy testing to definitively exclude pregnancy at screening.
5.2 Exclusion Criteria	Added exclusion criteria regarding participants with hypersensitivity to GSK2831781 or any excipients in the clinical formulation of GSK2831781.	Hypersensitivity excluded as per the Investigator brochure.
5.2 Exclusion Criteria	Exclusion criteria renumbered.	Enable alignment of eCRF with amended protocol.
6.6 Concomitant medications	Additional section added to concomitant medications section to include potential for drug-drug interactions and clinical monitoring of co-administered narrow therapeutic index drugs metabolised by cytochrome P450.	Potential impact from removal of down-regulation of metabolising enzymes because of reduction in pro-inflammatory cytokines.
10.4.2 Appendix 4: Contraceptive Guidance	Removed reference to 'Acceptable Methods' of contraception from the table and updated footnotes.	Ensure alignment with need for highly effective contraception as set out in protocol and Investigator Brochure. Footnotes updated to reflect changes made to table and align no need for male contraception as highlighted in protocol Section 2.3.1.

10.13.2. Amendment 2: 10-SEP-2019

Overall Rationale for amendment:

- Exclusion criteria adapted to allow participants following inadequate response, loss of response, or intolerance to up to three classes of approved advanced therapies for ulcerative colitis
- Amalgamation of comments from regulatory authorities
- Incorporation of stratification for Japanese ethnicity, and
- Protocol clarifications and corrections.

Section # and Name	Description of Change	Brief Rationale
Title and Section 6.4.2, Blinding	Protocol updated to remove mention of 'Sponsor Open' (repeated throughout the protocol).	Amended for clarity. Although the Data Review Committee can view limited data for decision making, the study team and wider organisation are blinded to study data.
Section 1.1, Number of Participants	Evaluable subjects changed from 280 to 242 (repeated throughout the protocol). Alignment of Secondary Objectives in Synopsis with main protocol.	Modelling demonstrates that the overall participant number can be reduced without impacting study robustness. However, the maximum number remains unchanged to enable sample size re-estimation if required. Correction of typographical errors to ensure consistency.
Section 1.3, Schedule of Activities	Corrected Days in Open Label Treatment SoA to align with the weeks from: 85, 99, **113, 127, 141, 155, 169, 183, 197** and 379 To: 85, 99, 127, 155, 183, 211, 239, 267, 295 and 379	Days (but not study weeks) were incorrect in previous versions of protocol
Section 1.3, Schedule of Activities	EIM activity assessment moved from Screening Visit 1 to Day 1 pre-dose	Day 1 considered more appropriate baseline for the study
Section 1.3, Schedule of	Footnote added to allow extension of screening window up to 6 weeks (although key safety and efficacy	Provides sites time to undertake retesting where indeterminate test results are returned for assays

Section # and Name	Description of Change	Brief Rationale
Activities	assessments must still be conducted within the previously specified time windows).	requiring long central laboratory turnaround times.
Section 1.3, Schedule of Activities	Steroid Taper included in Double-Blind Treatment and Open Label Treatment SoA at Week 12.	Provide greater clarity on mandatory steroid taper start date.
Section 2.3.1, Risk Assessment: Drug-drug interactions	Potential for indirect drug-drug interactions through releasing suppression of CYPs by ameliorating systemic cytokine response highlighted	Highlight theoretical risk to Investigators and advice to monitor patients receiving medicines with narrow therapeutic indices for evidence of changes in exposure.
Section 2.3.1, Risk Assessment: Reproductive toxicity	WOCBP who are partners of male subjects in the study will not be required to be protected from seminal fluid exposure or need to use a condom plus highly effective method of contraception**. Any pregnancy data however will be collected** Changed to: WOCBP who are partners of male subjects in the study will not be required to be protected from seminal fluid exposure or need to use a condom plus highly effective method of contraception.	Preclinical studies show no impact on testes and spermatogenesis and drug levels in semen will be at such low concentrations to be biologically meaningless.
Section 3, Objectives and Endpoints: Primary Endpoint (safety)	Primary endpoint limited to findings up to Week 10 Safety and tolerability with Sub Cutaneous administration during the Double-Blind Extended Treatment Phase moved to key secondary endpoint. Remaining safety findings including from open label treatment moved to separate safety objective	Align primary safety endpoint with timing of primary efficacy endpoint, to enable full reporting of safety findings at the time of primary analysis Enable reporting of safety findings by study phase.

Section # and Name	Description of Change	Brief Rationale
Section 3, Objectives and Endpoints: Primary Endpoint (efficacy)	Clarified that dose-response will be conducted on the **Complete** Mayo score	Complete (12-point) Mayo score has wider dynamic range for the assessment of dose-response than the Adapted (9-point) Mayo score.
Section 3, Objectives and Endpoints: Secondary Endpoints	Clarified analyses of key efficacy endpoints will be performed on the Adapted Mayo Score. Added endpoint of symptomatic remission (RB subscore=0, SF subscore ≤1, with no worsening from baseline).	Use of Adapted Mayo Score inline with FDA and EMA guidance on exclusion of PGA and presence of friability on endoscopy inconsistent with remission and mucosal healing. Symptomatic remission now recognised as important endpoint in recent trials.
Section 5.1, Inclusion criteria	Inclusion criteria for corticosteroids extended to also include patients who have loss of response to steroid therapy	Represents a subpopulation of patients with limited options for disease management of exacerbations of UC.
Section 5.1 and 5.2, Inclusion and Exclusion criteria	**Inclusion criteria changed from**: Inadequate response to, loss of response to, or intolerance to one biologic class ONLY for the treatment of UC: either one or more anti-TNF therapies (e.g. infliximab, adalimumab, golimumab, or biosimilar) OR vedolizumab **To**: • Inadequate response to, loss of response to, or intolerance to at least one approved advanced therapy for UC, including anti-TNF therapies (e.g. infliximab, adalimumab, golimumab, or biosimilar), anti-integrin therapies, anti-IL-12/23 monoclonal antibodies or JAK inhibitors. **Exclusion criteria changed from**: A history of treatment with	Inclusion/exclusion criteria changed to allow inclusion of participants having primary non response to two advanced therapies for treatment of UC. Clarified exclusion windows for anti-integrin therapies, anti-IL-12/23 and JAK inhibitor therapies. Exclusion window provide for faecal microbiota transplantation based on timing to microbial homeostasis in scientific investigations in humans. Clarified exclusion windows for clinical study experience for biologics and NCEs to reflect the different half-lives of these classes of therapies, but with provision for longer extensions in those with protracted pharmacodynamic effect. Timing of restriction also moved from Day 1 to screening endoscopy, as latter provides key baseline efficacy assessments.

Section # and Name	Description of Change	Brief Rationale
	vedolizumab AND an anti-TNF biologic, regardless of treatment response (unless exposure to one or both drugs was only within a clinical trial setting). To: 18. A history of inadequate response, loss of response, or intolerance to more than three classes of approved advanced therapies for UC (including; anti-TNF therapies, anti-integrin therapies, anti-IL-12/23 monoclonal antibodies, or JAK inhibitors; but excluding exposure within a clinical trial setting), but with primary non-response to more than two classes Updated exclusion criteria regarding biologics and JAK inhibitors to: 17. Treatment with an anti-TNF biologic within 8 weeks prior to baseline endoscopy, **or anti-integrin or anti-IL-12/23 biologics within 12 weeks** prior to baseline endoscopy, **or a JAK inhibitor within 4 weeks prior to baseline endoscopy**. 19. Received faecal microbiota transplantation within 4 weeks prior to baseline endoscopy. Clarified exclusion criterion 21 for prior/concurrent clinical trial experience to: a) Biologics: 3 months, 5 half-lives, or twice the duration of the biological effect of the investigational product (whichever is longer); b) New Chemical Entities (NCEs): 30 days, 5 half-lives or twice the duration of the biological effect	Changes also reflected in the concomitant medication tables.

Section # and Name	Description of Change	Brief Rationale
	(whichever is longer).	
Section 6.1 Study Intervention(s) Administration	Dose formulation concentration of Methionine changed from 80 to 8 mM.	Incorrect Methionine concentration in previous protocol version.
Section 6.4.1 Method of Treatment Assignment	Stratification criteria changed to include Japanese ethnicity as first strata followed by advanced treatment experience status.	Align stratification with inclusion of Japan in global study and updated exclusion criteria (biological experience status).
Section 6.6.2, Prohibited Concomitant Medications	Added the following concomitant medications: Intravenous corticosteroids Rituximab Leukocyte apheresis Faecal microbiota transplantation Amended Tofacitinib wash out period from 2 to 4 weeks Clarified prohibition windows for other biologic or small molecule therapies for UC.	IV steroids are prohibited within 2 weeks prior to baseline endoscopy, and requirement for IV steroid for treatment of UC following randomisation would be a rescue/salvage therapy. Leukocyte apheresis is prohibited within 4 weeks prior to baseline endoscopy. Faecal microbiota transplantation is prohibited within 4 weeks prior to baseline endoscopy. Extended washout period ensures no lasting PD effects from Tofacitinib for participants joining the study. Aligned exclusion windows for other biologic or small molecule therapies with exclusion criterion 21.
Section 8.2.1.1, Mayo Score	Definitions of the Complete, Adapted and Partial Mayo scores updated. Information regarding scoring of rectal bleeding and stool frequency domains changed from: The patient reported outcomes of Stool Frequency and Rectal Bleeding for Mayo scores will be calculated by the physician based on three consecutive days within the last week, but which should not include	Typographical errors fixed Scores are determined centrally in the eCRF following site input of participants daily scores from their eDiary.

Section # and Name	Description of Change	Brief Rationale
	days in which bowel preparations are administered. To: The patient reported outcomes of Stool Frequency and Rectal Bleeding for Mayo scores will be calculated from participant eDiary data, ideally based on three consecutive days within the last week (see SRM for full details). These should not include days in which bowel preparations are administered.	
Section 8.2.4.2.2, Short Form-36	Changed text: The measure uses a recall period of four weeks. To: The measure uses a recall period of **one week**.	Recall period incorrect.
Section 9.2.1, Sample Size Assumptions AND Section 9.5, Interim Analyses	Interim Analysis 5 removed and primary endpoint added. Assumptions changed to support the new 242 evaluable subjects target for recruitment. Deleted Interim Analysis 5 from the Interim Analysis Table.	Interim Analysis 5 now correctly named primary analysis. Assumptions aligned to reduced evaluable participant requirements of the study. Interim Analyses aligned with change of IA5 to primary endpoint.
Appendix 7, Mayo Clinical Score Definitions	Corrected language for rectal bleeding subscore to align with original MCS. Also changed Adapted MCS clinical response definition from: Adapted MCS ≤2, with no individual	Correction of language to align with eDiaries, which are primary source for this variable. Adapted MCS response definition updated to align with published clinical

Section # and Name	Description of Change	Brief Rationale
	subscore >1. To: Adapted MCS of ≤2 with no individual subscore > 1 and a rectal bleeding sub score of 0, and stool frequency subscore ≤1 and not greater than baseline	studies.
Appendix 8	Addition of country-specific requirement for the Netherlands.	Clarification based on current treatment pathways in the Netherlands.

10.13.3. Amendment 3: 03-SEP-2020

Overall Rationale for the Amendment:

- Provision for home healthcare (home nursing and telemedicine) approaches for selected study visits where applicable country and local regulations and infrastructure allow.
- Clarification of COVID-19 specific measures.
- Correction of protocol inconsistencies and clarification of study procedures and objectives, including the time frame of the collection of safety data in the induction period (primary endpoint).
- Estimands have been introduced following best practice and the term 'evaluable' has been removed for consistency. The study retains the principle that if more participants (of those required for the hypothetical estimand) drop out than has been planned for, then additional participants may be recruited.
- The primary analysis will now fit the originally planned dose-response model using a Bayesian framework with non-informative priors. This allows consistency in estimation across endpoints, including when data are missing, but does not change the sample size required.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Objectives and endpoints table and overall design updated. Remove the term 'evaluable' instead link attrition rate to participants not reaching and completing an adequate Week 10 assessment).	Clarification of study phases and endpoints. Remove the term 'evaluable' for consistency with estimands but retain principle that if more participants drop out than planned for, then additional participants may be recruited.
Section 1.2 Schema	Clarify that responder status is determined by a pre-specified algorithm in the electronic case report form (ECRF).	Clarify mechanism of defining responder status.
Section 1. 3 SoA	Added text related to home healthcare and clarified timing of events.	Allow home healthcare approaches during study conduct, and clarification of timings of activities.
Section 2.3.1 Risk Assessment	Amended cytokine release syndrome, neutropaenia, infection, hypersensitivity, infusion, local site reactions, immunogenicity and autoimmune-like reactions text based upon additional clinical study data. Also added mitigation strategies for home healthcare SC dosing.	Updated risks and mitigations based upon completed Phase I studies experience and implementation of home healthcare during study conduct.

Section # and Name	Description of Change	Brief Rationale
Section 3.	Objectives and endpoints table updated with respect to study phases and to extend time frame for collection of safety data in double blind induction. Addition of exploratory endpoint of extraintestinal manifestations. Addition of estimands for primary and key secondary efficacy endpoints.	Clarification of Objectives and Endpoints. Safety data will be reported against double blind induction until the first dose of the next study phase. Addition of extraintestinal manifestation endpoints. Addition of estimands to protocol following best practice.
Section 4.1.1 Double-Blind Treatment	Treatment phase and timing of randomisation updated.	Clarification for Investigators.
Section 4.1.2 Open Label Treatment for Non Responders	Additional text added to clarify eCRF calculation of responder status and Responder patient journey.	Clarification for Investigators.
Section 4.3.3 Open Label Treatment	Text updated to ensure non-responders proceed to Follow-Up visit 16 weeks post last dose.	Clarification for Investigators.
Section 5.1 Inclusion Criteria	*NUDT15* mutation added to precluding genetic mutations for thiopurines.	Mutation prevalence in Japan.
Section 6.2 Intervention administration	Reduced post SC dose monitoring period for first SC dose only.	Updated to reflect latest clinical experience and safety information.
Section 6.4 Method of Treatment Assignment	Timing of randomisation updated, including pre-requisites.	Clarification for Investigators.
Section 7.1.6 Temporary withholding of IP	Reasons for temporary withholding IP updated.	Clarification for Investigators.
Section 7.2 Participant discontinuation/Withdrawal from the study	Section updated to clarify that all participants withdrawn from study will complete the current study phase and follow-up visit approximately 16 weeks after last dose, and not the entire study.	Clarification for Investigators.
Section 8 Study Assessments & Procedures	Added text to highlight signed consent required and reference home healthcare and telemedicine approaches.	Implementation of healthcare approaches during study conduct.
Section 8.2.1.1 Mayo Score	Added text relating to capture of stool frequency and rectal bleeding for eCRF calculation during the study.	Clarification for Investigators to ensure correct days are chosen from diary for calculation of Mayo scores.
Section 8.3	Added text related to PK being	Clarification and

Section # and Name	Description of Change	Brief Rationale
Pharmacokinetics	undertaken on subset of participants and home healthcare and telemedicine approaches.	implementation of healthcare approaches during study conduct.
Section 8.6.1 Physical Examinations	Added text related to home healthcare and telemedicine approaches.	Implementation of healthcare approaches during study conduct.
Section 8.6.2 Vital signs	Added text indicating vital signs to be performed prior to blood collection.	Clarification for Investigators.
Section 9.1 Statistical Hypotheses	Specify that the primary dose-response analysis will be Bayesian.	A Bayesian implementation of the original planned Emax model will provide consistency of estimation and handling of missing data across endpoints in the study.
9.2.1 Sample size assumptions	Sample size section adjusted to reflect the Bayesian sample size assessment and assumptions. Section re-ordered to add clarity. Remove the term 'evaluable'. Instead, link attrition rate to participants not reaching and completing an adequate Week 10 assessment).	See justification for Section 9.1. No change has been made to the sample size of this study. Remove the term 'evaluable' for consistency with estimands but retain principle that if more participants drop out than planned for, then additional participants may be recruited.
9.3 Populations for Analyses	Intention to Treat population renamed to Intention to Treat Exposed (ITTE). Consolidation of 'Enrolled' and 'Screened' populations.	Renaming of Intention to Treat Exposed more precisely reflects the analysis population. Consolidation of populations removes effective duplication.
9.4.1 Efficacy analyses	Adjust specification of the primary dose-response analysis and details of model fitting to reflect the change to Bayesian. Added summary of estimation for inter current events for primary estimand.	See justification for Section 9.1.
Appendix 9 COVID-19	Added Appendix, including text to clarify: • Procedures including reporting COVID impact. • Home healthcare availability. • Data management.	Clarification of measures that may be applicable for any site impacted by the COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
Appendix 10 Home Healthcare & Telemedicine	Added Appendix to allow home healthcare and telemedicine, including exceptions and exclusions.	Implementation of healthcare approaches during study conduct.