Reporting and Analysis Plan

Study ID: 204869

Official Title of Study: Reporting and Analysis Plan for: 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

Date of Document: 02-JUN-2021

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for: 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
Compound Number	:	GSK2831781
Effective Date	:	Refer to Document Date

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204869.

RAP Author(s):

Author	Date
Lead: PPD Statistician (Biostatistics)	27-MAY-2021
Co-Author: PPD Lead Programmer (Biostatistics)	26-MAY-2021
Co-Author: PPD PPD Clinical Pharmacology (CPMS)	26-MAY-2021
Co-Author: PPD Manager Quantitative Clinical Pharmacology (CPMS)	26-MAY-2021

RAP Team Review Confirmations

(Method: E-mail)

Reviewer	Date
PPD Clinical Development Lead (Clinical Sciences)	25-MAY-2021
PPD SERM PPD (SMG Pharma Safety)	26-MAY-2021
PPD Clinical Science Lead (Clinical Sciences)	27-MAY-2021
PPD Clinical Development PPD (Clinical Sciences IBD)	25-MAY-2021
PPD Clinical Biomarker Lead (CPEM)	21-MAY-2021
PPD Manager, Clinical Data Management (GCDO DM)	26-MAY-2021

Clinical Statistics and Clinical Programming Approvals:

(Method: approval in the TMF system)

Approver
PPD PPD (Biostatistics)
PPD Hep/GI Clinical Programming PPD (Biostatistics)

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology of protocol 204869:		
2017N337668_00	15-OCT-2018	Original
2017N337668_01	17-JAN-2019	Amendment 1
2017N337668_02	10-SEP-2019	Amendment 2
2017N337668_03	03-SEP-2020	Amendment 3
TMF-2197350	12-NOV-2020	Amendment 4

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The following changes have been made to the originally planned statistical analysis specified in the 204869 protocol (amendment 4, dated 12-NOV-2020). The majority of the changes are due to GSK's decision to terminate study 204869 on 14-JAN-2021.

2.1.1. Changes to Analysis Populations

The analysis populations defined in the protocol relate to the induction phase and additional analysis populations have been introduced to account for reporting in the other phases of the trial.

Per Protocol populations in Double Blind Induction and Double Blind Extended Treatment phases have been removed to simplify the reporting of efficacy.

2.1.2. Changes to Interim and Final Analyses

Interim Analysis 2 (IA2), Interim Analysis 4 (IA4) and Primary Completion (PC) are documented in the protocol, but no outputs or reporting are planned due to the study team's decisions not to conduct IA2 and the termination of the study prior to IA4 and PC.

2.1.3. Changes to Endpoints and Definitions

2.1.3.1. Efficacy

Exploratory efficacy endpoints (excluding Serum C-Reactive Protein and Faecal Calprotectin) are documented in the protocol, but their analysis is not covered in this RAP due to the termination of the study.

2.1.3.2. Biomarkers

The following biomarker endpoints are documented in the protocol, but their analysis is not covered in this RAP and may be conducted using other analysis plans:

- Proteomic profiles

- Transcriptomic profiles, including but not limited to LAG3
- Composition of immune cell populations, including but not limited to $CD3^+$ cells by epigenetic counting or T cell receptor sequencing

The following biomarker endpoints are documented in the protocol, but their analysis is not covered in this RAP due to the termination of the study:

- 4β-hydroxycholesterol:cholesterol ratio
- Serum tryptase

Additionally, this RAP covers LAG3+ T Cells in Blood and Cell Counts in Colon reporting only in the Double Blind Induction phase because of projected lack of patients randomised to other treatment arms following study termination.

2.1.3.3. Patient Reported Outcomes

Exploratory Patient Reported Outcome (PRO) endpoints are documented in the protocol, but their analysis is not covered in this RAP due to the termination of the study.

2.1.4. Changes to Efficacy Estimands and Statistical Analyses

The "Hypothetical" additional estimand for Complete Mayo Score has been removed to simplify the reporting of efficacy.

The primary estimand (Complete Mayo Score) and key secondary estimand (Endoscopic Improvement) have been modified to account for "discontinuation due to sponsor's decision to terminate the study" intercurrent event.

New estimands are defined for secondary continuous and categorical efficacy endpoints. The populations and intercurrent event strategies for these estimand are the same as the Primary estimand for Complete Mayo Score (in the case of secondary continuous endpoints) or Key secondary estimand for Endoscopic Improvement (in the case of secondary categorical endpoints).

The primary dose response model for Complete Mayo Score has been modified to only analyse the 450mg IV and Placebo IV arms due to projected lack of patients randomised to other treatment arms following study termination.

2.2. Study 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.
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. 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

Objectives	Endpoints
	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 Score 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.
• 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.

Objectives	Endpoints
	• 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). • 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.

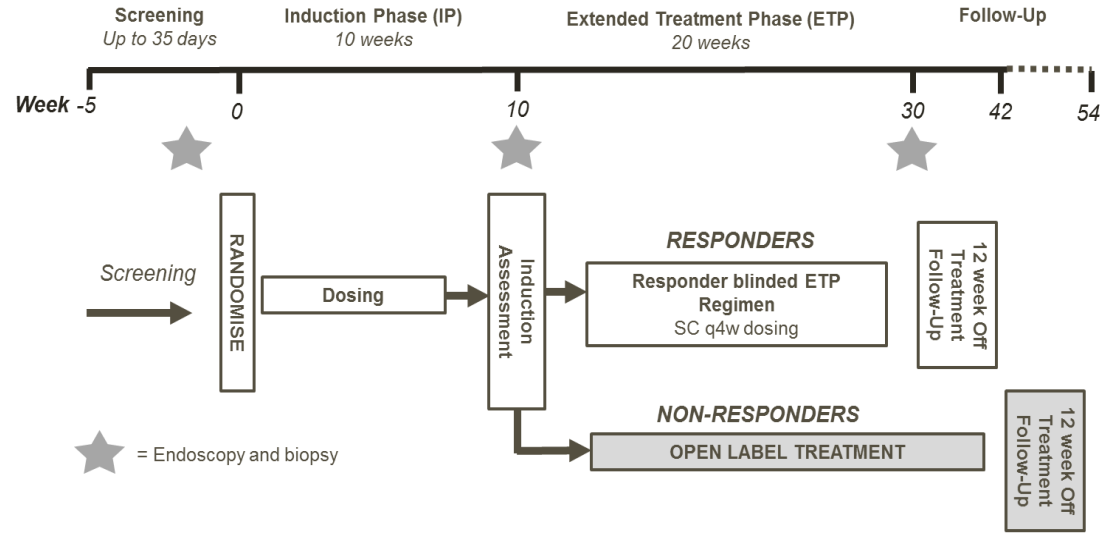
Objectives	Endpoints
	○ Composition of immune cell populations, including but not limited to $CD3^+$ cells by epigenetic counting or T cell receptor sequencing. ○ Transcriptomic profiles, including but not limited to LAG3. • Change from baseline in blood biomarkers, which may include but not be limited to: ○ Number of $LAG3^+$ cells at Week 10 and Week 30. ○ 4β-hydroxycholesterol:cholesterol ratio. ○ Serum tryptase. ○ 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 subcutaneous dosing in all Treatment Phases.	• GSK2831781 PK concentrations.
• 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

Objectives	Endpoints
	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:

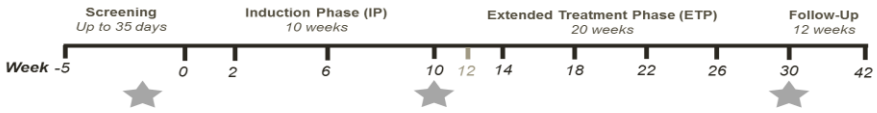
1 Potential clinical importance is defined in Section 15.8 for each relevant safety endpoint.
2 The Complete 4-domain Mayo score is used for the primary endpoint due to its wider dynamic range for assessment of dose-response compared to the Adapted Mayo score used for secondary and exploratory endpoints.
3 Clinical response and remission for the various iterations of Mayo score are defined in Appendix 7, Section 15.7.
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.

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Phase 2, multicentre, randomized, double-blind parallel, placebo-controlled • Double-blind Induction Phase up to 10 Weeks for all participants • At Week 10, all participants undergo an Induction Assessment, including centrally read endoscopy. Responder status is identified by the results of the assessment of clinical response calculated by the eCRF and determines the participant's subsequent path through the study. **Week 10 Responders** • Participants identified as Responders who received GSK2831781 during the Induction phase will then receive 300mg GSK2831781 subcutaneously (SC) every four weeks during the double-blind Extended Treatment Phase (ETP), from Week 14 until Week 26. • Week 10 Responders in the placebo group during the Induction phase will continue to receive placebo SC every four weeks in the double-blind ETP. • At Week 30, all participants in the Responder ETP will undergo an Assessment, including a centrally read endoscopy. Subsequently, all participants will remain in study, but off treatment, to Week 42 in the 12-week Follow-Up phase.

Overview of Study Design and Key Features

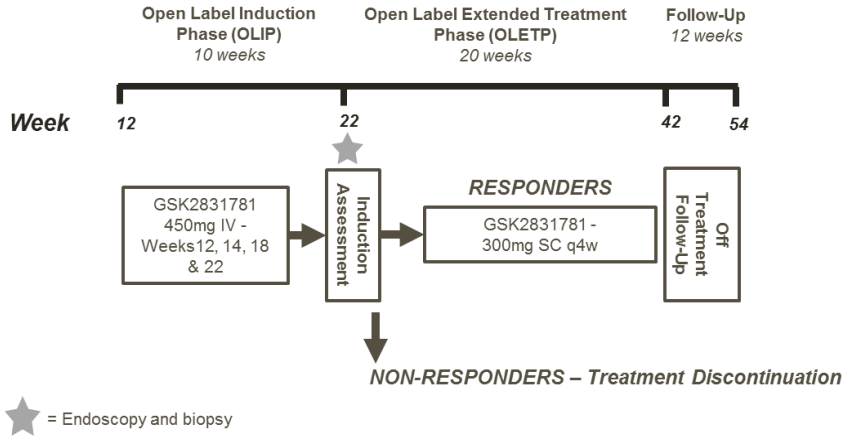
Extended Treatment Phase – Dosing regimen for Responders only



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

Open Label Treatment – Dosing Regimen for Non-Responders



= Endoscopy and biopsy

Week 10 Non-Responders

- Participants identified as Non-Responders at Week 10 will be assigned to open label treatment in the Open Label Induction Phase. 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. 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 in the Open Label part who respond at Week 22 will then receive 300mg GSK2831781 subcutaneously (SC) every four weeks during the Open Label Extended Treatment Phase (ETP), from Week 26 until Week 38.
- Subsequently, all Open Label participants will remain in study, but off treatment, to Week 54 in the 12-week Open Label Follow-Up phase.

Overview of Study Design and Key Features	
Dosing	**INDUCTION Phase:** • GSK2831781 450 mg IV • GSK2831781 300 mg IV • GSK2831781 150mg IV • GSK2831781 45mg IV • Placebo IV **EXTENDED Treatment Phase for RESPONDERS** • GSK2831781 300 mg SC • Placebo SC **OPEN LABEL Treatment Phase for NON-RESPONDERS** • GSK2831781 450 mg IV – weeks 12, 14, 18 and 22 • GSK2831781 300 mg SC for Open Label Responders (assessed at week 22) • Treatment discontinuation for Open Label Non-Responders (assessed at week 22)
Time & Events	• Refer to Appendix 2: Schedule of Activities (SoA)
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 participants CRF number (Participant number) and provide the randomisation number. The randomization is centrally controlled by RAMOS NG. Once the randomization number is assigned, it cannot be reassigned to another participant in the study. • At the start of the study, participants will be randomised in a 2:1 ratio to GSK2831781 450mg and Placebo. • When an appropriate number of participants have been randomised in these two arms for the interim analysis (Interim Analysis 3, see below), randomisation to all dose regimens (GSK2831781 450mg, 300mg 150mg, 45mg or placebo) will be opened in the ratio 2:3:3:3:2. • The randomisation will be stratified according to: 1. Country (Japan or not Japan); if not Japan further stratification by: 2. Prior advanced therapy experience (advanced therapy naïve, experienced a single class of advanced therapy, or experienced multiple classes of advanced therapies). • There is no re-randomisation for the ETP – if the participant is a placebo responder then the participant will stay on blinded placebo • At least 242 evaluable participants who complete all Week 10 assessments or withdraw will be recruited. The study size will not exceed 320 participants.
Interim Analysis	Up to 4 interim analysis will be conducted to assess the safety, pharmacokinetics, pharmacodynamics and efficacy of GSK2831781. Recruitment will continue while the interim analyses are being conducted, except in the case of a safety concern. • Interim Analysis 1 – PK • Interim Analysis 2 – Early Efficacy • Interim Analysis 3 – Efficacy futility

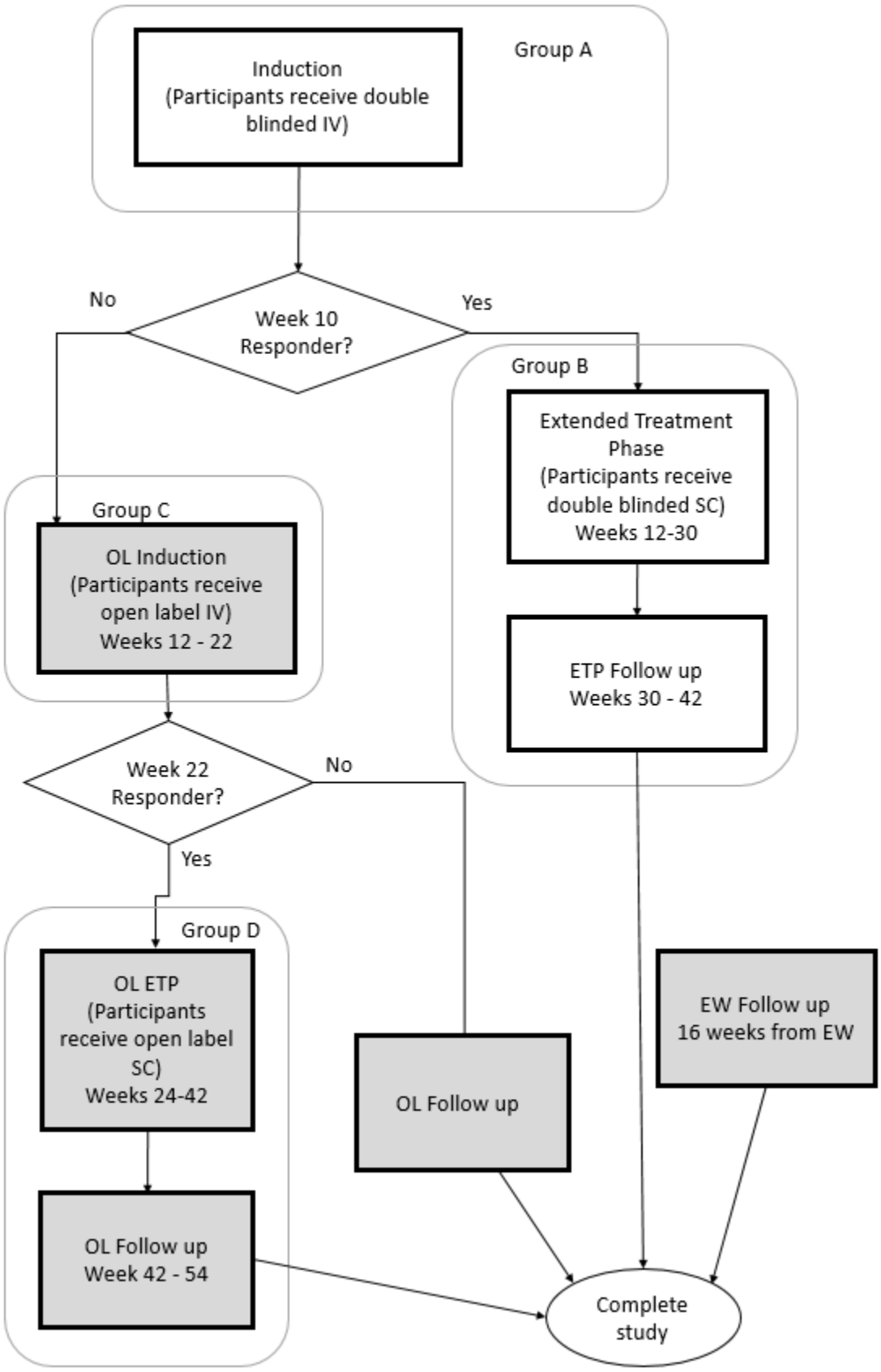
Overview of Study Design and Key Features	
	• Interim Analysis 4 – Pharmacodynamic Blinded safety data, including clinical laboratory parameters and adverse events will be reviewed at appropriate intervals during the study conduct by an internal GSK SRT team according to routine pharmacovigilance practice. At the interim analyses, the data will be reviewed by the Data Review Committee (DRC) to ensure objective medical and statistical review of safety and efficacy issues to protect the ethical and safety interests of participants and to protect the scientific validity of the study via review of unblinded study data.

Figure 1 below shows the paths that a participant can take through the study. White rectangles are double blinded phases, grey rectangles are unblinded (open label or off drug phases). Note that at any point participants can discontinue from study drug but continue in the study until the end of the study phase.

- Group A: Induction Phase
- Group B: Extended Treatment Phase (Week 10 Responders)
- Group C: Open Label Induction (Week 10 Non-Responders)
- Group D: Open Label ETP (Week 22 Responders)
- Week 22 Non-responders will complete a follow-up visit and withdraw from the study.

The strategy for reporting study phases is to use analysis populations to define the participants for each phase. Post-Week 22 data for Week 22 Non-responders will be listed, not summarised.

Figure 1 Participant Flow



2.4. Statistical Hypotheses / Statistical Analyses

The study has two primary objectives.

No formal hypothesis will be tested for the first, primary objective that assesses the safety and tolerability of GSK2831781 in participants.

The second primary study objective is to evaluate the dose-response relationship in the change from baseline in Complete Mayo score, following 10 weeks of treatment with GSK2831781 or placebo.

Due to the low number of participants in the 3 middle doses, this will be done by estimating the posterior probabilities of the difference between GSK2831781 450 mg IV and placebo, using Bayesian methodologies (Section 8.1.1 Primary Endpoint).

3. PLANNED 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. See the SRT charter for further details, including the team members of the SRT.

3.1. Interim Analyses

At the interim analyses, the data will be reviewed by the DRC (Data Review Committee). Further details of the DRC remit are provided in the DRC charter which outlines how the DRC will ensure data integrity and appropriate quality control of data prior to making decisions, as well as documenting membership of the DRC.

The following interim analyses are planned 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. Note: not all interim analyses may be conducted.

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)	Approximately 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)	Approximately sixty participants (across the highest dose and placebo) have	Assess futility based on the proportion of participants who

Interim Analysis	When	Objective
	completed Week 10 assessments.	achieve endoscopic mucosal 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. Unblinded safety data will be reviewed. Additional data may be reviewed.
4 (Pharmacodynamic)	A minimum of approximately twenty participants per GSK2831781 dose level have completed Week 10 assessments	Assessment of pharmacodynamic dose-response at Week 10. Data may 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. Unblinded safety data will be reviewed.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

- All participants have completed the study as defined in the protocol
- All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
- All criteria for unblinding the randomization codes have been met.
- Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

The strategy for reporting study phases is to use analysis populations to define the participants for each study phase.

4.1. Populations for the Induction Phase

The following analysis populations apply to the double-blind induction phase of the study.

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility this includes screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study as well as enrolled participants.	• Study Population
Enrolled	• All participants who were randomly assigned to treatment in the study. • This population will be based on the treatment the participant was randomised to. • Any participants who receive a treatment randomisation number will be considered to have been randomised	• Study Population
Safety	• All participants who received at least one dose of study treatment. • Participants who were not randomized but received at least one dose of study treatment will be listed. • This population will be based on the treatment the participant actually received. •	• Safety
Intent-To-Treat-Exposed (ITTE)	• All enrolled participants who received at least one dose of study treatment, and who have at least one valid post dose assessment. • This population will be based on the treatment the participant was randomised to.	• Efficacy • PD • Biomarker • PRO
Pharmacokinetic (PK)	• All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK

4.2. Populations for the Extended Treatment Phase

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat-Exposed ETP (ITTE_ETP)	• All participants who received at least one dose of study treatment in the ETP (e.g. placebo or 300mg SC). • This population will be based on the treatment that the participant was randomised to.	• Study Population • Efficacy • PD • Biomarker • PRO

Population	Definition / Criteria	Analyses Evaluated
Safety ETP	• All participants who received at least one dose of study treatment in the ETP (e.g. placebo or 300mg SC). • This population will be based on the treatment the participant actually received.	• Safety
Pharmacokinetic ETP (PK_ETP)	All participants in the Safety ETP population who had at least 1 non-missing PK assessment in the ETP phase (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK

4.3. Populations for the Open Label Induction Phase

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat-Exposed OL_I (ITTE_OL_I)	• All participants who received at least one dose of study treatment in the Open Label Induction Phase. • This population will be based on the treatment that the participant was allocated to.	• Study Population • Efficacy • PD • Biomarker • PRO
Safety OL_I	• All participants who received at least one dose of study treatment in the Open Label Induction phase. • This population will be based on the treatment the participant actually received.	• Safety
Pharmacokinetic (PK_OL)	• All participants in the Safety_OL_I population who had at least 1 non-missing PK assessment in Open Label Induction phase (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK

4.4. Populations for the Open Label Extended Treatment Phase

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat-Exposed OL_ETP (ITTE_OL_ETP)	• All participants who received at least one dose of study treatment in the OL ETP • This population will be based on the treatment that the participant was allocated to.	• Study Population • Efficacy • PD • Biomarker • PRO
Safety OL_ETP	• All participants who received at least one dose of study treatment in the OL_ETP. • This population will be based on the treatment the participant actually received.	• Safety
Pharmacokinetic ETP (PK_OL_ETP)	• All participants in the Safety OL_ ETP population who had at least 1 non-missing PK assessment in OL ETP (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK

Refer to Section 15.5.2: Reporting Standards for rules used to define 'treatment actually received'.

Refer to Appendix 12: List of Data Displays which details the population used for each display.

4.5. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations may define Intercurrent Events (ICEs) that affect Efficacy analyses, as described in Section 8.1.1.1 and Section 8.2.1.1. ICEs will be listed as described in Appendix 12: List of Data Displays.

Protocol deviations will be tracked by Robarts and monitored by the GSK study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan which will be updated throughout the study

- The protocol deviations for those participants included in each interim analysis, up to the point of the data cut-off will be reviewed prior to unblinding.
- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised consistently on the protocol deviations datasets.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

5.1.1. Randomised, Double Blind Treatments

For within-study phase reporting the following descriptions will be used.

Treatment Group Descriptions			
RandAll NG Randomization System		Data Displays for Reporting where characters are limited	
Code	Description	Description	Order in TLF
A	GSK2831781 450 mg IV	GSK2831781 450 mg IV	2
B	GSK2831781 300 mg IV	GSK2831781 300 mg IV	3
C	GSK2831781 150 mg IV	GSK2831781 150 mg IV	4
D	GSK2831781 45 mg IV	GSK2831781 45 mg IV	5

Treatment Group Descriptions			
RandAll NG Randomization System		Data Displays for Reporting where characters are limited	
Code	Description	Description	Order in TLF
P	Placebo IV	Placebo IV	1
X	GSK2831781 300mg SC	GSK2831781 300mg SC	7
Y	Placebo SC	Placebo SC	6

Treatment comparisons in induction will be displayed as follows using the descriptors as specified:

1. GSK2831781 450 mg IV vs Placebo IV
2. GSK2831781 300 mg IV vs Placebo IV
3. GSK2831781 150 mg IV vs Placebo IV
4. GSK2831781 45 mg IV vs Placebo IV
5.
6. For reporting **within** the extended treatment phase the following treatment descriptions will be used.

7. Treatment Group Descriptions – Extended Treatment Phase for week 10 responders			
RandALL NG Randomization System		Data Displays for Reporting where characters are limited	
Code	Description	Description	Order in TLF
8. AX	9. GSK2831781 450 mg IV induction, 300 mg subcutaneous from week 14	10. 11. 12. 13. 14. GSK2831781 300mg SC	15. 2
16. BX	17. GSK2831781 300 mg IV induction, 300 mg subcutaneous from week 14		18. 2
19. CX	20. GSK2831781 150 mg IV induction, 300 mg subcutaneous from week 14		21. 2
22. DX	23. GSK2831781 45 mg IV induction, 300 mg subcutaneous from week 14		24. 2
25. PY	26. Placebo IV induction, Placebo subcutaneous from week 14	27. Placebo SC	28. 1

Treatment comparisons in the extended treatment phase will be displayed as follows using the following descriptor as specified:

GSK2831781 300 mg SC vs Placebo SC

5.1.2. Partial doses

If an incomplete IV dose is given then the dose received will be calculated as a proportion of the planned dosing duration (see below), this makes the simplifying assumption that the IP will be dosed at a constant rate. If an incomplete SC dose is given, the number of injections will be used to derive the received dose. For details of these calculations see Section 15.6 Appendix 6: Derived and Transformed Data.

Planned dose duration for IV doses

Phase	Visit	Planned duration of IV dose
Induction	Day 1	2 hr
Induction	Week 2	2 hr
Induction	Week 6	32 min
Induction	Week 10	32 min
Open label induction	Week 12	2 hr
Open label induction	Week 14	2 hr
Open label induction	Week 18	32 min
Open label induction	Week 22	32 min
See protocol Table 1 and Table 2 for further context		

5.2. Baseline Definitions

The baseline value will be the latest pre-dose assessment with a non-missing value, including those from screening and unscheduled visits

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

5.3. Multicentre Studies

In this multicentre global study, enrolment will be presented by the investigative site. Participants will be enrolled from approximately 100 centres. There are no planned adjustments made for multiple centres in this study.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The following list of covariates and other strata will be used in descriptive summaries and statistical analyses of primary and key secondary efficacy endpoints, some of which will also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered. For change from baseline endpoints, the baseline will also be included as a covariate.

Category	Details	Notes
Advanced therapy experience (Stratification factor)	Categorical variable with three levels: • Advanced therapy naïve, • Single class of advanced therapy experience • Multiple classes of advanced therapy experience	Derived from 'previous UC medications' in medical history. This is the stratification factor used in RAMOS, recorded at baseline in the eCRF for each participant; in case of conflict between the stratification in RAMOS and medical history, medical history will be used.
TNF failure (Covariate)	Categorical variable with three levels: • No TNF failure • Single TNF failure • Multiple TNF failures	Derived from medical history, covariate will be used as secondary analysis at primary completion
biologic experience type (Covariate)	Categorical variable with three levels: • Biologic naïve • TNF experience (no Vedolizumab) • Vedolizumab (including participants who have both TNF and Vedolizumab experience) Note: if participant has experience of other biologics, they will be assigned based on experience of TNF and Vedolizumab.	Derived from medical history. Comparison made as secondary analysis.
Baseline mucosal CD3+LAG3+ cell count (Covariate)	Continuous variable derived from biopsy. CD3 positive and Lag3 positive cells per mm2 of Lamina Propria tissue taken at screening biopsy.	
Duration of disease (Covariate)	Duration of disease, years	If day and month of diagnosis are missing, duration of disease will be calculated by using day=1 and month=July
Baseline Complete Mayo Score	Where the endpoint is derived from a version of the Mayo score, that version's baseline will be used.	

Category	Details	Notes
Baseline Adapted Mayo Score	Where the endpoint is derived from a version of the Mayo score, that version's baseline will be used.	

5.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered. The following subgroup analyses will only be performed at final analysis unless otherwise specified.

- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Categories	Timing	Motivation
Any advanced therapy experience	Advanced therapy naïve vs. Advanced therapy experienced	Interims, SAC	Prior expectation of clinical importance

5.5. Multiple Comparisons and Multiplicity

In general, no multiplicity adjustments will be made however for relevant data types standard analysis methods that correct for multiplicity may be employed, for example in the analysis of exploratory transcriptomic data.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the following appendices:

Section	Component
15.3	Appendix 3: Assessment Windows
15.4	Appendix 4: Treatment Phases and Study Phases Study Phases and Treatment Emergent Adverse Events
15.5	Appendix 5: Data Display Standards & Handling Conventions
15.6	Appendix 6: Derived and Transformed Data
15.7	Appendix 7: Reporting Standards for Missing Data
15.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The induction study population analyses will be based on the "Screened" and "Enrolled" populations, unless otherwise specified.

Population outputs will be generated for the participants in the four study phases illustrated in Figure 1 Participant Flow:

- Group A: Induction Phase
- Group B: Extended Treatment Phase (Week 10 Responders)
- Group C: Open Label Induction (Week 10 Non-Responders)
- Group D: Open Label ETP (Week 22 Responders)

This pattern will continue for all reported domains in this study.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

7. SAFETY ANALYSES

All safety evaluations will be based on the safety population. Displays of adverse events, laboratory values, ECG and vital signs will be generated. These data will be clinically interpreted based on a number of factors, including taking account the investigator-reported relationships of either adverse events or laboratory abnormalities to investigational product.

Safety endpoints of all types will be reported by study phase (Induction phase, Extended Treatment Phase, Open Label Induction Phase, Open Label Extended Treatment Phase). All study phases will use the same pre-dose baseline. The details of planned displays are provided in Appendix 12: List of Data Displays.

No formal statistical testing will be performed on safety data.

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards.

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

The immunogenicity of GSK2831781 will be characterized with summary statistics of incidence, i.e. the count of participants with positive confirmed anti-drug antibodies by treatment over time. Immunogenicity testing involves a screening assay and a confirmation assay that together produce three results:

- Screening assay result (binary (yes/no))
- Confirmatory assay result (binary (yes/no))
- Titre result (numeric)

8. EFFICACY ANALYSES

Unless otherwise specified, endpoints / variables defined in this section will be summarised by treatment using descriptive statistics, graphically presented (where appropriate) and listed.

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

8.1. Primary Efficacy Analyses

The primary efficacy endpoint is change from baseline over the induction phase.

8.1.1. Primary Endpoint

The Complete Mayo Score will be analysed with a Bayesian ANCOVA model, using the following estimands.

8.1.1.1. Primary Estimand – Treatment Policy

Primary estimand: "Treatment policy"	
Objective:	To characterise the efficacy of GSK2831781 during the Induction Phase.

Estimand:	**Primary efficacy estimand**
	
	Description
	
	Mean change from baseline to Week 10 in Complete 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.
	
	Attributes
	
	• **Treatment**: Placebo and four doses of GSK2831781 IV: 450mg, 300mg, 150mg and 45mg 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 Mayo score.
	• **Intercurrent events and strategy:**
	  • Intercurrent event (ICE): Discontinuations due to the COVID-19 pandemic
	  ○ Strategy: hypothetical, setting assessments to missing with missing at Random [MAR] assumption.
	  • ICE: Discontinuations due to sponsor's decision to terminate the study

Primary estimand: "Treatment policy"	
	○ Strategy: hypothetical, setting assessments to missing with missing at Random [MAR] assumption. • ICE: Discontinuations not due to the COVID-19 pandemic or to sponsor's decision to terminate the study ○ Strategy: treatment policy (no imputation). • **Population-level summary:** Mean change from baseline.

Estimation and missing data details for the primary estimand ("Treatment Policy")
Discontinuations due to reasons related to the COVID-19 pandemic or to sponsor's decision to terminate the study will be handled with a hypothetical strategy; the subsequent assessments will be set to missing in the analysis dataset (even if post discontinuation data is collected). Assessments following IP discontinuations for other reasons will be used in analysis. In all cases, the missing endpoint will be assumed to be MAR in the statistical analysis. The MAR assumption is implicit in the planned Bayesian analysis.

8.1.1.2. Statistical Analysis

Bayesian analysis for continuous endpoint	
Endpoints	Change from baseline in Complete Mayo Score at Week 10
Statistical analysis	Linear regression
Predictors	• TRT = study treatment(categorical) • Advanced Therapy Experience (categorical) (includes interaction with study treatment) • Baseline Complete Mayo (continuous) • Duration of disease, years (continuous)
Model	$y_i \sim \text{Normal}(\text{mean}=\mu, \text{SD}=\sigma)$ $\mu = (\text{TRT=Placebo})\times(\text{Experienced=Y})\times\beta_1 + (\text{TRT=450mg})\times(\text{Experienced=Y})\times\beta_2 + (\text{TRT=Placebo})\times(\text{Naive=Y})\times\beta_3 + (\text{TRT=450mg})\times(\text{Naive=Y})\times\beta_4 + (\text{Duration*})\times\beta_5 + (\text{Baseline*})\times\beta_6$

Bayesian analysis for continuous endpoint	
Population-level coefficients (**β**)	• **β** = fixed effects, parameters associated to predictors β_k: non-informative prior distributions, $\beta_k \sim$ Normal(mean=0, SD=100) • Standard deviation **σ**: Non-informative prior Gamma distribution (shape=2, rate=0.1) (Chung, 2013)

* Unless otherwise specified the predictors (not including study treatment) will be centred around their estimated mean in the model

Further details of primary analysis
Model diagnostics and checking
• Each chain will initially have length 0f 1,000,000, thin of 10 and burn-in length of 50,000. • Chain convergence diagnostics will be saved in HARP (refdata folder) and inspected. • The MCSE will be compared with the standard deviation of the posterior distribution (SD) to ensure that only a fraction of the posterior variability is due to simulation error, i.e., the ratio MCSE/SD should be close to 0.01
Model results presentation
• The posterior distribution of each arm and the treatment difference (overall and by Advanced Therapy Experience) will be summarized using median and equal-tailed 95% credible region and the probability of being above specific thresholds specified in the programming notes for this output. • Posterior density plots will be available in model output but will not be presented

8.1.1.3. Additional analyses for the Primary Endpoint

Frequentist analysis of change from baseline in Complete Mayo score at Week 10
A fixed-effect normal linear model will be used to compare the primary endpoint (change from baseline in Complete Mayo score at Week 10 Double-Blind Induction) between 450mg GSK2831781 IV and Placebo IV. The following variables will be used as covariates: Duration of disease (continuous), Advanced Therapy Experience (Categorical), Baseline Complete Mayo (continuous) and treatment. The estimated difference in change from baseline in Complete Mayo score at Week 10 will be displayed with 95% confidence interval (and associated p-value).

8.2. Secondary Efficacy Analyses

8.2.1. Key Secondary Endpoint

8.2.1.1. Estimand

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 o Not discontinuing IP due to reasons unrelated to the COVID-19 pandemic or to sponsor's decision to terminate the study, and o Not taking medications excluded by the protocol or increasing dose of corticosteroid. • **Intercurrent events and strategy:** o *ICE: discontinuation from IP, unrelated to COVID-19 pandemic or to sponsor's decision to terminate the study.* o Strategy: included in outcome via composite strategy (i.e. post-ICE result set to non-response). o *ICE: discontinuation from IP, due to COVID-19 pandemic.* o Strategy: hypothetical, setting response status to missing. o *ICE: discontinuation from IP, due to sponsor's decision to terminate the study.* o Strategy: hypothetical, setting response status to missing. o *ICE: valid endoscopy result not available, due to COVID-19 pandemic*

Key secondary estimand for decision making: "Composite"	
	○ Strategy: hypothetical, setting response status to missing. ○ *ICE: valid endoscopy result not available, for technical reasons* ○ Strategy: hypothetical, setting response status to missing. ○ *ICE: prohibited medication taken* ○ Strategy: included in outcome via composite strategy (i.e. post-ICE result set to non-response). ○ *ICE: increase in dose of permitted medications* ○ Strategy: included in outcome via composite strategy (i.e. post-ICE result set to non-response). • **Population-level summary:** Difference in proportion of participants who achieve response between placebo and relevant active doses

Estimation and missing data details for the key secondary estimand for decision making ("Composite")
Participants who have a missing assessment at Week 10 for reasons unrelated to the COVID-19 pandemic will be counted as non-responders in the analysis. The ICEs that will be dealt with using a hypothetical strategy will have response status set to missing In all cases, the missing response status will be assumed to be MAR in the statistical analysis. The MAR assumption is implicit in the planned Bayesian analysis.

8.2.1.2. Statistical Analysis

Bayesian analysis for binary endpoint	
Endpoints	Endoscopic Mucosal Healing (Endoscopic Improvement)
Statistical analysis	Logistic regression
Predictors	• TRT = study treatment(categorical) • Advanced Therapy Experience (categorical) • Baseline Adapted Mayo (continuous) • Duration of disease, years (continuous)
Model	$y_i \sim Ber(p_i)$ $logit(p_i) = (TRT=Placebo)\times\beta_1 + (TRT=450mg)\times\beta_2 + (Duration^*)\times\beta_3 + (Baseline^*)\times\beta_4 + (Experience^*)\times\beta_5$
Outcome	y_i = response (0/1) for participant *i*
Population-level coefficients (**β**)	• **β** = fixed effects, parameters associated to predictors β_1 : informative prior distribution, $logit^{-1}(\beta_1) \sim$ mixture of Betas** β_2 : non-informative prior distribution, $logit^{-1}(\beta_2) \sim Beta(1/3, 1/3)$ β_k for other predictors: non-informative prior distributions, $\beta_k \sim Normal(mean=0, SD=100)$

* Unless otherwise specified the predictors (not including study treatment) will be centred around their estimated mean in the model

** The parameterisation of the priors used in the analysis will be described in Appendix 14: Details of the Informative Placebo Prior and reported in the clinical study report

Further details of key secondary analysis
Overview of approach
For interim 2 and 3 the predictive probability of meeting the end of study success criteria will be assessed after the Week 10 endoscopy (or withdrawal) has been observed on the number of participants specified for that data cut. A sample from the posterior distribution of the difference in response rates between each treatment arm and placebo will be obtained using Markov chain Monte Carlo (MCMC). This analysis will account for historical placebo data by using an informative prior distribution for the placebo arm and a vague Beta (1/3,1/3) distribution for the active arm (Kerman, 2011).

Informative Placebo Prior

- The prior distribution is a robust mixture prior based on historical data following the approach of (Schmidli, 2014). A meta analytic predictive (MAP) prior of relevant historical data is created, with a covariate for the proportion of Advanced Therapy Experienced in each historical trial.
- The MAP prior is obtained via an MCMC model with the following specifications:
  - For each historical trial *s* with *r* responders in *N* placebo patients and percentage of Advanced Therapy Experienced *%Exp*:

$$r_s \sim Binomial(size = N_s, rate = rate_s)$$

$$rate_s = logit^{-1}(\alpha + \beta * \%Exp_s + \epsilon_s)$$

$$\epsilon_s \sim Normal(0, \tau)$$

  - Prior for between-trial heterogeneity τ: half-normal with μ=0, σ=z/2 where z is derived via the n-∞ method (Neuenschwander., 2010):
    - p = mean of r/N of historical trials
    - z = [sqrt(p*(1-p))]$^{-1}$
  - Priors for coefficients α, β: normal with μ=0, σ=100
- The MCMC samples of the placebo response are approximated using appropriate parametric distributions, typically a mixture of two to three Beta distributions. Unless stated otherwise, the number of Beta distributions in the mixture is decided via AIC.
- The prior used for analysis will use the proportion of Advanced Therapy Experienced participants observed in this trial at the relevant interim or final analysis.
- The rules for including historical data used for this analysis will be documented in Appendix 14: Details of the Informative Placebo Prior.
- The MAP prior distribution is 'robustified' by further mixing with a non-informative Beta(1/2,1/2) distribution with 40% weight for the non-informative prior.
- The final prior distribution and supporting information will be documented in the trial master file before the study is unblinded for interim analysis 3.
- Examples of the parametric distributions used at different levels of the covariate are documented in Appendix 14: Details of the Informative Placebo Prior.

Model Checking & Diagnostics

- Each chain will initially have length 0f 1,000,000, thin of 10 and burn-in length of 50,000.
- Chain convergence diagnostics will be saved in HARP (refdata folder) and inspected.
- The MCSE will be compared with the standard deviation of the posterior distribution (SD) to ensure that only a fraction of the posterior variability is due to simulation error, i.e., the ratio MCSE/SD should be close to 0.01

Model Results Presentation

- At IA3, the predictive probability that the end of study success will be achieved according to specific thresholds will be displayed (thresholds will be specified in the programming notes for this output).
    - The predictive probability of end of study success is obtained by simulating 10,000 trials
    - In each simulated trial, post-IA3 Endoscopic Improvement results for Placebo and 450mg are simulated using the posterior samples for the response rates obtained in the MCMC model at IA3. The IA3 Endoscopic Improvement counts for Placebo and 450mg are summed to the simulated post-IA3 data to obtain simulated results for the full study.
    - In each simulated trial, end of study success is calculated using the posterior distributions for 450mg and Placebo (without covariates):
        - In the Active arm, a non-informative Beta(1/3,1/3) is used as prior.
        - In the Placebo arm, the MAP prior described above (an informative mixture of Betas) is used as prior.
        - The mixture Placebo prior will take the following form:

$$\sum_{k=1}^{K} w_k * Beta(a_k, b_k)$$

        - When computing the Placebo posterior using simulated results (*r1* responders out of *n1* participant) each of the *k* mixture components takes the following form (Röver, 2020):

$$w_k * \binom{n1}{r1} * \frac{\Gamma(a_k + b_k)\Gamma(a_k + r1)\Gamma(b_k + n1 - r1)}{\Gamma(a_k)\Gamma(b_k)\Gamma(n1 + a_k + b_k)} * Beta(a_k + r1, b_k + n1 - r1)$$

- The posterior distribution of each arm and the treatment difference will be summarized using mean and equal-tailed 95% credible region and the probability of being above specific thresholds specified in the programming notes for this output.
- Posterior density plots will be available in model output but will not be presented.

8.2.2. Other Secondary Endpoints - Categorical

The ICE strategy for the Key Secondary Estimand described in Section 8.2.1.1 above will be replicated in the following secondary Efficacy endpoints:

Endpoint	Endpoint name to be displayed for Estimand Analysis
Adapted Mayo Clinical Remission at Week 10	Secondary – Adapted Mayo Clinical Remission
Adapted Mayo Clinical Response at Week 10	Secondary – Adapted Mayo Clinical Response
Symptomatic Remission at Week 10	Secondary – Symptomatic Remission

The "Secondary Estimand – Clinical Remission" will be analysed by replicating the statistical model described in Section 8.2.1.2 above. The other two estimands in the table above will be summarised only.

8.2.3. Other Secondary Endpoints - Continuous

The ICE strategy for the Primary Estimand described in Section 8.1.1.1 above will be replicated in the following secondary Efficacy endpoints:

Endpoint	Endpoint name to be displayed for Estimand Analysis
Change from Baseline in Partial Mayo Score at Weeks 2, 4, 6, 10	Secondary – Partial Mayo Score
Change from Baseline in Adapted Mayo Score at Week 10	Secondary – Adapted Mayo Score
Change from Baseline in Adapted Mayo endoscopic score at Week 10	Secondary – Endoscopic Score
Change from Baseline in UCEIS at Week 10	Secondary – UCEIS Total Score

The four estimands in the table above will be summarised in tables.

In addition, a Bayesian repeated measures analysis will be conducted for the Partial Mayo score, the estimand is described below and the analysis details below that.

8.2.3.1. Statistical Analysis

Bayesian Repeated Measures Analysis for Continuous Endpoint	
Endpoint	Change from baseline in Partial Mayo Score
Statistical analysis	GLMM with natural link (equivalent to MMRM)
Model	$\boldsymbol{y}_i \sim Normal(\boldsymbol{\mu}_i,\ \sigma^2\ I_j)$ $\boldsymbol{\mu}_i = X_i\ \boldsymbol{\beta} + Z_i \boldsymbol{b}_i$
Outcome	$\boldsymbol{y}_i =$ vector of change from baseline values for participant *i*
Prior for σ	σ = between-participant SD, $\sim Gamma\left(2, \frac{1}{A}\right)$ with A reasonably large e.g. A=10 (Chung, 2013)
Population-level coefficients (**β**)	• **β** = fixed effects, parameters associated to predictors β_0 = intercept, two possible prior distributions*: Vague: $Normal(0, sd = 100)$ Weakly informative: see Appendix 14: Details of the Informative Placebo Prior $\beta_k \sim Normal(0, sd = 100)$

Bayesian Repeated Measures Analysis for Continuous Endpoint	
Predictors (**X**)	• TRT = study treatment(categorical) • visit = visit (categorical) • TRT*visit = study treatment by-visit interactions (categorical) • BASE = baseline value of dependent variable (continuous) • Partial Mayo Score • BASE*visit =baseline value by-visit interactions (continuous) • Advanced therapy experience (categorical stratification variable)
Random effects (***b***)	• Z_i = known design matrix for the random effects • b_i = unknown subject-level random effects, ~ Normal(0, Σ_b), where Σ_b within-subject covariance matrix • Σ_b ~ Inverse Wishart (J, S), with J = number of visits (degree of freedom), S = covariance matrix (identity matrix)

* The parameterisation of the priors used in the analysis will be reported in the clinical study report.

The details of the scores and indexes including the Complete, Partial and Adapted Mayo scores, and the corresponding definition of response and remission are described in Section 15.6 Appendix 6: Derived and Transformed Data.

Note that the absolute values for each endpoint listed as change from baseline will also be reported for each timepoint.

8.3. Exploratory Efficacy Analyses

Exploratory efficacy endpoints include the primary and secondary endpoints in the post-induction study phases (ETP, OL, OL ETP). Unless stated otherwise, exploratory efficacy endpoints will be listed but not summarised.

9. PATIENT REPORTED OUTCOMES ANALYSES

Exploratory Patient reported outcomes (PROs) are not covered by this RAP.

10. PHARMACODYNAMIC AND BIOMARKER ANALYSES

10.1. Pharmacodynamic and Biomarker Analyses

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Biomarker endpoints will be summarised in Double Blind Induction by treatment using descriptive statistics, graphically presented and listed. Figures summarising these endpoints will show Geometric Mean with 95% CI.

10.1.1. Endpoint / Variables

- Serum C-reactive protein over time in participants with elevated CRP at baseline (e.g. CRP $\geq$ 5 mg/L)
- Faecal calprotectin over time
- Absolute and ratio to baseline in number of CD3 and LAG3 cells by Immunofluorescence (IF) in colon biopsies taken in two tissue types (Lamina Propria or Crypt/Epithelium) for the following derived parameters:

Description	**Name in outputs (superscript not available)**	**Units for derived variables**
% CD3 negative and Lag3 positive from total Lag3 positive cell population (% Lag3 positive non-T cells)	CD3-LAG3+ as % of Total LAG3+	%
% CD3 positive and Lag3 positive from total Lag3 positive cell population (% Lag3 positive T cells)	CD3+LAG3+ as % of Total LAG3+	%
CD3 positive cells per mm^2 tissue	CD3+	cells/mm2
Lag3 positive cells per mm^2 tissue	LAG3+	cells/mm2
CD3 positive and Lag3 negative cells per mm^2 tissue	CD3+LAG3-	cells/mm2
CD3 negative and Lag3 positive cells per mm^2 tissue	CD3-LAG3+	cells/mm2
CD3 positive and Lag3 positive cells per mm^2 tissue	CD3+LAG3+	cells/mm2
$CD3^+LAG3^+$ cells/mm^2 in Lamina Propria are the primary biopsy endpoint (also referred to as **mucosal $CD3^+LAG3^+$ cell count**) and will also be a potential covariate for efficacy and biomarker analysis.		

- Ratio to baseline in the following cell types from flow cytometry. The table below shows the cell description and the endpoint name shown in outputs for flow cytometry data.

Description	Name in outputs (superscript not available)
J11L1^{+} memory T helper cells	CD3+CD4+CD45RA-J11L1+
REA351^{+} memory T helper cells	CD3+CD4+CD45RA-REA351+
J11L1^{+} memory CD4^{-} T cells	CD3+CD4-CD45RA-J11L1+
REA351^{+} memory CD4^{-} T cells	CD3+CD4-CD45RA- REA351+
Note: REA351+ represents cell depletion, J11L1+ represents receptor occupancy.	

11. PHARMACOKINETIC ANALYSES

The purpose of the pharmacokinetic analysis is to characterize the PK after repeat IV and subcutaneous dosing of GSK2831781.

11.1. Pharmacokinetic Analyses

11.1.1. Endpoint / Variables

- AUC(0-tau)
- Cmax
- tmax
- PK concentration
- Soluble LAG3 (sLAG3) concentration

11.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 15.5.3 Reporting Standards for Pharmacokinetic)

11.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis of PK concentration according to current working practices and using the currently supported version of WinNonlin (version 6.3 or higher). All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-tau)	Area under the concentration curve to the end of the dosing period
Cmax	Maximum concentration observed
tmax	Time at which the maximum concentration Cmax is observed

NOTES:

- Additional parameters may be included as required.

11.1.2. Summary Measure

- All endpoints/variables defined in Section 11.1.1 will be summarized by treatment over time using descriptive statistics, graphically presented (PK and sLAG3 concentrations) and listed.

11.1.3. Population of Interest

The pharmacokinetic analyses will be based on the “Pharmacokinetic” population, unless otherwise specified.

11.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Descriptive statistics (e.g., n, arithmetic mean and corresponding 95% confidence interval, standard deviation, minimum, median, maximum, CVb%) will be calculated for all pharmacokinetic endpoints by treatment. For tmax, CVb% will be calculated for each treatment as: CVb%=100 x (SD/mean), where SD and mean are the standard deviation and mean of the untransformed data. For AUC(0-tau) and Cmax, geometric means and between subject CVs will be calculated for each treatment as:

Geometric mean=exp(mean on loge scale)

$CVb(\%)=\sqrt{\exp(SD^2)-1}\times 100$,

where SD is the standard deviation of the loge transformed data.

12. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

The primary goal of this analysis is to characterize the population pharmacokinetics of GSK2831781 following repeat intravenous and subcutaneous dosing in participants with active ulcerative colitis. The influence of participant demographics, baseline characteristics, including disease activity, and impact of anti-drug antibodies on the pharmacokinetics of GSK2831781 in this population will be investigated. The individual participant PK parameters will be estimated and documented for the purposes of any subsequent exposure-response (PK/PD) analyses.

12.1. Statistical Analyses / Methods

A summary of the planned population pharmacokinetic analyses is outlined below:

- Drug GSK2831781 concentration-time data will be subjected to nonlinear mixed effects modelling using the program NONMEM to develop a population PK model.
- To support this analysis a PopPK dataset will be generated. The details for the dataset specifications are provided in a separate document.

Detailed PopPK methodology is presented in Appendix 9: Population Pharmacokinetic (PopPK) Analyses.

A population PK report will be produced by CPMS and presented separately from the main clinical study report (e.g. as an appendix).

13. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The primary goal of this analysis is to characterize the pharmacokinetic / pharmacodynamic relationship of GSK2831781 following repeat intravenous and subcutaneous dosing in participants with active ulcerative colitis. The influence of subject demographics and baseline characteristics, including disease activity in this population will be investigated.

13.1. Statistical Analyses / Methods

A summary of the planned population pharmacokinetic / pharmacodynamic analyses is outlined below:

- Drug GSK2831781 concentration (or pharmacokinetic parameter) and pharmacodynamic data will be subjected to nonlinear mixed effects modelling using the program NONMEM to develop a population PK/PD model.
- To support this analysis, a PK/PD dataset will be generated. The details for the dataset specifications are provided in a separate document.
- Detailed PK/PD methodology is presented in Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses.

A PK/PD report will be produced by CPMS and presented separately from the main clinical study report (e.g. as an appendix).

14. REFERENCES

Bornkamp, B. (2014). *Practical considerations for using functional uniform prior distributions for dose-response estimation in clinical trials.* Biometrical Journal, 56(6), 947–962.

Chung, Y., Rabe-Hesketh, S., Dorie, V., Gelman, A., Liu, J. (2013). *A nondegenerate penalized likelihood estimator for variance parameters in multilevel models.* Psychometrika, 78, 685–709.

Clinical Study Report 2017N352860_00 A randomised, double blind (sponsor unblinded), placebo controlled, single ascending dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of a IV dose of GSK2831781 in healthy volunteers and patients with plaque psoriasis

Hanauer S, Panaccione R, Danese S, et al. (2019) *Tofacitinib induction therapy reduces symptoms within 3 days for patients with ulcerative colitis*. Clin Gastroenterol Hepatol 2019;17:139–146.

Kerman, J. (2011). *Neutral noninformative and informative conjugate beta and gamma prior distributions.* Electronic Journal of Statistics 5, 1450–1470

Marchal-Bressenot A, et al. (2017) *Development and validation of the Nancy histological index for UC.* Gut 2017; 66:43–49.

Neuenschwander, B., Capkun-Niggli, G., Branson, M. and Spiegelhalter, D.J. (2010) *Summarizing historical information on controls in clinical trials.* Clinical Trials, 7(1): 5-18.

Röver, C. and Friede, T. (2020) *Dynamically borrowing strength from another study through shrinkage estimation.* Statistical Methods in Medical Research, 29(1): 293-308

Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B. (2014). *Robust meta-analytic-predictive priors in clinical trials with historical control information*. Biometrics, 70(4), 1023-32.

Spiegelhalter, DJ; Best, N; Carlin, BP; van der Linde, A. (2002). "Bayesian measures of model complexity and fit (with discussion)". Journal of the Royal Statistical Society, Series B. 64 (4): 583–639. doi:10.1111/1467-9868.00353

Study Protocol 2017N337668_02 – A multicentre randomized, double-blind (sponsor open), 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.

15. APPENDICES

15.1. Appendix 1: Protocol Deviation Management and Definitions for Analysis Population Exclusions

As Per-Protocol populations will not be used, participants will not be excluded from analyses due to protocol deviations.

15.2. Appendix 2: Schedule of Activities (SoA):

Double Blind Treatment

	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 Protocol Section 5.1), and at any timepoint if clinically indicated.
3 ECG in triplicate at screening and single at all other time points. See Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol 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.

Open Label Treatment

	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 Protocol 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).

15.3. Appendix 3: Assessment Windows

15.3.1. Definitions of Assessment Windows for Analyses

Note that assessment windows will be applied on an endpoint by endpoint basis.

Early Withdrawal and Unscheduled visits will be assigned to assessment windows according to actual dates rather than the nominal visit labels recorded against the observation.

A window around a target Study Day will typically include all days from the midpoints between it and the target Study Days of the previous and the proceeding visits. In general, the nominal target Study Day for week w is (7 * w) +1. The window around the last visit prior to follow up will be symmetrical so that it will be determined by the midpoint between it and the previous visit.

If using assessment windows leads to more than one observation being allocated to a visit then the closest observation to the target date will be taken. If the difference between the two observations is the same, the latest will be used.

If an Early Withdrawal or Unscheduled assessment for any given parameter is allocated to a visit that contains multiple planned time assessments for said parameter, then it will be labelled as "Unscheduled/EW" in summary tables.

Note that all observations will be listed and used for calculation of 'worst case' outputs for safety (for example "Summary of Worst-Case Chemistry Results by PCI Criteria Post Baseline Relative to Baseline").

Assessment windows do not cross study phases

An exception to the general rule of allocating observations to the nearest visit concerns the transition between study phases. Assessment windows should not allocate a visit to a study phase until the study phase begins for that participant (i.e. the Study Day that they receive their first dose for that study phase).

For example, even if an Unscheduled visit on Week 13 for a responding participant is closest to the first visit for the Extended Treatment Phase, the observations from the Unscheduled visit would be allocated to the Induction Phase because the Extended Treatment Phase has not started.

Screening and Post dose records:

The post-dose records will be summarized under the last study phase in which participants received a dose. The visit windowing algorithm will be based on the following:

1. CRF assessments/events collected after 'Last Dose Date + 16 Weeks (+ 7 days)' (i.e. post-treatment study phase) will not be analysed/summarised. These records will only be listed.

2. For CRF assessments/events collected after Last Dose Date but before 'Last Dose Date + 16 Weeks (+ 7 days)':
   a) All records collected in event datasets will be summarized as well as listed (e.g. AE, CM).
   b) All records collected for any other assessments will be included for 'Worst-Case' summaries (e.g. LABs, Mayo score/endpoints etc).
   c) Unless stated otherwise, all records for any other assessments will be included in visit-based summaries as described in two scenarios below –
      i. The visits collected in the same study phase will be summarized against the visit in CRF or using windowing RAP algorithm for 'Unscheduled'.
      ii. The visits collected in subsequent study phases will be windowed as 'Follow-up IND/ETP' visit (even CRF collected scheduled visits will be mapped). For summaries, the latest assessment among 'Follow-up IND/ETP' will be used.

Note that after the final visit (Week 30 / OL Week 42) the next visit would be the Follow-Up and it is not expected that a participant would have an Early Withdrawal visit after these visits.

Target Day	Analysis Window (Days)		Analysis Timepoint
	Beginning Timepoint	Ending Timepoint	
Note: Windowing applies to all domains except Extra Intestinal Manifestations of UC.			
1	1	2	DAY 1
15	3	22	WEEK 2
29	23	36	WEEK 4
43	37	57	WEEK 6
71	58	A day prior to participant's first dose of next phase. For participants who do not take a subsequent dose, maximum of 'Week 10 dosing date +3' and day 85	WEEK 10
99* (First Dose of Period + 1)	Participant's first dose of ETP	102* (First dose of Period + 4)	WEEK 14
127* (First dose of Period + 29)	103* (First dose of Period + 5)	141* (First dose of Period + 43)	WEEK 18
155* (First dose of Period + 57)	142* (First dose of Period + 44)	169* (First dose of Period + 71)	WEEK 22

Target Day	Analysis Window (Days)		Analysis Timepoint
	Beginning Timepoint	Ending Timepoint	
183* (First dose of Period + 85)	170* (First dose of Period + 72)	197* (First dose of Period + 99)	WEEK 26
211* (First dose of Period + 113)	198* (First dose of Period + 100)	225* (First dose of Period + 127)	WEEK 30
85* (First Dose of Period + 1)	Participant's first dose of OL	92* (First dose of Period + 8)	OL WEEK 12
99* (First dose of Period + 15)	93* (First dose of Period + 9)	113* (First dose of Period + 29)	OL WEEK 14
127* (First dose of Period + 43)	114* (First dose of Period + 30)	141* (First dose of Period + 57)	OL WEEK 18
155* (First dose of Period + 71)	142* (First dose of Period + 58)	A day prior to participant's first dose of OL ETP. For participants who do not take a subsequent dose, maximum of 'OL Week 22 dosing date +3' and day 197	OL WEEK 22
183* (First Dose of Period + 1)	Participant's first dose of OL ETP	186* (First dose of Period + 4)	OL WEEK 26
211* (First dose of Period + 29)	187* (First dose of Period + 5)	225* (First dose of Period + 43)	OL WEEK 30
239* (First dose of Period + 57)	226* (First dose of Period + 44)	253* (First dose of Period + 71)	OL WEEK 34
267* (First dose of Period + 85)	254* (First dose of Period + 72)	281* (First dose of Period + 99)	OL WEEK 38
295* (First dose of Period + 113)	282* (First dose of Period + 100)	309* (First dose of Period + 127)	OL WEEK 42
* For delayed first dose in the study phase : - If the first dose of a study phase is within the first visit window of that study phase, then use the number outside brackets in each subsequent window. - If the first dose of a study phase is post-ending timepoint of the first visit window of that study phase, then use the bracketed derivation in each subsequent window.			

15.4. Appendix 4: Treatment Phases and Study Phases

15.4.1. Treatment Phases

The table below defines treatment phases. Note that if a participant receives study drug at all visits and completes the study, all visits will be categorised as 'on-treatment' including the follow-up visit. Note: follow-up visits for participants who early withdraw in Double Blind Induction and for participants who early withdraw in other study phases without completing all protocol-defined visits in that phase will not be summarised (they will be listed).

Where treatment is discontinued during the study (i.e. the 'study treatment discontinuation' form has been completed in the eCRF), the Study Treatment Stop Date will be defined as the date that the last treatment was given.

Treatment Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date + 16 weeks (+ 7 days, the visit window)
Post-Treatment	Date > Study Treatment Stop Date + 16 weeks

15.4.2. Study Phases

A study phase will start when the first dose for that phase is taken. The phase will end at either:

- The day before the subsequent phase starts
- The end of the follow up visit (note, this is 16 weeks after the last dose)

15.4.2.1. Study Phases for Adverse Events

If a participant discontinues treatment (i.e. the 'study treatment discontinuation' form has been completed) but continues to attend visits AEs will be associated with the study phase until 16 weeks (+7 days) after the last dose. If an AE onset date is during the post-treatment period the AE will not be summarised against a study phase.

If an AE onset date is in one phase and resolution date is in a subsequent phase, the AE will be associated with the phase in which the AE starts. AEs that cross phases where the maximum severity is greater than the severity at onset will be listed separately.

Following the standard rules for summarising AEs, if an AE of a category repeats in the same study phase this will be counted once in that phase, however if the same AE repeats in a subsequent phase, it will be counted in both the first phase and the subsequent phase because AEs in each study phase are summarised in separate tables.

15.4.2.2. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before first dose of study treatment.
Concomitant	Any medication that is not a prior and that has start date before or during the on-treatment phase.
Post-Treatment	Any medication that has a start date after the end of the on-treatment phase.

15.4.3. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date (and time) is after treatment start date (and time) and during the On-treatment period, the AE will be considered Treatment Emergent.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

15.5. Appendix 5: Data Display Standards & Handling Conventions

15.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: \arenv\arprod\gsk2831781\

Reporting effort type	HARP path
N30 Dry Run	: \arenv\arprod\gsk2831781\mid204869\data_look_01
N30	: \arenv\arprod\gsk2831781\mid204869\safety_01
IA3 Dry Run 1	: \arenv\arprod\gsk2831781\mid204869\data_look_02
IA3 Dry Run 2	: \arenv\arprod\gsk2831781\mid204869\data_look_04
IA3 Headline	: \arenv\arprod\gsk2831781\mid204869\ internal_02
Final CSR Dry Run	: \arenv\arprod\gsk2831781\mid204869\data_look_05
Final CSR	: arenv\arprod\gsk2831781\mid204869\final_01

Analysis Datasets
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1. If the Study Data Standardization Plan (SDSP) exists for a study, ensure the CDISC versions are consistent.
Generation of RTF Files
• RTF files will be generated for the primary completion and final SAC described in the RAP.

15.5.2. Reporting Standards

General

- The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  - 4.03 to 4.23: General Principles
  - 5.01 to 5.08: Principles Related to Data Listings
  - 6.01 to 6.11: Principles Related to Summary Tables
  - 7.01 to 7.13: Principles Related to Graphics
- Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

Formats

- GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated.
- Numeric data will be reported at the precision collected on the eCRF.
- The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.

Planned and Actual Time

- Reporting for tables, figures and formal statistical analyses:
  - Assessment windows will allocate actual visit time to planned visits which will be used in summary figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  - The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
- Reporting for Data Listings:
  - Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  - Unscheduled or unplanned readings will be presented within the subject's listings.

Treatment Actually Received

- If a participant has been dosed at more than one dose level within a phase (i.e. they have been incorrectly dosed) then their 'actual' treatment allocation will be defined as the highest dose received.

Treatment

- In listings where results are reported per visit, the treatment received in each phase will be associated with the visits in that phase. Where order is 'by treatment' the order will be based on treatment received in the induction phase.
- Note that summaries are, in general, reported separately for each study phase whereas, in general, there will be a single listing across all phases.

Unscheduled Visits

- Observations from Unscheduled visits will follow the rules for assessment windows but will not be separately summarised as 'Unscheduled' in summary tables or figures.
- All unscheduled visits will be included in listings.

Descriptive Summary Statistics

Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays
• Refer to IDSL Statistical Principles 7.01 to 7.13.

15.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to GUI_51487. Note: Concentration values will be imputed as per GUI_51487.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification (separate document).
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification (separate document).
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	No PK parameters will be derived by the Programmer
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to SOP_314000 [Standards for Handling NQ Impacted PK Parameters].
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to GUI_51487.

15.6. Appendix 6: Derived and Transformed Data

This appendix describes how data are derived for further reporting. In general, these instructions apply at the participant level prior to any summaries being created.

15.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

15.6.2. Study Population

Exposure
Partial Doses
• For partial IV doses, the quantity of IP given to the participant will be calculated using the simplifying assumption that IP is dosed at a constant rate using the following formula: **IP dose received = IP dose expected * ((dose stop time – dose start time) / expected duration of dosing)** • Section 5.1.2 shows the expected duration of dosing which is dependent on visit. • For partial SC doses, the quantity of IP given to the participant will be calculated based on the number of injections received. The expected SC dose is always two injections (2 x 150mg) so a single injection will dose 150mg.
Number of Doses
Summarise the number of doses received by participants within each study phase.
Cumulative Dose
The cumulative received dose in mg will be calculated across all phases and within each study phase for each participant.
Duration of Exposure
The number of days of exposure will be calculated for each participant within study phase and across all study phases. 1. The following algorithm will be used for calculating days exposed across all study phases: Duration of Exposure = Last dose date - first dose date + 1

2. The following algorithm will be used for calculating days exposed in a study phase:

Duration of Exposure = Last dose date of phase - first dose date of phase + 1

Note: subjects with multiple missed doses in a phase are not expected to start the next phase.

Smoking History: Pack years

- Pack years = (number of daily cigarettes / 20) x number of years smoked
  - If frequency reported is weekly; number of daily cigarettes = weekly cigarettes x 7 days
  - If frequency reported is monthly; number of daily cigarettes = monthly cigarettes x 30.44 days

15.6.3. Efficacy

15.6.3.1. Mayo score versions

All Mayo scores are the sum of the components. The number of components and their definition vary as described below and will be derived programmatically. Stool Frequency and Rectal Bleeding will be derived from eDiary data.

Complete 4-Domain Mayo Clinic Score (MCS)

Sign/Symptom	Score
CCI	

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.

Complete 4-Domain Mayo Clinic Score (MCS)

The Complete Mayo score (sum of four components, range 0-12) includes a physician global assessment, and CCI [redacted] at endoscopy contributes to an endoscopic score of CCI [redacted] The following categorical endpoints are derived from this score:

- **Clinical remission (Complete Mayo)** is defined as: Complete MCS ≤2, with no individual sub-score >1
- **Clinical response (Complete Mayo)** is defined as: Reduction in complete MCS ≥3 points from baseline **AND** ≥30% from baseline **AND** decrease in the rectal bleeding sub-score of ≥1 point from baseline (or a score of 0 or 1)
- **Symptom Control** for rectal bleeding is defined as a sub-score of 0
- **Symptom Control** for stool frequency is defined as a sub-score of 0 or 1 with no worsening from baseline
- **Symptomatic Remission** is defined as **Symptom Control** for both rectal bleeding and stool frequency

Partial Mayo Clinical Score

Sign/Symptom	Score
CCI [redacted]	

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

The Partial Mayo Clinical Score (sum of three components, range 0-9) is based on the complete 4-domain MCS, but without the endoscopy sub-score

- The definitions of **Clinical Remission (Partial Mayo)** and **Clinical Response (Partial Mayo)** are the same as described for complete Mayo with the baseline being the partial Mayo score instead of the complete Mayo score. Note that the baseline visit for the Partial Mayo score differs from Complete and Adapted.

Adapted 3-domain Mayo Clinical Score

Sign/Symptom	Score
	CCI

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

The Adapted 3-domain Mayo Clinical Score (sum of three components, range 0-9) is based on the complete 4-domain MCS, but without the physician global assessment and with an alternative definition of the endoscopy scores. The following categorical endpoints are derived from this score:

- **Clinical Remission (Adapted Mayo)** is defined as adapted MCS of <=2 with no individual sub-score > 1 and a rectal bleeding sub score of 0 with stool frequency sub score not greater than baseline.
- The definition of **Clinical Response (Adapted Mayo)** is the same as described for complete Mayo with the baseline being the adapted Mayo score instead of the complete Mayo score
- The definition of **Clinical Remission (FDA)** requires an absolute stool number of 3 or fewer (*average daily stool number during 3 days before a visit*), a Mayo rectal bleeding sub-score of 0, and an adapted Mayo endoscopic sub-score of 0 or 1.
- **Endoscopic Remission** is defined as: **Adapted** Mayo endoscopic score = 0
- **Endoscopic Improvement** is defined as: **Adapted** Mayo endoscopic score = 0 or 1, this endpoint is also referred to as '**Endoscopic Mucosal Healing**' in the project.

Extended Treatment Phase endpoints:

- **Steroid Free Clinical Remission** will be reported at Week 30 only. It is defined as **Clinical Remission (Adapted Mayo)** at Week 30 **AND** participant has not received a steroid dose in the 28 days prior to the day of the efficacy assessment.
- **Maintained Steroid Free Clinical Remission** will be reported at Week 42 only. It is defined as participants who were in **Steroid Free Clinical Remission** at Week 30 **AND** who are in **Clinical Remission (partial Mayo)** at Week 42 (follow up) **AND** that did not receive any dose of steroid between Week 30 and Week 42.
- **Maintained Clinical Response (Week 10 to 30 Adapted Mayo)** will be reported at Week 30 only. It is defined as **Clinical Response (Adapted Mayo)** at Week 10 **AND Clinical Response (Adapted Mayo)** at Week 30.

Adapted 3-domain Mayo Clinical Score
• **Maintained Clinical Remission (Week 10 to 30 Adapted Mayo)** will be reported at Week 30 only. It is defined as **Clinical Remission (Adapted Mayo)** at Week 10 **AND Clinical Remission (Adapted Mayo)** at Week 30.

15.6.3.2. Mayo sub scores

Mayo sub scores will be derived from the daily eDiary. For each calculated Mayo score the following steps are required:

- Select days to be used as source data from the previous seven.
- Calculate Stool Frequency sub-score (derived from relevant daily stool counts)
- Calculate Rectal Bleeding sub-score (simple average of relevant daily entries)
- Calculate Absolute Stool Number (simple average of relevant daily stool counts)

Day selection algorithm

The eDiary should be used daily and should not allow a participant to save partial data (i.e. if an entry for stool count is available, then an entry for rectal bleeding should also be available), it is therefore assumed that both Stool Frequency and Rectal Bleeding will be present on a specific day, or both will be missing.

The scores reflect a patient's experience over an entire day and so can only be calculated once the day is complete. The previous day's score is therefore used at a study visit (i.e. entered into the eCRF by the site) but by contrast, the eDiary will be analysed after all data has been collected and so the daily sub-score will be reported against the latest study day in the window of possible days (the 'named day'). When daily sub-scores are presented they use the named day, for example daily sub-scores reported at study Day 1 will include the day of the first dose of IP (Day 1) but the (Partial) Mayo score reported at the Day 1 visit will use the value from Day -1 for consistency with the value recorded by the site and general practice in using the Mayo score. This reporting of daily sub-scores is consistent with practice in the literature (Hanauer, 2019).

Considering the last 7 days (including the named day) exclude any days where a participant:

- Received bowel preparation medication for an endoscopy
- Had an endoscopy
- Is the day after an endoscopy

From the remaining days, working backwards from the most recent available day, use the following hierarchy to select the most appropriate days:

1. Three consecutive days of data, as close to the endoscopy visit as possible.
2. If three consecutive days are not available, three non-consecutive days of data, as close to the endoscopy visit as possible.
3. If fewer than three days' data are available in the prior seven days, set both SF and RB sub-scores to missing.

See the table at the end of the 'Rectal Bleeding' section for examples of day choice in different circumstances.

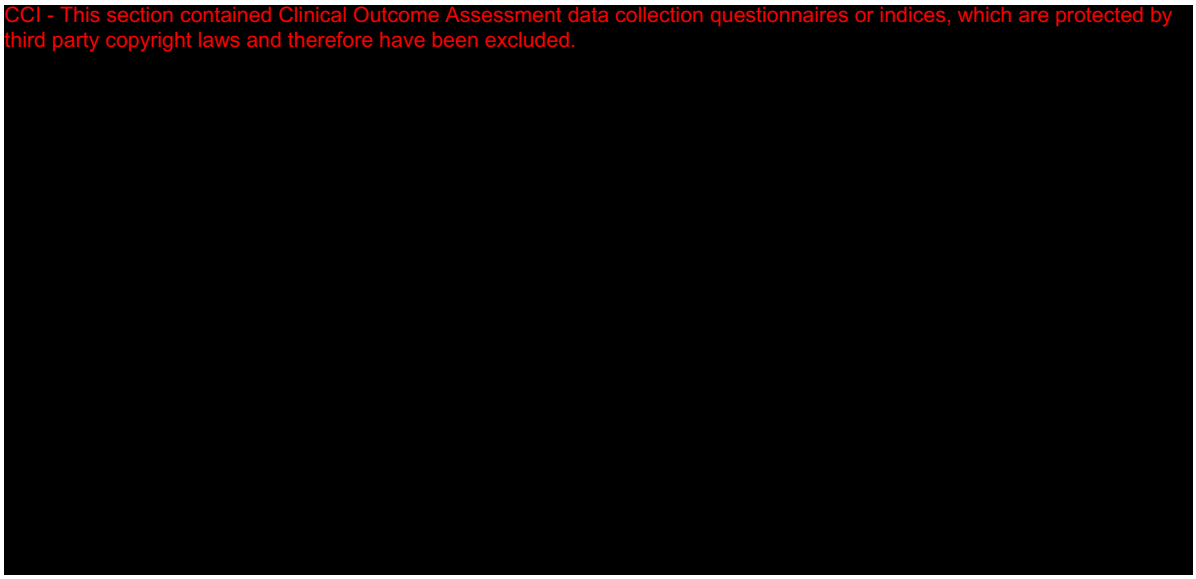
Note that the following alternative algorithm will also be calculated for sensitivity analyses:

1. Three consecutive days of data, as close to the endoscopy visit as possible.
2. If three consecutive days are not available, three non-consecutive days of data, as close to the endoscopy visit as possible.
3. If fewer than three days' data are available in the prior seven days, use data from the two most recent days.
4. If fewer than two days' data are available in the prior seven days, set both SF and RB sub-scores to missing.

If there is a greater than 5% difference between the number of participants in the main algorithm and in the sensitivity algorithm (i.e. participants with only two days at Day 1 or Week 10), then a sensitivity analysis will be run.

Stool Frequency

The following formula should be used for calculating the Mayo stool frequency sub score:



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.

Rectal Bleeding

The rectal bleeding sub score will be the average of the daily scores, rounded.

The following table illustrates day selection and RB calculation under different scenarios. The daily score calculated in the example would be reported day -1 for daily scores but used for the calculation of the Partial Mayo score on the Day 1 visit.

Example	**Diary Day**							**Valid days for calculation of scores**	**Notes**	**Average sub-score**	**RB**
	-7	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**				
A	3	1	**2**	**2**	**3**	M	3	-3,-4,-5	Consecutive > recent	2.33	**2**
B	3	**1**	**2**	**2**	M	2	3	-4,-5,-6	Consecutive > recent	1.67	**2**
C	3	1	2	M	**3**	**2**	**3**	-1,-2,-3		2.67	**3**
D	**3**	**1**	**2**	X	E0	E1	3	-5,-6,-7		2.00	**2**
E	**3**	**1**	M	M	X	E0	E1	Missing (primary analysis); -7,-6 (sensitivity analysis)		2.00 (in the sensiti-vity analysis)	**2**
F	3	**1**	M	M	**2**	M	**2**	-1,-3,-6	3 days recent	1.67	**2**
G	**3**	**1**	**2**	M	2	X	E0	-5,-6,-7	Consecutive > recent	2.00	**2**
H	**3**	**1**	**2**	M	2	2	M	-5,-6,-7	Consecutive > recent	2.00	**2**

Example	Diary Day							Valid days for calculation of scores	Notes	Average sub-score	RB
	-7	-6	-5	-4	-3	-2	-1				
I	M	1	M	M	X	E0	E1	Missing		.	.

M = Missing, X = Bowel prep, E0=Endoscopy, E1=Day after endoscopy

Absolute Stool Number

The calculation of absolute stool number will follow the same methodology as the calculation of the rectal bleeding sub score.

Note that the categorisation of Mayo sub scores is defined above along with full Mayo score definitions.

15.6.3.3. Endoscopy scores

Clinical Efficacy

UCEIS

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.

Clinical Efficacy

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

The following endpoint for the UCEIS is to be considered at each visit:

- **UCEIS Total Score**: Sum of all likert scale anchor points scores (this will range from 0 – 8).

15.6.3.4. Histology scores

Geboes

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

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

Robarts Histology Index (RHI)

The RHI will be derived by GSK as an additional tool to measure histologic disease activity using the following two tables to derive the RHI from the Geboes sub-scores.

Mapping of Geboes score to Robarts Criteria

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

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

[redacted]

Robarts Histology Index Conversion from Geboes

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]

The RHI Score is a continuous score, ranging from 0-33 with higher scores indicating more severe disease. The following categorical endpoints are derived from this score:

- "**RHI Remission**" will be defined as an RHI score <= 6
- "**RHI Deep Remission**" will be defined as an RHI score <= 3

Nancy Index

The Nancy Index will be provided by Robarts as an additional tool to measure histological disease activity.

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.

15.6.3.5. Intercurrent Events Selection

If more than one intercurrent event occurs for a subject, then the earliest event will be considered for reporting. If two events occur at the same timepoint, then (for the respective Estimand) the event listed first in the list below will be prioritized:

- Secondary Efficacy Estimand:
  - Discontinuation from IP
  - Valid endoscopy result not available
  - Excluded medication

Note that no distinction is made in the above list between COVID-related discontinuations, discontinuations due to sponsor's decision to terminate the study and other discontinuations, as they are mutually exclusive and a participant can only experience one of these three ICEs. For the same reason, a list for the Primary Efficacy Estimand is not needed.

15.6.4. Safety

Adverse Events
Exposure Adjusted Incidence Rates
o For selected Preferred Terms, the exposure adjusted incidence rate of AEs will be reported within a study phase. Derive the exposure adjusted incidence rate as : Subject months (Person months) = sum of subject total exposure duration in days for a study phase (across all subjects)/30.4375, where subject total exposure duration in days is calculated as below – o if they DO experience the AE, then start date of first AE – treatment start date of the study phase + 1. o if they DO NOT experience the AE, then treatment stop date of the study phase – treatment start date of the study phase + dose specific days (Refer to Section 15.6.2 : Study Population/Duration of Exposure) Number of subjects with event per 100 subject-months = 100*number of subjects with event in the study phase/subject months. Note that an event is only counted once per subject.

ECG Parameters
RR Interval
• If RR interval (msec) is not provided directly, then RR can be derived as: (1/HR)/1000(i.e. 1 / heart rate where the heart rate is taken as part of the ECG) • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.

ECG Parameters
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. QTcF or QTcB values entered by the site will always be presented in output. • IF RR interval (msec) is provided (or can be derived from HR) then missing QTcB and/or QTcF will be derived as: $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ $QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$
Handling of Multiple Measurements
• If multiple ECG findings (interpretations/clinical significance) are collected at the same timepoint and categorised as Normal or Abnormal (Clinically Significant or not), the worst classification for each participant at the timepoint will be used in summary tables.

ECG Parameters
Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. Similarly, if a character value starting with '<=x' or '>=x' is present, x will be used as the corresponding numeric value. o Example 1: 2 decimal places: '< x' becomes x – 0.01 o Example 2: 1 decimal places: '> x' becomes x + 0.1 o Example 3: 0 decimal places: '< x' becomes x – 1 o Example 4: 2 decimal places: '<= x' becomes x o Example 5: 1 decimal places: '>= x' becomes x o Example 6: 0 decimal places: '<= x' becomes x
• Corrected calcium will be calculated, by GSK Biostatistics as: *Corrected Calcium [mmol/L] = Serum Calcium [mmol/L] + 0.02 * (40[g/L] – Serum Albumin[g/L])* Where Normal Serum Albumin = 40 [g/L]
• eGFR (estimated Glomerular Filtration Rate) will be calculated by GSK Biostatistics at all timepoints, this will also be provided directly by the vendor at screening. The GSK calculated value at screening will be used as primary for reporting (e.g. will be used as baseline if appropriate). • The calculation will be as follows: *SI Results MDRD (GFR) (ml/min/1.73m2) = 175 * (PD9S3/88.4)* *power -1.154 * Age power - 0.203 * Race * Sex* *Where PD9S3 = Serum Creatinine (UMOL/L),* *Race = 1.212 for Black & 1.000 for other, Sex = 1.00 for males and 0.742 for females.*

15.6.5. Immunogenicity

Immunogenicity
• A participant will be classed as having persistently positive immunogenicity results within a study phase if they have a positive result for two or more sequential post baseline samples when pre-existing antibodies were not detected, or alternatively two or more sequential post baseline samples where the titre shows a 4 x increase in titre from pre-dose samples. • A participant will be classed as having transient immunogenicity results within a study phase if: o They are not classified as having persistent immunogenicity; and

Immunogenicity
○ They have a positive result for one or more post baseline samples when pre-existing antibodies were not detected, or alternatively one or more post baseline samples where the titre shows a 4 x increase in titre from pre-dose samples.

15.6.6. Pharmacodynamic and Biomarker

Colon Biopsy Cell Counts by Immunofluorescence
The following parameters will be derived for each tissue type.

Derived parameter name	Derivation	Unit
CD3-LAG3+ as % of Total LAG3+	(CD3-LAG3+/ LAG3+) * 100	%
CD3+LAG3+ as % of Total LAG3+	(CD3+LAG3+/ LAG3+) * 100	%
CD3+	CD3+ / tissue area	cells / mm2
LAG3+	LAG3+ / tissue area	cells / mm2
CD3+LAG3+	CD3+LAG3+ / tissue area	cells / mm2
CD3-LAG3+	CD3-LAG3+ / tissue area	cells / mm2
CD3+LAG3-	CD3+LAG3- / tissue area	cells / mm2
Raw data from colon biopsies using CD3/LAG3 co-stain		

15.7. Appendix 7: Reporting Standards for Missing Data

15.7.1. Premature Withdrawals

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Participant study completion (i.e. as specified in the protocol) was defined as a participant who has completed all phases of the study including the last scheduled assessment.
A Week 10 completer will be defined as a participant that has a Week 10 assessment of the Complete 4-domain Mayo score.
For the purposes of describing the disposition of participants, the participant will be defined as having ‘completed’ the study phase when they take the first dose of the next phase or, for the final phase, have an assessment on the last visit. These events are summarised below:

<table>
<tr><th>Phase</th><th>Event used in definition of completion</th></tr>
<tr><td>Induction phase completion</td><td>First SC dose for Extended Treatment Phase or

first IV dose for Open Label Induction Phase</td></tr>
<tr><td>Extended treatment phase completion</td><td>Any assessment at Week 30 visit</td></tr>
<tr><td>Open Label Induction phase</td><td>First SC dose for Open Label Extended Treatment Phase</td></tr>
<tr><td>Open Label Extended Treatment phase</td><td>Any assessment at OL Week 42 visit</td></tr>
</table>

If a participant does not continue into the next phase by receiving treatment, they will be considered as ‘withdrawn’ from the previous phase.
All available data from participants who were withdrawn from the study will be listed and all available planned data will be considered for inclusion in summary tables and figures according to the same rules as non-withdrawn participants, unless otherwise specified.
Early Withdrawal visits will be mapped as specified in Appendix 3: Assessment Windows.

Note that estimands and analysis population definitions may exclude these participants from some outputs.

</td></tr>
</table>

15.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data are not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.

Element	Reporting Detail
	○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

15.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Treatment Phases and Study Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the end date of On-Treatment period in which case the On-Treatment Period end date will be used. ○ Note that AEs with completely missing dates will not be allowed.
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

15.8. Appendix 8: Values of Potential Clinical Importance

15.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male	0.201	0.599
		Female	0.201	0.599
Hemoglobin	g/L	Male	80	180
		Female	80	180
		Δ from BL	↓25	
Lymphocytes	GI/L		0.8	
Neutrophils Absolute	GI/L		1.5	
Platelet Count	GI/L		100	550
White Blood Cell Count (WBC)	GI/L		3	20
Eosinophil	GI/L			>=1

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	55
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 26
Glucose	mmol/L		3.5	7.9
eGFR	Ml/min/1.73m^2		60	
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total protein	g/L		50	85
Urea nitrogen	mmol/L			10.5
CRP	Mg/L			30

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

15.8.2. Urinalysis

Urinalysis			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
Bilirubin		High	>1+
Glucose		High	>1+
Ketone		High	>2+
Leukocytes (dipstick)		High	>1+
Nitrite		High	Positive
Occult blood (dipstick)		High	>1+
pH		Low	<4.6
		High	>8
Protein		High	>1+
RBC (microscopy)	cells/hpf	High	>3
Specific gravity		Low	<1.001
		High	>1.035
Urobilinogen	mg/dL	High	>1
WBC (microscopy)	cells/hpf	High	>5

15.8.3. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec	> 30	≤ 59
	msec	≥ 60	

Categories for QTc summaries			
ECG Parameter	**Units**	**Range for each category**	
		Lower	**Upper**
Absolute			
Absolute QTcB and QTcF Interval	msec	< 450	
		≥ 450	≤ 479
		≥ 480	≤ 499
		≥ 500	
Change from Baseline			
Change from Baseline in QTcB and QTcF	msec	< 30	
		≥ 30	≤ 59

Categories for QTc summaries			
ECG Parameter	Units	Range for each category	
		Lower	Upper
		≥ 60	

Note that < 450 msec in Absolute and <30 msec in Change from Baseline QTcB/QTcF are not of clinical concern

15.8.4. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110
Temperature	C	< 35	> 38

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
Systolic Blood Pressure	mmHg		≥ 40		≥ 40
Diastolic Blood Pressure	mmHg		≥ 20		≥ 20
Heart Rate	bpm		≥ 30		≥ 30

15.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

15.9.1. Population Pharmacokinetic (PopPK) Dataset Specification

The dataset specification for the PopPK analysis will be described in a separate document.

15.9.2. Population Pharmacokinetic (PopPK) Methodology

An exploratory graphical analysis of the drug plasma and sLAG3 concentration-time data will be performed by generating the plots as presented in Appendix 12.

A previous PopPK model developed from the first-time in human study 200630 (GSK Document Number 2017N352860_00), incorporating linear and non-linear (target mediated drug disposition (TMDD), Michaelis-Menten) elimination pathways, will be used to fit the drug plasma concentration-time data. The model will be updated to describe the absorption profiles after SC doses of GSK2831781. For this update it will be assumed that the distribution and elimination of GSK2831781 will be the same regardless of the route of administration (IV or SC).

The appropriateness of the updated model will be assessed by the objective function value (OFV), successful convergence, covariance estimation, shrinkage, parameter uncertainty, and standard Goodness-of-Fit (GoF).

The GoF plots may include, but are not limited to:

- Population and individual predictions versus observations
- Conditional weighted residuals versus population predictions and time

If a Visual Predictive Check (VPC) is done, this will be based on 1000 simulations with the model and the design structure of the observed data (i.e. dose level and time, route of administration, time of PK sampling and individual values of model covariates, if any). The median and the 10th and 90th will be compared to the observed data. Stratification by dose level, treatment group and model covariates, if any, will be used. VPC's may also be presented stratified by geographic ancestry.

The individual PK parameters will be computed from the PopPK model for further PK/PD analysis.

15.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

15.10.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

The dataset specification for the PK/PD analysis will be described in a separate document.

15.10.2. Pharmacokinetic / Pharmacodynamic Methodology

An exploratory graphical analysis of the drug effect on $LAG3^+$ T cell depletion in blood and colon biopsies, and clinical effect (partial Mayo Score) will be performed by generating the plots as presented in Appendix 12.

PK/PD Analysis of $LAG3^+$ T Cell Depletion in Blood

A previous indirect response model developed from all available cell depletion data in blood from the first-time in human study 200630 (GSK Document Number 2017N352860_00) will be fitted to the current $LAG3^+$ T cell data in blood using the nonlinear mixed effects modelling software NONMEM. Data relative to $CD4^+CD45RA^-REA351^+$ cell count will be used to model T cell depletion.

The appropriateness of the PopPK/PD model will be assessed by the OFV, successful convergence, covariance estimation, shrinkage, parameter uncertainty, and standard GoF.

The GoF plots may include, but are not limited to:

- Population and individual predictions versus observations
- Conditional weighted residuals versus population predictions and time

If a Visual Predictive Check (VPC) is done, this will be based on 1000 simulations with the model and the design structure of the observed data (i.e. dose level and time, route of administration, time of PD sampling and individual values of model covariates, if any). The median and the 10th and 90th will be compared to the observed data. Stratification by dose level, treatment group and model covariates, if any, will be used. VPC's may also be presented stratified by geographic ancestry.

PK/PD Analysis of $LAG3^+$ Cell Depletion in Colon Biopsies

Data relative to $CD3^+LAG3^+$ cell count will be used to model T cell depletion in colon using the nonlinear mixed effects modelling software NONMEM

The initial PK/PD model of choice for the effect of GSK2831781 on T cell depletion in colon will be an Emax model. Further model development will be data driven.

The appropriateness of the PopPK/PD model will be assessed by the OFV, successful convergence, covariance estimation, shrinkage, parameter uncertainty, and standard GoF.

The GoF plots may include, but are not limited to:

- Population and individual predictions versus observations
- Conditional weighted residuals versus population predictions and time

If a Visual Predictive Check (VPC) is done, this will be based on 1000 simulations with the model and the design structure of the observed data (i.e. dose level and time, route of administration, time of PD sampling and individual values of model covariates, if any). The median and the 10th and 90th will be compared to the observed data. Stratification by dose level, treatment group and model covariates, if any, will be used. VPC's may also be presented stratified by geographic ancestry.

Exposure/Response Analysis of Complete Mayo Score

Data relative to Complete Mayo Score will be used to model the relationship between exposure (PK) and clinical efficacy using the nonlinear mixed effects modelling software NONMEM.

The initial PK/PD model of choice for this model will be an Emax model. Further model development will be data driven.

The appropriateness of the exposure/response model will be assessed by the OFV, successful convergence, covariance estimation, shrinkage, parameter uncertainty, and standard GoF.

The GoF plots may include, but are not limited to:

- Population and individual predictions versus observations
- Conditional weighted residuals versus population predictions and time

If a Visual Predictive Check (VPC) is done, this will be based on 1000 simulations with the model and the design structure of the observed data (i.e. dose level and time, route of administration, time of Complete Mayo Score observations and individual values of model covariates, if any). The median and the 10th and 90th will be compared to the observed data. Stratification by dose level, treatment group and model covariates, if any, will be used. VPC's may also be presented stratified by geographic ancestry.

15.11. Appendix 11: Abbreviations & Trademarks

15.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CRP	C-Reactive Protein
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DB	Double Blind
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DRC	Data Review Committee
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
ETP	Extended Treatment Phase
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
H0	Null hypothesis
HA	Alternative hypothesis
IA	Interim Analysis
IBDQ	Inflammatory Bowel Disease Questionnaire
ICE	Intercurrent Event
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITTE	Intent-To-Treat (Exposed)
IV	Intravenous
LAG3	Lymphocyte activation gene-3
MMRM	Mixed Model Repeated Measures
OL	Open Label
OL ETP	Open Label Extended Treatment Phase

Abbreviation	Description
OLIP	Open Label Induction Phase
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PGA	Physician's Global Assessment
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PPI	Per Protocol Induction
PPE	Per Protocol Extended Treatment Phase
PopPK	Population PK
PRO	Patient Reported Outcome
RB	Rectal Bleeding
SC	Subcutaneous
SF	Stool frequency
SF36	Short Form Health Survey 36
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RHI	Robarts Histology Index
sLAG3	Soluble lymphocyte activation gene-3
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	Upper Limit of Normal
WBC	White blood cells

15.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

15.12. Appendix 12: List of Data Displays

15.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Population Pharmacokinetic (PopPK)	5.1 to 5.n	5.1 to 5.n
Pharmacodynamic and / or Biomarker	6.1 to 6.n	6.1 to 6.n
Pharmacokinetic / Pharmacodynamic	7.1 to 7.n	7.1 to 7.n
Patient Reported Outcomes	8.1 to 8.n	8.1 to 8.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

15.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln
Patient Reported Outcomes (PRO)	PRO_Fn	PRO_Tn	PRO_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

15.12.3. Deliverables

Delivery [Priority]	Description	Additional details
N30	N=30 at 2 weeks, blinded safety summary	For Hungarian ethics/regulatory committee
IA2	Interim Analysis 2 Statistical Analysis Complete	Note that for interim analyses
IA3 H	Interim Analysis 3 Headline	

Delivery [Priority]	Description	Additional details
IA3	Interim Analysis 3 Statistical Analysis Complete	reporting efficacy, outputs in the efficacy domain produced by Biostatistics will only be reported for participants who have completed the induction phase (i.e. completed Week 10 visit)
IA4	Interim Analysis 4 Statistical Analysis Complete	
PC	Primary Completion Statistical Analysis Complete	
PC [2]	Primary Completion Statistical Analysis Complete if development will continue	
SAC	Final Statistical Analysis Complete	
None	Displays planned in previous versions of the RAP and removed after study termination decision	

15.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Enrolled	ES1	Summary of Subject Disposition for the Subject Conclusion Record	ICH E3, FDAAA, EudraCT Programming note: this is a summary of all subjects across all study phases. Use dose level and method to record last dose subject was taking at withdrawal/conclusion. Footnote "Withdrawal recorded against dose allocated at randomization"	SAC
1.2.	Enrolled	ES4	Summary of Subject Disposition at Induction Phase	ICH E3 Five induction doses as columns Footnote "A subject completes the induction phase when they receive the first dose of the subsequent phase"	SAC
1.3.	Enrolled	ES4	Summary of Subject Disposition in Post-Induction Phases	ICH E3 Programming note: Four doses in columns. OL IV and OL SC will be associated with those phases so there will be blank cells off the diagonal. Footnote "A subject completes the phase when they receive the first dose of the subsequent phase or the final visit in the ETP / OL ETP"	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.4.	Enrolled	ES5	Summary of Reasons for Study Withdrawal in Induction Phase	Five induction doses as columns	SAC
1.5.	Enrolled	ES5	Summary of Reasons for Study Withdrawal in Post-Induction Phases	Programming note: Four doses in columns. OL IV and OL SC will be associated with those phases so there will be blank cells off the diagonal.	SAC
1.6.	Enrolled	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment in Induction Phase	ICH E3 Reviewer's note: This table summarises reasons for treatment discontinuation. Reasons for withdrawal are summarised in the table above	IA3H, SAC
1.7.	Enrolled	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment in Post-Induction Phases	ICH E3 Reviewer's note: This table summarises reasons for treatment discontinuation. Reasons for withdrawal are summarised in the table above	SAC
1.8.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.9.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID	EudraCT/Clinical Operations	SAC
Protocol Deviation					
1.10.	Screened	DV1	Summary of Important Protocol Deviations in Induction Phase	ICH E3	SAC
1.11.	ITTE_ETP	DV1	Summary of Important Protocol Deviations in Extended Treatment Phase	ICH E3	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.12.	ITTE_OL	DV1	Summary of Important Protocol Deviations in Open Label Induction Phase	ICH E3	SAC
1.13.	ITTE_OL_ETP	DV1	Summary of Important Protocol Deviations in Open Label Extended Treatment Phase	ICH E3	SAC
Population Analysed					
1.14.	Screened	SP1	Summary of Study Populations in Induction Phase	IDSL	SAC
1.15.	Safety_ETP	SP1	Summary of Study Populations in Extended Treatment Phase	IDSL	SAC
1.16.	Safety_OL	SP1	Summary of Study Populations in Open Label Induction Phase	IDSL	SAC
1.17.	Safety_OL_ETP	SP1	Summary of Study Populations in Open Label Extended Treatment Phase	IDSL	SAC
1.18.	ITTE	SP2	Summary of Protocol Deviations Leading to Exclusion from the Per Protocol Population	IDSL	None
1.19.	ITTE_ETP	SP2	Summary of Protocol Deviations Leading to Exclusion from the Per Protocol ETP Population	IDSL	None
Demographic and Baseline Characteristics					
1.20.	Safety	DM1	Blinded Summary of Demographic Characteristics		N30
1.21.	ITTE	DM1	Summary of Demographic Characteristics in Induction Phase	ICH E3, FDAAA, EudraCT Add smoker status ("Currently Smoke" from SU1)	IA3H, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.22.	ITTE_ETP	DM1	Summary of Demographic Characteristics in Extended Treatment Phase	ICH E3, Consort	SAC
1.23.	ITTE_OL	DM1	Summary of Demographic Characteristics in Open Label Induction Phase	ICH E3, Consort	SAC
1.24.	ITTE_OL_ETP	DM1	Summary of Demographic Characteristics in Open Label Extended Treatment Phase	ICH E3, Consort	SAC
1.25.	Enrolled	DM11	Summary of Age Ranges by Induction Phase Treatment	Rationale: EudraCT (requires enrolled population)	SAC
1.26.	Safety	DM5	Summary of Race and Racial Combinations by Induction Phase Treatment	ICH E3, FDA, FDAAA, EudraCT	SAC
Medical History					
1.27.	ITTE	MH1	Summary of Current and Past Medical Conditions by Induction Phase Treatment	ICH E3	SAC
1.28.	ITTE	POP_T1	Summary of Ulcerative Colitis Disease Characteristics at Baseline in Induction Phase	Include Complete and Adapted Mayo	IA3H, SAC
Prior and Concomitant Medications					
1.29.	ITTE	CM1	Summary of Concomitant Medications taken in Induction Phase	ICH E3 Note that prior medications should only be UC medical history and are reported in a separate table below	SAC
1.30.	ITTE_ETP	CM1	Summary of Concomitant Medications taken in Extended Treatment Phase		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.31.	ITTE_OL	CM1	Summary of Concomitant Medications taken in Open Label Induction Phase		SAC
1.32.	ITTE_OL_ETP	CM1	Summary of Concomitant Medications taken in Open Label Extended Treatment Phase		SAC
1.33.	ITTE	POP_T2	Summary of Ulcerative Colitis Therapeutic History for Induction Treatment Phase Subjects		IA3H, SAC
1.34.	ITTE_ETP	POP_T2	Summary of Ulcerative Colitis Therapeutic History for Extended Treatment Phase Subjects		SAC
Exposure and Treatment Compliance					
1.35.	Safety	EX5	Blinded Summary of Exposure to Study Treatment in Induction Phase	Programmers: Summarise number of doses received in the study phase.	N30
1.36.	ITTE	Take elements from EX1 and EX5	Summary of Exposure to Study Treatment in Induction Phase	ICH E3 **Length of exposure (days)** within study phase and in the study **Cumulative dose (mg)** [in shell EX1] report cumulative dose only for current study phase Summarise **number of doses received** as categorical [replaces cycles, shell EX5] (use levels 1, 2, 3, 4 doses). Footnotes: ““Dose” is planned dosing events, not number of injections, and includes partial doses.”	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.37.	ITTE_ETP	EX1 and EX5	Summary of Exposure to Study Treatment in Extended Treatment Phase	ICH E3 Items as for induction phase, except for length of exposure in the study. Footnote: "Exposure is summarised within the current study phase except where specified. "Dose" is planned dosing events, not number of injections, and includes partial doses."	SAC
1.38.	ITTE_OL_I	EX1 and EX5	Summary of Exposure to Study Treatment in Open Label Induction Phase	ICH E3 Items as for induction phase, except for length of exposure in the study. Footnote: "Exposure is summarised within the current study phase. "Dose" is planned dosing events, not number of injections, and includes partial doses."	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.39.	ITTE_OL_ETP	EX1 and EX5	Summary of Exposure to Study Treatment in Open Label Extended Treatment Phase	ICH E3 Items as for induction phase, except for length of exposure in the study. Footnote: "Exposure is summarised within the current study phase. "Dose" is planned dosing events, not number of injections, and includes partial doses."	SAC

15.12.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Clinical Efficacy – Continuous endpoints					
2.1.	PPI	PD1	Summary of Mayo Score by Endpoint – Induction Phase Per Protocol Analysis	Produce table by absolute and change from baseline for the following endpoints: Complete Mayo score, Adapted Mayo Score and Partial Mayo Score for each relevant timepoint (partial Mayo reported more frequently) Change from shell: replace SD with SE on shell	None

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.2.	ITTE	PD1	Summary of Mayo Score by Endpoint in Induction Phase - Observed	Produce table by absolute and change from baseline for the following endpoints: Complete Mayo score, Adapted Mayo Score, Adapted Mayo Endoscopic Score and Partial Mayo Score for each relevant timepoint (partial Mayo reported more frequently) Change from shell: replace SD with SE on shell	SAC
2.3.	ITTE ETP	PD1	Summary of Mayo Score by Endpoint – Extended Treatment Phase	Endpoints as above. Change from shell: replace SD with SE on shell	None
2.4.	ITTE ETP	PD1	Summary of Mayo Score by Endpoint – Extended Treatment Phase (by Induction Dose)	Condition ETP efficacy summaries on induction treatment dose. Endpoints as above. Change from shell: replace SD with SE on shell	None
2.5.	ITTE_OL_I	PD1	Summary of Mayo Score by Endpoint – Open Label Induction	Endpoints as above. Change from shell: replace SD with SE on shell	None
2.6.	ITTE_OL_ETP	PD1	Summary of Mayo Score by Endpoint – Open Label Extended Treatment Phase	. Change from shell: replace SD with SE on shell	None

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.7.	ITTE	PD1	Summary of Daily Diary Scores at Selected Timepoints in Induction Phase	By endpoint Every third day from Study Day 3 until Study Day 21, then every week i.e. Day 28, 35, 42, 56, 63, 70) Endpoints: Stool Frequency sub-score Rectal Bleeding sub-score	SAC
2.8.	ITTE	PD1	Summary of UCEIS Total Score in Induction Phase - Observed		SAC
2.9.	ITTE ETP	PD1	Summary of UCEIS Total Score – Extended Treatment Phase		None
2.10.	ITTE_OL_I	PD1	Summary of UCEIS Total Score – Open Label Induction		None
2.11.	PPI	EFF_T1	Statistical Analysis of Dose Response Relationship for Complete Mayo Score – Per Protocol Population		None
2.12.	ITTE	EFF_T1	Statistical Analysis of Complete Mayo Score in Induction Phase	SAC: Change from Baseline in Complete Mayo Score at Week 10	SAC
2.13.	ITTE	EFF_T1	Statistical Analysis of Dose Response Relationship for Mayo Score by subgroup in Induction Phase	Complete Mayo Score only Subgroups: • Advanced therapy experience • • Race • Race2 •	None

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.14.	ITTE	PRO_T02	Statistical Analysis of Absolute and Change from Baseline in Partial Mayo Score in Induction Phase	By Endpoint then visit Note: Repeated measures, Bayesian	SAC
Corticosteroid use					
2.15.	ITTE_ETP	EFF_T06	Summary of Corticosteroid Use After Mandatory Taper in Extended Treatment Phase	Add footnote: "Note: Average Daily Prednisolone Equivalent Dose is calculated from the start of the taper to the end of the study phase. Note that the taper starts at Week 12 and the Extended Treatment Phase (ETP) starts at Week 14. subjects that start the taper but don't start the ETP are not included in this summary and are listed separately"	None
2.16.	ITTE_OL_ETP	EFF_T6	Summary of Corticosteroid Use After Mandatory Taper in Open Label Extended Treatment Phase	Add footnote: "Note: Average Daily Prednisolone Equivalent Dose is calculated from the start of the taper to the end of the study phase. Note that the taper starts at Week 24 and the Open Label Extended Treatment Phase (OL ETP) starts at Week 26. Subjects that start the taper but don't start the OL ETP are not included in this summary and are listed separately"	None

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Clinical Efficacy – Categorical Endpoints					
2.17.	ITTE	EFF_T2	Summary of Categorical Efficacy by Endpoint in Induction Phase - Observed	Report by endpoint, visit. Report the endpoints below at different interims. Additionally, report summaries by each level of advanced therapy experience' and 'all' Endoscopic Improvement, Clinical Remission (Adapted Mayo), Symptomatic Remission, Endoscopic Remission	IA3H, SAC
2.18.	ITTE ETP	EFF_T2	Summary of Categorical Efficacy by Endpoint in Extended Treatment Phase	Report by endpoint, visit. Include the following ETP only endpoints: • Maintained Clinical Response (Week 10 to 30 Adapted Mayo) • Maintained Clinical Remission (Week 10 to 30 Adapted Mayo • Steroid Free Clinical Remission • Maintained Steroid Free Clinical Remission	None
2.19.	ITTE_OL_I	EFF_T2	Summary of Categorical Efficacy by Endpoint in Open Label Phase	Report by endpoint, visit.	None
2.20.	ITTE_OL_ETP	EFF_T2	Summary of Categorical Efficacy by Endpoint in Open Label Extended Treatment Phase	Report by endpoint, visit. •	None

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.21.	ITTE	EFF_T7	Statistical Analysis of Categorical Efficacy in Induction Phase	Report the endpoints below, Induction phase only: Endoscopic Improvement, Clinical Remission Also report estimate for each level of 'Advanced Therapy experience' (i.e. subgroup)	IA3H, SAC
2.22.	ITTE	EFF_T7	Statistical Analysis of Categorical Efficacy in Induction Phase – Sub Group	Endoscopic Improvement and Clinical Remission only. Subgroup for each level of stratification factor (advanced therapy experience) Full population: • Subgroup Race and Race2 Sub-population of biologic experience: • Biologic experience type Sub-population of TNF failure • TNF failure mechanisms •	None

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.23.	ITTE	EFF_T3	Statistical Analysis of Dose Response Relationship for Categorical Endpoints	By Endpoint then estimand. • Endoscopic Improvement (IA4 and PC) • Endoscopic Improvement, Clinical Response, Clinical Remission, (PC only) • Present analysis results for both 'Treatment Policy' and 'Hypothetical' estimands if conducted	None
Histological assessments					
2.24.	ITTE	EFF_T2	Summary of Categorical Histology at each Dose Level by Endpoint in Induction Phase	Report by endpoint, visit. Geboes Histological Remission RHI Remission RHI Deep Remission Nancy Index Remission	SAC
2.25.	ITTE ETP	EFF_T2	Summary of Categorical Histology by Endpoint in Extended Treatment Phase	Report by endpoint, visit.	None

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Extra Intestinal Manifestations					
2.26.	ITTE	EFF_T4	Summary of Extra Intestinal Manifestations (EIMs) - Incidents by Severity, across Study Phases.	For EIMs without severity (Peripheral Arthritis and Axial Arthropathy) set levels of severity to missing Slot early withdrawal visits to next EIM visit (there is one EIM visit at the end of each study phase) Summary is cross-phase: Report by treatment sequence, not by treatment in an individual study phase	None
Continuous Efficacy – Pairwise Statistical Analysis					
2.27.	ITTE	EFF_T5	Statistical Analysis of Change from Baseline in Complete Mayo Score in Induction Phase		IA3H
Summaries of Efficacy after Estimand Imputations					
2.28.	ITTE	EFF_T2	Summary of Categorical Efficacy by Endpoint in Induction Phase - Estimands		IA3H, SAC
2.29.	ITTE	PD1	Summary of Mayo Score by Endpoint in Induction Phase - Estimands		SAC
2.30.	ITTE	PD1	Summary of UCEIS Total Score in Induction Phase - Estimands		SAC

15.12.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Continuous Efficacy					
2.1.	ITTE	EFF_F01	Forest plot of Observed Mayo Score Change from Baseline	By "Overall" then Advanced Therapy Experience level then by endpoint: Complete, Adapted, Partial (at matching timepoint only). Note: categorical axis shows dose level.	SAC
2.2.	ITTE	EFF_F02	Forest plot of Estimated Difference from Placebo in Mayo Score Change from Baseline	By "Overall" then Advanced Therapy Experience level then by endpoint: Complete, Adapted, Partial (Partial at matching timepoint only). Note: categorical axis shows dose level	SAC
2.3.	IIT_ETP	EFF_F01	Forest plot of Observed Mayo Score Change from Baseline – Extended Treatment Phase	By "Overall" then Advanced Therapy level then **panelled by endpoint:** Complete, Adapted, Partial (Partial at matching timepoint only). Note: categorical axis shows (both) dose levels	None
2.4.	ITTE	Study 200630, Figure 2.5	Mean (±SE) Plot of Partial Mayo Score over time in induction phase	By dose Page by Absolute and Change from Baseline	SAC
2.5.	IIT_ETP	EFF_F01	Forest plot of Observed UCEIS Total Score – Induction Phase	By "Overall" then Advanced Therapy Experience level Note: categorical axis shows dose level	None

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Categorical Efficacy					
2.6.	ITTE	EFF_F03	Forest plot of Proportions for Categorical Endpoints in Induction Phase - Observed	Panel by Endpoint, then Visit, then Dose. Subgroup (within panel) Advanced Therapy Experience level (Note that proportions / odds ratios are on the same scale across endpoints).	IA3H, SAC
2.7.	ITTE	EFF_F04	Forest Plot for Estimated Response Rates for Categorical Endpoints in Induction Phase	Panel by Endpoint, then Visit, then Dose, then rate/delta. Subgroup (within panel) Advanced Therapy Experience level (Note that proportions / odds ratios are on the same scale across endpoints). Endoscopic Improvement and Clinical Remission	IA3H, SAC
2.8.	ITTE_ETP	EFF_F03	Forest plot of Observed Proportions for Categorical Endpoints in Extended Treatment Phase	Panel by Endpoint, then Visit, then Dose. Subgroup (within panel) Advanced Therapy Experience level (Note that proportions / odds ratios are on the same scale across endpoints). **Some reporting efforts will not report all endpoints.** Footnote: Median and equal tailed credible intervals using non-informative priors in a beta-binomial model.	None

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.9.	ITTE	EFF_F03	Forest plot of Proportions for Categorical Endpoints in Induction Phase - Estimands		IA3H, SAC
Daily Diary Scores					
2.10.	ITTE	EFF_F05	Mean (+/-SE) Plot of Daily Diary Scores in Induction Phase	Intervals of 3 days in the x-axis	SAC
2.11.	ITTE	EFF_F06	Plot of Daily Diary Scores for Individual Subjects in Induction Phase - Subgroups	Use the non-rounded versions of derived Rectal Bleeding and Absolute Stool Number Show patients with Discontinuation and Ulcerative Colitis AEs in induction as a separate groups; Intervals of 3 days in the x-axis	SAC

15.12.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE5A	Summary of All Adverse Events by Intensity, System Organ Class and Preferred Term in Induction Phase	N30: blinded output, do not report treatment group.	N30, SAC
3.2.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term in Induction Phase	ICH E3 Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	On request by DRC and SAC
3.3.	Safety ETP	AE5A	Summary of All Adverse Events by Intensity, System Organ Class and Preferred Term in Extended Treatment Phase	Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	On request by DRC and SAC
3.4.	Safety OL I	AE5A	Summary of All Adverse Events by Intensity, System Organ Class and Preferred Term for Open Label Induction Phase	Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	On request by DRC and SAC
3.5.	Safety OL ETP	AE5A	Summary of All Adverse Events by Intensity, System Organ Class and Preferred Term for Open Label Extended Treatment Phase	Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	On request by DRC and SAC
3.6.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency for Induction Phase	Rationale: ICH E3 Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	SAC
3.7.	Safety ETP	AE3	*As above for Extended Treatment Phase*		None
3.8.	Safety OL I	AE3	*As above for Open Label Induction Phase*		None
3.9.	Safety OL ETP	AE3	*As above for Open Label Extended Treatment Phase*		None

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.10.	Safety	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term for Induction Phase	Rationale: ICH E3 Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	SAC
3.11.	Safety ETP	AE1	*As above for Extended Treatment Phase*		SAC
3.12.	Safety OL I	AE1	*As above for Open Label Induction Phase*		SAC
3.13.	Safety OL ETP	AE1	*As above for Open Label Extended Treatment Phase*		SAC
3.14.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) for Induction Phase	Rationale: disclosure for FDAAA, EudraCT Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	SAC
3.15.	Safety ETP	AE15	Summary of Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) for Extended Treatment Phase		SAC
3.16.	Safety OL I	AE15	*As above for Open Label Induction Phase*		SAC
3.17.	Safety OL ETP	AE15	*As above for Open Label Extended Treatment Phase*		SAC
Serious and Other Significant Adverse Events					
3.18.	Safety	AE16	Blinded summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) for Induction Phase	This is a blinded output, do not report treatment group.	N30

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.19.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) for Induction Phase	Rationale: disclosure for FDAAA, EudraCT Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	SAC
3.20.	Safety ETP	AE16	*As above for Extended Treatment Phase*		SAC
3.21.	Safety OL I	AE16	*As above for Open Label Induction Phase*		SAC
3.22.	Safety OL ETP	AE16	*As above for Open Label Extended Treatment Phase*		SAC
3.23.	Safety	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Overall Frequency for Induction Phase	IDSL Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	SAC
3.24.	Safety ETP	AE3	*As above for Extended Treatment Phase*		None
3.25.	Safety OL I	AE3	*As above for Open Label Induction Phase*		None
3.26.	Safety OL ETP	AE3	*As above for Open Label Extended Treatment Phase*		None
Laboratory: Chemistry					
3.27.	Safety	LB1	Summary of Chemistry Changes from Baseline for Induction Phase	Rationale: ICH E3	SAC
3.28.	Safety ETP	LB1	*As above for Extended Treatment Phase*	Rationale: ICH E3	SAC
3.29.	Safety OL I	LB1	*As above for Open Label Induction Phase*	Rationale: ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.30.	Safety OL ETP	LB1	*As above for Open Label Extended Treatment Phase*	Rationale: ICH E3	SAC
3.31.	Safety	LB17	Summary of Worst-Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline for Induction Phase	Rationale: ICH E3 and disclosure	SAC
3.32.	Safety ETP	LB17	Summary of Worst-Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline for Extended Treatment Phase	Rationale: ICH E3 Footnote: "Note: Induction phase baseline used"	SAC
3.33.	Safety OL I	LB17	Summary of Worst-Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline for Open Label Induction Phase	Rationale: ICH E3 Footnote: "Note: Induction phase baseline used"	SAC
3.34.	Safety OL ETP	LB17	Summary of Worst-Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline for Open Label Extended Treatment Phase	Rationale: ICH E3 Footnote: "Note: Induction phase baseline used"	SAC
Laboratory: Haematology					
3.35.	Safety	LB1	Summary of Haematology Changes from Baseline for Induction Phase	Rationale: ICH E3	SAC
3.36.	Safety ETP	LB1	*As above for Extended Treatment Phase*	Rationale: ICH E3	SAC
3.37.	Safety OL I	LB1	*As above for Open Label Induction Phase*	Rationale: ICH E3	SAC
3.38.	Safety OL ETP	LB1	*As above for Open Label Extended Treatment Phase*	Rationale: ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.39.	Safety	LB17	Summary of Worst-Case Haematology Results by PCI Criteria Post-Baseline Relative to Baseline for Induction Phase	Rationale: ICH E3 and disclosure	SAC
3.40.	Safety ETP	LB17	Summary of Worst-Case Haematology Results by PCI Criteria Post-Baseline Relative to Baseline for Extended Treatment Phase	Rationale: ICH E3 Footnote: "Note: Induction phase baseline used"	SAC
3.41.	Safety OL I	LB17	Summary of Worst-Case Haematology Results by PCI Criteria Post-Baseline Relative to Baseline for Open Label Induction Phase	Rationale: ICH E3 Footnote: "Note: Induction phase baseline used"	SAC
3.42.	Safety OL ETP	LB17	Summary of Worst-Case Haematology Results by PCI Criteria Post-Baseline Relative to Baseline for Open Label Extended Treatment Phase	Rationale: ICH E3 Footnote: "Note: Induction phase baseline used"	SAC
Laboratory: Urinalysis					
3.43.	Safety	UR1	Summary of Worst-Case Urinalysis Results by PCI Criteria Post-Baseline Relative to Baseline for Induction Phase	ICH E3	SAC
3.44.	Safety ETP	UR1	Summary of Worst-Case Urinalysis Results by PCI Criteria Post-Baseline Relative to Baseline for Extended Treatment Phase	ICH E3	SAC
3.45.	Safety OL I	UR1	Summary of Worst-Case Urinalysis Results by PCI Criteria Post-Baseline Relative to Baseline for Open Label Induction Phase	ICH E3	SAC
3.46.	Safety OL ETP	UR1	Summary of Worst-Case Urinalysis Results by PCI Criteria Post-Baseline Relative to Baseline for Open Label Extended Treatment Phase	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
3.47.	Safety	EG1	Summary of ECG Findings for Induction Phase	IDSL	SAC
3.48.	Safety ETP	EG1	*As above for Extended Treatment Phase*		SAC
3.49.	Safety OL I	EG1	*As above for Open Label Induction Phase*		SAC
3.50.	Safety OL ETP	EG1	*As above for Open Label Extended Treatment Phase*		SAC
3.51.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit for Induction Phase		None
3.52.	Safety ETP	EG2	*As above for Extended Treatment Phase*		None
3.53.	Safety OL I	EG2	*As above for Open Label Induction Phase*		None
3.54.	Safety OL ETP	EG2	*As above for Open Label Extended Treatment Phase*		None
3.55.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category for Induction Phase	IDSL	SAC
3.56.	Safety ETP	EG10	*As above for Extended Treatment Phase*	Footnote: “Note: Induction phase baseline used”	SAC
3.57.	Safety OL I	EG10	*As above for Open Label Induction Phase*	Footnote: “Note: Induction phase baseline used”	SAC
3.58.	Safety OL ETP	EG10	*As above for Open Label Extended Treatment Phase*	Footnote: “Note: Induction phase baseline used”	SAC
3.59.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category for Induction Phase	Rationale: disclosure IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.60.	Safety ETP	EG11	*As above for Extended Treatment Phase*	Footnote: "Note: Induction phase baseline used"	SAC
3.61.	Safety OL I	EG11	*As above for Open Label Induction Phase*	Footnote: "Note: Induction phase baseline used"	SAC
3.62.	Safety OL ETP	EG11	*As above for Open Label Extended Treatment Phase*	Footnote: "Note: Induction phase baseline used"	SAC
Vital Signs					
3.63.	Safety	VS1	Summary of Change from Baseline in Vital Signs for Induction Phase	ICH E3	SAC
3.64.	Safety ETP	VS1	*As above for Extended Treatment Phase*		SAC
3.65.	Safety OL I	VS1	*As above for Open Label Induction Phase*		SAC
3.66.	Safety OL ETP	VS1	*As above for Open Label Extended Treatment Phase*		SAC
3.67.	Safety	VS7	Summary of Worst-Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline for Induction Phase	IDSL Note: Adjust shell to include temperature (required for disclosure). Use footnote and title of middle category from VS7 (i.e. change 'normal' to 'within range') Include change from baseline for Systolic Blood Pressure, Diastolic Blood Pressure and Heart Rate	SAC
3.68.	Safety ETP	VS7	*As above for Extended Treatment Phase*		SAC
3.69.	Safety OL I	VS7	*As above for Open Label Induction Phase*		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.70.	Safety OL ETP	VS7	*As above for Open Label Extended Treatment Phase*		SAC
Immunogenicity					
3.71.	Safety	sb240563/mid205050/final_02/ Table 3.38	Summary of Confirmed Positive Binding Antibody by Visit for Induction Phase		SAC
3.72.	Safety ETP	sb240563/mid205050/final_02/ Table 3.38	*As above for Extended Treatment Phase*		SAC
3.73.	Safety OL I	sb240563/mid205050/final_02/ Table 3.38	*As above for Open Label Induction Phase*		SAC
3.74.	Safety OL ETP	sb240563/mid205050/final_02/ Table 3.38	*As above for Open Label Extended Treatment Phase*		SAC
3.75.	Safety	sb240563/mid205050/final_02/ Table 3.39	Summary of Confirmed Positive Neutralising Antibody by Visit for Induction Phase		None

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.76.	Safety ETP	sb240563/mid205050/final_02/ Table 3.39	*As above for Extended Treatment Phase*		None
3.77.	Safety OL I	sb240563/mid205050/final_02/ Table 3.39	*As above for Open Label Induction Phase*		None
3.78.	Safety OL ETP	sb240563/mid205050/final_02/ Table 3.39	*As above for Open Label Extended Treatment Phase*		None
Adverse Events – Additional Summaries					
3.79.	Safety	AE17	Summary of Exposure Adjusted Incidence Rates for Adverse Events in Induction Phase	For selected Preferred Terms – 1) All Preferred terms in System Organ class of Infections and Infestations 2) Preferred Term – Colitis Ulcerative	SAC
3.80.	Safety	TTE1	Summary of Time to Ulcerative Colitis Adverse Event in Induction Phase	For selected Preferred Terms – 1) Preferred Term – Colitis Ulcerative	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
COVID-19 Pandemic Impact					
3.81.	Safety	PAN4	Summary of COVID-19 Pandemic Visit Impacts		SAC

15.12.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	AE10	Plot of Common (>=5%) Adverse Events for Induction Phase	Incidence ≥5% on either active or placebo Separate page for each treatment compared to placebo; plus combined treatment compared to placebo Add following footnote and use in programming rules: "Note: All displayed Adverse Events (AEs) have occurrence >= 5% in an active treatment group and the AE has to have at least 1 occurrence in the placebo group for relative risk to be calculated. Only AEs with calculated relative risk are displayed."	SAC
Hepatobiliary (Liver)					
3.2.	Safety	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT for Induction Phase		SAC
3.3.	Safety_ETP	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT for Extended Treatment Phase	Footnote: "Note: Induction phase baseline used"	None
3.4.	Safety_OL_I	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT for Open Label Induction Phase	Footnote: "Note: Induction phase baseline used"	None
3.5.	Safety_OL_ETP	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT for Open Label Extended Treatment Phase	Footnote: "Note: Induction phase baseline used"	None

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.6.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin for Induction Phase		SAC
3.7.	Safety_ETP	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin for Extended Treatment Phase		None
3.8.	Safety_OL_I	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin for Open Label Induction Phase		None
3.9.	Safety_OL_ETP	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin for Open Label Extended Treatment Phase		None

15.12.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK concentration					
4.1.	PK	PKCT1	Summary of Plasma GSK2831781 Concentration-Time Data (ng/mL) for Induction Phase	Note: LLQ=10 ng/mL. SE and 95% CI (Lower, Upper) are set to missing if No. Imputed/n > 0.3.	SAC
4.2.	PK_ETP	PKCT1	Summary of Plasma GSK2831781 Concentration-Time Data (ng/mL) in Extended Treatment Phase	Note: LLQ=10 ng/mL. SE and 95% CI (Lower, Upper) are set to missing if No. Imputed/n > 0.3. Programming note: data should be summarised by dose group of Induction Phase	SAC
4.3.	PK_OL	PKCT1	Summary of Plasma GSK2831781 Concentration-Time Data (ng/mL) in Open Label Induction Phase by Double Blind Induction Treatment	Note: LLQ=10 ng/mL. SE and 95% CI (Lower, Upper) are set to missing if No. Imputed/n > 0.3. Please add a note: “Note that subjects had different doses during the Induction Phase”	SAC
4.4.	PK_OL_ETP	PKCT1	Summary of Plasma GSK2831781 Concentration-Time Data (ng/mL) in Open Label Extended Treatment Phase by Double Blind Induction Treatment	Note: LLQ=10 ng/mL. SE and 95% CI (Lower, Upper) are set to missing if No. Imputed/n > 0.3.	SAC
PK derived parameters					
4.5.	PK_ETP	PK03	Summary of derived plasma GSK2831781 pharmacokinetic parameters in Extended Treatment Phase (SC dosing)		SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.6.	PK_ETP	PK05	Summary of log-transformed derived plasma GSK2831781 pharmacokinetic parameters in Extended Treatment Phase (SC dosing)		SAC

15.12.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK_ETP	PKCF1P	Individual GSK2831781 Plasma Concentration-Time Plot by Subject (Linear and Semi-Log) at Week 14 and Week 15 in Extended Treatment Phase	Note for programmers: Please use only the data from Week 14 and Week 15 – ie from pre-dose at Week 14, until the very last sample at Week 15. Footnote for all PK and PK/PD figures: 'Note: LLQ=10 ng/mL. Values below LLQ have been imputed to 0.' Use actual time (days) as x axis (where days is a continuous variable)	None
4.2.	PK	PKCF4	Mean (+SD) Plasma GSK2831781 Concentration-Time Plots by Treatment (Linear and Semi-log) in Induction Phase (pre-dose samples only)	Use planned time (days) as x axis (where days is a continuous variable) Plot data from all dose groups on 1 graph, colour coded by dose group	None

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.3.	PK_ETP	PKCF4	Mean (+SD) Plasma GSK2831781 Concentration-Time Plots (Linear and Semi-Log) in Extended Treatment Phase (pre-dose samples only)	Use planned time (days) as x axis (where days is a continuous variable) Add footnote "Note: samples are taken pre-dose, **and do not include Week 14 and 15 samples**" Plot all data on 1 graph, colour coded by dose group of Induction Phase	None
4.4.	PK_ETP	PKCF4	Mean (+SD) Plasma GSK2831781 Concentration-Time Plots (Linear and Semi-Log) in Extended Treatment Phase (Week 14 and Week 15 only)	Use planned time (days) as x axis (Weeks 14 and 15 only) (where days is a continuous variable) Add footnote "Sub-set of subjects with post-dose samples taken according to one of two protocol defined schedules are plotted."	None
4.5.	PK_OL	PKCF4	Mean (+SD) Plasma GSK2831781 Concentration-Time Plots (Linear and Semi-Log) in Open Label Induction Phase (pre-dose samples only)	Use planned time (days) as x axis (where days is a continuous variable) tick marks for Week 12 and Week 22 only. Add x-axis jitter if necessary to separate points	None
4.6.	PK	201246/final/ Figure 4.9	Mean (+SD) Plasma GSK2831781 Concentration-Time Plots grouped by Treatment (Linear and Semi-log) in Induction Phase	As Figure 4.3 but on a single page, grouped by treatment. See Figure 4.9 and Figure 4.10 in ad-hoc reporting effort. Add footnote "Note: samples are taken pre-dose except for post-dose samples on Day 1 and Week 6."	None

15.12.11. Pharmacokinetic Population (PopPK) Tables

Pharmacokinetic Population (POPPK): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1.	PK		Summary of final PK model tested	To be generated by CPMS	IA3, SAC
5.2.	PK		Parameter estimates of final PK model	To be generated by CPMS	IA3, SAC
Note: dependent on the results of the analysis, additional tables may be generated by CPMS					

15.12.12. Pharmacokinetic Population (PopPK) Figures

Pharmacokinetic Population (POPPK): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1.	PK		Mean (±SD) PK and sLAG3 data versus time	To be generated by CPMS PK and sLAG3 will be in the same graph to show how the concentration-time profiles compare to each other	IA3, SAC
5.2.	PK		Individual fits of final PK model	To be generated by CPMS	IA3, SAC
5.3.	PK		Standard diagnostics of final PK model	To be generated by CPMS	IA3, SAC
5.4.	PK		NPDEs of final PK model	To be generated by CPMS	IA3, SAC
5.5.	PK		PK versus time overlaid with population mean predictions from final PK model	To be generated by CPMS	IA3, SAC
5.6.	PK		sLAG3 versus time overlaid with population mean predictions from final PK model	To be generated by CPMS Note: this graph may show individual data, or median & range for each time point	IA3, SAC
Note: dependent on the results of the analysis, additional figures may be generated by CPMS.					

15.12.13. Pharmacodynamic / Biomarker Tables

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
sLAG3					
6.1.	ITTE	PKCT1	Summary of Plasma sLAG3 Concentration-Time Data (ng/mL) in Induction Phase		SAC
6.2.	ITTE _ETP	PKCT1	Summary of Plasma sLAG3 Concentration-Time Data (ng/mL) in Extended Treatment Phase		None
6.3.	ITTE _OL_I	PKCT1	Summary of Plasma sLAG3 Concentration-Time Data (ng/mL) in Open Label Induction Phase		None
6.4.	ITTE_OL_ETP	PKCT1	Summary of Plasma sLAG3 Concentration-Time Data (ng/mL) in Open Label Extended Treatment Phase		None
Flow cytometry					
6.5.	ITTE	PD1	Summary of Flow Cytometry by Visit in Induction Phase	Programming note: By Analyte and then by Summary (absolute(raw),and change from baseline). This will require non-standard programming as in shell. Note: use ABSCOUNT rather than COUNT for all Flow Cytometry outputs.	SAC
6.6.	ITTE_ETP	PD1	Summary of Flow Cytometry by Visit in Extended Treatment Phase	Programming note: By Analyte and then by Summary (absolute and change from baseline). This will require non-standard programming as in shell.	None

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunohistochemistry (IFC) in Colon Biopsies					
6.7.	ITTE	PD1	Summary of Colon Biopsy Cell Counts in Induction Phase	Produce table by: 1) absolute and change from baseline 2) tissue type For: All **derived** parameters. Geometric mean with 95% Confidence Interval	IA3, SAC
6.8.	ITTE ETP	PD1	Summary of Colon Biopsy Cell Counts – Extended Treatment Phase	as above. Change from shell: replace SD with SE on shell	None
6.9.	ITTE	BIO_T01	Statistical Analysis of CD3 positive and Lag3 positive cell count in Colon	Estimated difference in change from baseline for CD3+LAG3+ cells/mm2 in Lamina Propria	None
6.10.	ITTE ETP	BIO_T01	Statistical Analysis of Colon Biopsy Cell Counts in Extended Treatment Phase	Precision estimate for change from baseline for cell counts for CD3+LAG3+ cells/mm2 in Lamina Propria.	None
Disease Biomarkers					
6.11.	ITTE	PD1	Summary of Disease Biomarkers in Induction Phase	For following endpoints: • Faecal Calprotectin • CRP where elevated at baseline. Footnote: "Note that CRP for all subjects is reported in "Chemistry" summaries".	SAC

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.12.	ITTE ETP	PD1	Summary of Disease Biomarkers in Extended Treatment Phase	For following endpoints: • Faecal Calprotectin • Serum Tryptase	None
6.13.	ITTE_OL_I	PD1	Summary of Disease Biomarkers in Open Label Phase	For following endpoints: • Faecal Calprotectin • Serum Tryptase	None
6.14.	ITTE_OL_ETP	PD1	Summary of Disease Biomarkers in Open Label Extended Treatment Phase	For following endpoints: • Faecal Calprotectin • Serum Tryptase	None
6.15.	ITTE	BIO_T01	Statistical Analysis of Disease Biomarkers in Induction Phase	Estimated difference in change from baseline for: • FCP • CRP	None

15.12.14. Pharmacodynamic / Biomarker Figures

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
sLAG3					
6.1.	ITTE	PKCF4	Mean (+SD) Plasma sLAG3 Concentration-Time Plots by Treatment (Linear and Semi-log) in Induction Phase (Pre-Dose samples only	Use planned time (days) as x axis (where days is a continuous variable)	None
6.2.	ITTE_ETP	PKCF4	Mean (+SD) Plasma sLAG3 Concentration-Time Plots by Treatment (Linear and Semi-Log) in Extended Treatment Phase (Week 14 and Week 15 only)	Use planned time (days) as x axis (where days is a continuous variable) Add footnote "Note: samples are taken pre-dose, **week 14 and 15 samples were only taken in a sub-set of subjects**"	None
6.3.	ITTE_OL_I	PKCF4	Mean (+SD) Plasma sLAG3 Concentration-Time Plots (Linear and Semi-Log) in Open Label Induction Phase	Use planned time (days) as x axis (where days is a continuous variable) tick marks for Week 12 and Week 22 only. Add x-axis jitter if necessary to separate points	None
6.4.	ITTE	201246/final/ Figure 4.9	Mean (+SD) Plasma sLAG3 Concentration-Time Plots **grouped** by Treatment (Linear and Semi-log) in Induction Phase	As Figure 4.3 but on a single page, grouped by treatment. See Figure 4.9 and Figure 4.10 in ad-hoc reporting effort. Add footnote "Note: samples are taken pre-dose except for post-dose samples on Day 1 and Week 6."	None

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Flow cytometry					
6.5.	ITTE	207823/ Figure 5.1	LAG3+ T Cells in Blood for Individual Subjects in Induction Phase	As shell, combine flow marker and summary type in 'by' title. Use week on x axis. Add footnote: "Flow cytometry performed at a sub-set of sites". Note: plot for induction phase only	SAC
6.6.	ITTE	207823/ Figure 5.2	Geometric Mean (± 95% CI) Plot of LAG3+ T Cells in Blood by Treatment in Induction Phase	As shell, combine flow marker and summary type in 'by' title. Use week on x axis. Add footnote: "Flow cytometry performed at a sub-set of sites". Note: plot for induction phase only	SAC
Immunohistochemistry (IFC) in colon					
6.7.	ITTE	200630/ postcsr_2019_01/ Figure 1	Cell Count in Colon Biopsies for Individual Subjects in Induction Phase	Copy shell but don't use panel By parameter, by induction dose.	IA3, SAC
6.8.	ITTE	200630/ postcsr_2019_01/ Figure 2	Geometric Mean (± 95% CI) Plot of Cell Counts in Colon Biopsies by Treatment in Induction Phase	By parameter, Copy shell, include all treatments in a plot Footnote for interims: "Note that the longer lead time for this assay means that fewer subjects are analysed than for efficacy endpoints" Induction phase only.	IA3, SAC

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.9.	ITTE	200630/ postcsr_2019_01/ Figure 3 for panel structure but use 2 x 2	Mean (±SE) Plot of Change from baseline in Cell Counts in Colon Biopsies by Treatment in Induction Phase	By parameter, Copy shell, include all treatments in a plot Induction phase only.	None
6.10.	ITTE_ETP	200630/ postcsr_2019_01/ Figure 2	Mean (±SE) Plot of Cell Counts in Colon Biopsies by Induction Treatment across Phase in Extended Treatment Phase	By parameter, Copy shell, include all treatments in a plot Only use ETP population and ETP timepoints. Footnote: "Summaries are by induction treatment, responders on any active dose received 300mg SC in ETP"	None
6.11.	ITTE	200630/ postcsr_2019_01/ Figure 3 for panel structure but use 2 x 2	Mean (±SE) Plot of Change from baseline in Cell Counts in Colon Biopsies by Treatment in Extended Treatment Phase	By parameter, Copy shell, include all treatments in a plot Induction phase only.	None

15.12.15. Pharmacokinetic / Pharmacodynamic Tables

Pharmacokinetic / Pharmacodynamic Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
7.1.	ITTE		Summary of final PK/PD model tested	To be generated by CPMS	IA3, IA4, PC, SAC
7.2.	ITTE		Parameter estimates of final PK/PD model	To be generated by CPMS	IA3, IA4, PC, SAC
Note: dependent on the results of the analysis, additional tables may be generated (by CPMS).					

15.12.16. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
7.1.	ITTE		PK, receptor occupancy and cell depletion data versus time	To be generated by CPMS (as Figure 7.01 from FTIH study 200630)). Cell depletion data in blood and colon will be presented.	IA3, SAC
7.2.	ITTE		PK and cell depletion data versus time	To be generated by CPMS (as Figure 7.06 from FTIH study 200630)). Cell depletion data in blood and colon will be presented.	IA3, SAC
7.3.	ITTE		Individual fits of final PK/PD model	To be generated by CPMS	IA3, SAC
7.4.	ITTE		Standard diagnostics of final PK/PD model	To be generated by CPMS	IA3, SAC
7.5.	ITTE		NPDEs of final PK/PD model	To be generated by CPMS	IA3, SAC
7.6.	ITTE		Cell depletion versus time overlaid with individual predictions from final PK/PD model	To be generated by CPMS	IA3, SAC
Note: dependent on the results of the analysis, additional figures may be generated (by CPMS).					

15.12.17. Patient Reported Outcome Tables

Patient Reported Outcome: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Patient Reported Outcomes					
8.1	ITTE	PRO_T01	Observed Proportion of Subjects with Reported Symptom Control by Day in Induction Phase	By study day. Endpoints: • Symptomatic Remission • Symptom Control for rectal bleeding • Symptom Control for stool frequency Footnote: All eDiary entries are summarised over three observed days in the last seven following rules specified in the RAP.	None
8.2.	ITTE_ETP	PRO_T01	Observed Proportion of Subjects with Reported Symptom Control by Day in Extended Treatment Phase	By study day. Footnote: All eDiary entries are summarised over three observed days in the last seven following rules specified in the RAP.	None
8.3.	ITTE_OLI	PRO_T01	Observed Proportion of Subjects with Reported Symptom Control by Day in Open Label Induction Phase	By study day. Footnote: All eDiary entries are summarised over three observed days in the last seven following rules specified in the RAP.	None
8.4.	ITTE_OL_ETP	PRO_T01	Observed Proportion of Subjects with Reported Symptom Control by Day in Open Label Extended Treatment Phase	By study day. Footnote: All eDiary entries are summarised over three observed days in the last seven following rules specified in the RAP.	None

Patient Reported Outcome: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.5.	ITTE	PD1	SF-36 Summary, Induction Phase	By study part and visit For each component summary score and each domain score: PCS, MCS, GH, PF, RP, RE, SF, BP, VT, MH	None
8.6.	ITTE_ETP	PD1	*As above for ETP*		None
8.7.	ITTE_OLI	PD1	*As above for OL_I*		None
8.8.	ITTE_OL_ETP	PD1	*As above for OL_ETP*		None
8.9.	ITTE	PRO_T02	SF-36 Estimated Difference from Placebo, Induction Phase	For each component summary score and each domain score: PCS, MCS, GH, PF, RP, RE, SF, BP, VT, MH	None
8.10.	ITTE_ETP	PRO_T02	SF-36 Estimated Difference from Placebo, Extended Treatment Phase	For each component summary score and each domain score: PCS, MCS, GH, PF, RP, RE, SF, BP, VT, MH	None
8.11.	ITTE	PD1	IDBQ Summary by study part	For each Domain score and Total score: Total and Bowel Symptoms, Systemic Symptoms, Functional Emotion and Social Emotion	None
8.12.	ITTE_ETP	PD1	*As above for ETP*		None
8.13.	ITTE_OLI	PD1	*As above for OL_I*		None
8.14.	ITTE_OL_ETP	PD1	*As above for OL_ETP*		None
8.15.	ITTE	PRO_T02	IDBQ Estimated Difference from Placebo, Induction Phase	For each Domain score and Total score: Total and Bowel Symptoms, Systemic Symptoms, Functional Emotion and Social Emotion	None

Patient Reported Outcome: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.16.	ITTE_ETP	PRO_T02	IDBQ Estimated Difference from Placebo, Extended Treatment Phase	For each Domain score and Total score: Total and Bowel Symptoms, Systemic Symptoms, Functional Emotion and Social Emotion	None
8.17.	ITTE	PD1	Facit-Fatigue Summary, Induction Phase		None
8.18.	ITTE_ETP	PD1	*As above for ETP*		None
8.19.	ITTE_OLI	PD1	*As above for OL_I*		None
8.20.	ITTE_OL_ETP	PD1	*As above for OL_ETP*		None
8.21.	ITTE	PRO_T02	Facit-Fatigue. Estimated Difference from Placebo, Induction Phase		None
8.22.	ITTE_ETP	PRO_T02	Facit-Fatigue. Estimated Difference from Placebo, Extended Treatment Phase		None
8.23.	ITTE	PRO_T03	Patient Global Assessments Summary, Induction Phase	By endpoint: PGIS PGIC	None
8.24.	ITTE_ETP	PRO_T03	*As above for ETP*		None
8.25.	ITTE_OLI	PRO_T03	*As above for OL_I*		None
8.26.	ITTE_OL_ETP	PRO_T03	*As above for OL_ETP*		None

15.12.18. Patient Reported Outcome Figures

Patient Reported Outcomes: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.1	ITTE	PRO_F01	SF-36 Component Scores Difference from Placebo for Paired Weeks by Study Part	By study part (Induction and ETP) Each SF-36 score is recorded in week pairs eg.6 and 10, 22 and 30 align them in facets to minimize number of plots and time order. These need to cover every visit.	None
8.2.	ITTE	PRO_F02	SF-36 Domain Scores Estimated Difference from Placebo	By Visit for Induction and ETP study parts. Keep facet headings as small as possible whilst still being readable	None
8.3.	ITTE	PRO_F03	IDBQ Total and Domain Scores Estimated Difference from Placebo	By Visit for Induction and ETP study parts. Keep facet headings as small as possible whilst still being readable	None
8.4.	ITTE	PRO_F04	Facit-F Score Estimated Difference from Placebo	By Visit for Induction and ETP study parts. Keep facet headings as small as possible whilst still being readable	None
8.5.	ITTE	PRO_F05	PGIC Count Stacked Bar Chart	By Visit for Induction and ETP study parts. Stacked bar chart, please check colours with statistician during development (before stage 1 QC).	None
8.6.	ITTE	PRO_F05	PGIS Count Stacked Bar Chart	By Visit for Induction and ETP study parts. Stacked bar chart, colour scheme consistent with figure above.	None

Patient Reported Outcomes: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.7.	ITTE	PRO_F06	Observed Proportion of Subjects with Reported Symptom Control by Day, Induction Phase	Line plot with points and ASE, Page by Categorical endpoint: • Symptomatic Remission, • Symptom control for: o Rectal Bleeding o Stool Frequency Group by treatment group. Start from Day 1, include 28 days per page	None
8.8.	ITTE_ETP	PRO_F06	Observed Proportion of Subjects with Reported Symptom Control by Day, Extended Treatment Phase	Line plot with points, Page by Categorical endpoint: • Symptomatic Remission • Symptom control for: o Rectal Bleeding o Stool Frequency o Bowel Urgency o Tenesmus o Night Time Awakenings to go to the Toilet Group by treatment group. 28 days per page	None

Patient Reported Outcomes: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.9.	ITTE_OL_I	PRO_F06	Observed Proportion of Subjects with Reported Symptom Control by Day, Open Label Induction	Line plot with points, Page by Categorical endpoint: • Symptomatic Remission, • Symptom control for: o Rectal Bleeding o Stool Frequency o Bowel Urgency o Tenesmus o Night Time Awakenings to go to the Toilet Group by treatment group. 28 days per page	None
8.10.	ITTE_OL_ETP	PRO_F06	Observed Proportion of Subjects with Reported Symptom Control by Day, Open Label Extended Treatment Phase	Line plot with points, Page by Categorical endpoint: • Symptomatic Remission, • Symptom control for: o Rectal Bleeding o Stool Frequency o Bowel Urgency o Tenesmus o Night Time Awakenings to go to the Toilet Group by treatment group. 28 days per page	None

15.12.19. ICH Listings

Reviewer's note: Listings will be produced at interims but, following the DRC charter, will not be shared unless requested.

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	All listings: follow a single subject through study phases; order by induction treatment.	SAC
2.	Enrolled	ES2xo	Listing of Reasons for Study Withdrawal	All listings with "xo" shell: replace "Period" column with "Phase"; change column title from 'Randomised Treatment' to 'Randomised/Planned Treatment'; as per shell report by country then site.	SAC
3.	Enrolled	SD2xo	Listing of Reasons for Study Treatment Discontinuation		IA3H, SAC
4.	Enrolled	BL1xo	Listing of Subjects for Whom the Treatment Blind was Broken		SAC
5.	Enrolled	TA1xo	Listing of Planned and Actual Treatments	Page by centreid	SAC
6.	Screened	ES9	Listing of Subjects Who Were Rescreened		SAC
7.	Enrolled	POP_L5	Listing of Study Phases		SAC
Protocol Deviations					
8.	Enrolled	DV2	Listing of Important Protocol Deviations		SAC
9.	Enrolled	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Populations Analysed					
10.	Screened	SP3xo	Listing of Subjects Excluded from Any Population		None
Demographic and Baseline Characteristics					
11.	Enrolled	DM2xo	Listing of Demographic Characteristics		SAC
12.	Enrolled	DM9xo	Listing of Race		SAC
Prior and Concomitant Medications					
13.	Enrolled	CM10xo	Listing of Concomitant Medications		SAC
Exposure and Treatment Compliance					
14.	Enrolled	EX3xo	Listing of Exposure Data		SAC
Adverse Events					
15.	Safety	AE8xo	Blinded Listing of All Serious and Non-Serious Adverse Events	Change row order so that 'Serious' is above 'Maximum Intensity' in stack. Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	N30
16.	Safety	AE8xo	Listing of All Adverse Events	Reviewer's note: Listings will be produced at interims but, following the DRC charter, will not be shared unless requested. Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	On request by DRC, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
17.	Safety	AE8xo	Listing of Adverse Events with Increasing Severity that Cross Study Phases	Study specific selection of AEs: Select AEs where AE onset date is in a different study phase to AE resolution date and maximum severity is greater than severity at onset. Footnotes: "Note: Severity at onset and maximum severity are recorded, the date of increase in severity is not recorded" "Note: Onset date of Adverse Event is used to associate AE to study phase."	SAC
18.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	SAC
19.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
20.	Safety	AE8xo	Listing of Fatal Serious Adverse Events	Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	None
21.	Safety	AE8xo	Listing of Serious Adverse Events	Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	On request by DRC, SAC
22.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	SAC
23.	Safety	AE8xo	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	Add footnote: Note: Onset date of Adverse Event is used to associate AE to study phase.	SAC
All Laboratory					
24.	Safety	LB5xo	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance		SAC
25.	Safety	LB5xo	Listing of Laboratory Values of Potential Clinical Importance		SAC
26.	Safety	LB14	Listing of Laboratory Data with Character Results		None
27.	Safety	UR2xo	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
28.	Safety	EG3xo	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC
29.	Safety	EG3xo	Listing of ECG Values of Potential Clinical Importance		SAC
30.	Safety	EG5xo	Listing of All ECG Findings for Subjects with an Abnormal ECG Finding		None
31.	Safety	EG5xo	Listing of Abnormal ECG Findings		SAC
Vital Signs					
32.	Safety	VS4xo	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance		None
33.	Safety	VS4xo	Listing of Vital Signs of Potential Clinical Importance		SAC
Hepatobiliary (Liver)					
34.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	No data to display unless a subject experiences a liver stopping event	None
35.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	No data to display unless a subject experiences a liver stopping event	None
36.	Safety	LB14	Listing of Viral Results for Subjects with Liver Stopping Events	No data to display unless a subject experiences a liver stopping event	None
37.	Safety	LIVER5	Listing of Liver Biopsy Details	No data to display unless a subject experiences a liver stopping event	None
38.	Safety	LIVER5	Listing of Liver Imaging Details	No data to display unless a subject experiences a liver stopping event	None
Note for RAP authors: listing numbers continue in the follow section. Any additional listings must follow highest listing number.					

15.12.20. Non-ICH Listings

Reviewer's note: Listings will be produced at interims but, following the DRC charter, will not be shared unless requested.

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunogenicity					
39.	Safety	IMM2	Listing of Immunogenicity Results	Produce for all phases, order by induction treatment, subject ID, visit. Display treatment at each visit in separate column.	SAC
40.	Safety	Custom (from OSM)	Listing of Anti-GSK2831781 Neutralising and Binding Antibody (ADA) Positive Subjects		None
Study conduct					
41.	ITTE	POP_L1	Listing of Subject Responder Status In eCRF and on Clinical Database	Reports the recorded responder status and the decision that was made by eCRF for subjects (week 10 and week 22)	None
42.	Safety	POP_L2	Listing of Subjects Who Remained in Study after Withdrawing from Study Medication	Include last dosing visit (date) last actual visit (date).	None
43.	ITTE	EFF_L2	Listing of Subjects who Started Corticosteroid Taper but did not Start Subsequent Study Phase	By Study Phase (i.e. Induction, OL Induction) then subject	None
Substance Use					
44.	Safety	SU_L01	Listing of Substance Use	Based on SU1, include variables from smoking status at screening and those from 'change in substance use' at W10,30,FU42 Addition to shell: Include 'Pack years'	None

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Medical History / Concomitant Medications					
45.	ITTE	POP_L3	Listing of Ulcerative Colitis Disease Characteristics at Baseline		IA3H, SAC
46.	ITTE	POP_L4	Listing of Ulcerative Colitis Therapeutic History		IA3H, SAC
Efficacy					
47.	ITTE	EFF_L1	Listing of Mayo Score		None
48.	ITTE	EFF_L1	Listing of UCEIS Total Score		None
49.	ITTE	EFF_L2	Listing of Corticosteroid Use During Mandatory Taper in Extended Treatment Phase and Open Label Extended Treatment Phase		None
50.	ITTE	EFF_L3	Listing of Categorical Efficacy		None
51.	ITTE	EFF_L3	Listing of Categorical Histology		None
52.	ITTE	EFF_L4	Listing of Extra Intestinal Manifestations (EIMs)		None
Pharmacokinetic					
53.	PK	PK07xo	Listing of Plasma GSK2831781 Concentration-Time Data		SAC
54.	PK	PK13xo	Listing of Derived Plasma GSK2831781 Pharmacokinetic Parameters		SAC
Biomarker					
55.	ITTE	PK07xo	Listing of Plasma sLAG3 Concentration-Time Data		None
56.	ITTE	BIO_L1	Listing of Flow Cytometry		None
57.	ITTE	BIO_L1	Listing of Colon Biopsy Cell Counts		IA3, SAC
58.	ITTE	BIO_L1	Listing of Disease Biomarkers		None
Patient Reported Outcome					
59.	ITTE	PRO_L1	Listing of Reported Symptom Control		None

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
60.	ITTE	PRO_L2	Listing of SF-36		None
61.	ITTE	PRO_L2	Listing of IDBQ		None
62.	ITTE	PRO_L2	Listing of Facit-Fatigue		None
63.	ITTE	PRO_L3	Listing of PGIS		None
Population PK					
64.	PK		PK and sLAG3 data excluded from population PK modelling	To be generated by CPMS	SAC
65.	PK		Text output of final PK model (lst-file)	To be generated by CPMS	SAC
PK / PD					
66.	ITTE		PD data excluded from population PK/PD modelling	To be generated by CPMS	SAC
67.	ITTE		Text output of final PK/PD model (lst-file)	To be generated by CPMS	SAC
Estimands and Intercurrent Events					
68.	ITTE	EFF_L5	Listing of Intercurrent Events		IA3H, SAC
69.	ITTE	EFF_L6	Listing of Estimand Imputations for Efficacy		IA3H
COVID-19 Pandemic					
70.	Safety	PAN12	Listing of COVID-19 Assessments and Symptom Assessments		SAC

15.13. Appendix 13: Example Mock Shells for Data Displays

Note: Mock shells are in a separate document.

15.14. Appendix 14: Selection criteria for the Informative Placebo Priors

Placebo data from studies using the following selection criteria will be used

Criteria	Rationale
Age: Publication after 2012.	This marks the start of the post-TNF era when anti-TNF medications for Ulcerative Colitis were widely available and late-phase studies with molecules with other targets were recruiting. The clinical team believe that the environment prior to this was quite dissimilar to the current study.
Trial type and disease inclusion criteria: All randomised double-blind trials will be included with inclusion criteria that includes Mayo score 6-12 at baseline or equivalent	This 'moderate to severe' population is similar to key phase 2 and 3 pharmaceutical industry sponsored trials and matches the inclusion criteria of this study (204869).
Number of sites: Single site studies are excluded	The current study, and most competitor studies of interest, are multi-site studies.
Size: Studies with fewer than 40 participants on the placebo arm are excluded	To ensure that trials with very uncertain estimates are excluded.
Assessments: Exclude trials with locally read endoscopies Include induction studies where endpoint in range 6 – 12 weeks, where multiple timepoints existing for the same endpoint, chose primary where available and latest if not.	Centrally read endoscopies are used in this trial (204869) and most recent and future trials. Induction timepoint range is consistent with this study and most competitors
Endpoint: ***Clinical Remission*** Use Clinical Remission definitions that include RB=0, where documented.	**Clinical remission** This endpoint has changed between trials with a recent shift to using a modified/adapted Mayo score which excludes the Physician Global Assessment and some studies report multiple versions of the score. Where multiple versions of the scores are available for a study, the

Criteria	Rationale
Do include Complete Mayo clinical remission. ***Endoscopic Improvement*** Use endoscopic score of 0 or 1. Where available, use 'adapted Mayo' endoscopic score (where any CCI [redacted] is a score of [redacted])	modified/adapted Mayo definition will be used as will a definition that includes RB=0 which is consistent with the criterion used in 204869. **Endoscopic Improvement** This definition has changed over the period in scope, with historical trials using a slightly different definition of endoscopic score, this data will still be used, where multiple scores are available for a study the modified/adapted Mayo definition will be used.
Note that the data used for the placebo priors will be extracted from the Certara clinical outcomes database for Ulcerative Colitis which includes data from abstracts and scientific posters as well as published scientific articles. Note that only studies where the placebo response rate can be calculated from the number of placebo responders and the total number of participants in the placebo arm will be used. No strata are used, to resolve duplicates where appropriate the results from the primary statistical analysis is used.	

15.14.1. Examples of robustified prior for endoscopic mucosal healing (key secondary endpoint)

Examples of priors derived as best-fitting mixture of Beta distributions are provided below for four different levels of Advanced Therapy stratification (% Naïve) in endoscopic mucosal healing. Each prior is the weighted sum of the three components, including the non-informative prior (component 1) used for robustification.

	Component 1: weight, distribution	Component 2: weight, distribution	Component 3: weight, distribution
Prior 1: 20% naive	40%, Beta(1/2,1/2)	46%, Beta(3,20)	14%, Beta(1,4)
Prior 2: 40% naive	40%, Beta(1/2,1/2)	46%, Beta(3,17)	14%, Beta(1,4)
Prior 3: 60% naive	40%, Beta(1/2,1/2)	44%, Beta(4,16)	16%, Beta(1,4)
Prior 4: 80% naive	40%, Beta(1/2,1/2)	41%, Beta(4,13)	19%, Beta(1,3)

40% robustification applied to each prior

Signature Page for 204869 TMF-13801863 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 02-Jun-2021 09:18:46 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 02-Jun-2021 10:40:10 GMT+0000

Signature Page for TMF-13801863 v1.0