Official Title: A Phase II, Multicenter Induction Study with an Active Treatment Extension to Evaluate the Efficacy, Safety, and Pharmacokinetics of Vixarelimab in Patients with Moderate to Severe Ulcerative Colitis

NCT Number: NCT06137183

Document Date: Protocol Amendment Version 2: 29-Oct-2024

PROTOCOL

TITLE:	**A PHASE II, MULTICENTER INDUCTION STUDY WITH AN ACTIVE TREATMENT EXTENSION TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF VIXARELIMAB IN PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS**
PROTOCOL NUMBER:	GA44839
VERSION NUMBER:	2
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 167385 EU CT Number: 2023-506655-19-00
TEST PRODUCT:	Vixarelimab (RO7622888; KPL-716)
SPONSOR NAME AND ADDRESS:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Region-Specific Protocols		
Version	**Date Final**	**Region**	**Version**	**Date Final**
2	See electronic date stamp on final page.	—	—	—
1	11 October 2023	European Economic Area	2	12 April 2024
		China	1	26 January 2024
		European Economic Area	1	24 October 2023

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol GA44839 has been amended primarily to incorporate changes made in the latest European Economic Area (EEA)-specific and China-specific versions of the protocol, as well as to incorporate additional new changes. Changes to the protocol, along with a rationale for each change, are summarized below.

Changes Incorporated from Version 1 (China)

The following changes were previously implemented in Version 1 (China) to enhance suitability of the study for the patient population in China and to clarify laboratory assessments specific to China. These changes have been included in this amended global version of the protocol:

- The retesting period for patients with cytomegalovirus or *Clostridium difficile* at screening has been reduced from 60 days to 30 days to enable easier enrollment of patients with resolved infections (Sections 3.1.1 and 4.1.2).
- The exclusion criteria regarding tuberculosis (TB) testing has been expanded to enable patients with latent TB to be included in the study if they are on treatment to enable enrollment of patients with TB infection with minimal risk of reactivation. The concomitant medications section reflects this change, and additional frequency of chemistry testing has been implemented to enable safe usage of these medications (Sections 4.1.2, 4.4.2.1, and 4.5.8; Appendices 1 and 2).
- Because of the operational complexity of sample shipment and processing, certain laboratory assessments for exploratory biomarker research and genomic analyses will not be collected or analyzed in China (Section 4.5.8; Appendices 1 and 2). The description of central laboratories for testing, analysis, and sample destruction in China has been added, as well as a summary of laboratory samples which will not be collected in China (Appendix 9).
- The monitoring parameters and discontinuation parameters have been expanded to clarify how patients on latent TB treatment or patients who develop active TB should be managed (Section 4.6.1).
- Serum chemistry testing has been included at the Week [redacted] and Week [redacted] timepoints and hematology testing at the Week [redacted] timepoint for the monitoring of patients while on TB medications (Appendix 1).

Changes Incorporated from Version 2 (EEA)

The following changes were previously implemented in Version 2 (EEA) primarily to address requests from the European Medicines Agency. These changes have been included in this amended global version of the protocol:

- Text has been added to indicate that the selected dosing regimens are based on the developed population PK model outlined in the Vixarelimab Investigator's Brochure (Section 3.4.1).

- An exclusion criterion has been modified to clarify that patients will be excluded if they have a history of known or suspected allergic reaction or anaphylactic reaction to vixarelimab or its excipients (Section 4.1.2).
- Text has been added to specify the timing for blinding of study site personnel, patients, and the Sponsor and to clarify that unblinded Sponsor personnel will consist of a limited set of individuals who are not directly involved with study conduct and require access to patient treatment assignments to fulfill their jobs during the study (Section 4.2.2).
- Text has been added to describe the statistical methods for multiplicity adjustment and subgroup (advanced failure) analysis for the primary efficacy endpoint (Sections 6.4 and 6.4.1).
- [redacted]
- The schedule of activities has been revised to include additional chemistry tests (including ALT, AST, and ALP) at Week [redacted] (Appendix 1).
- Text has been added to clarify that serum pregnancy tests will be performed at a central laboratory (Section 4.5.8).
- For consistency with the schedule of activities, text has been modified to clarify that all patients will undergo urine drug screening, regardless of history of drug abuse (Section 4.5.8).

Additionally, the open-label treatment part of the study and all associated text in Version 2 (EEA) of the protocol (originally added in Version 1 [EEA]) have now been removed. The Sponsor has determined that the rate of global enrollment into the randomized part of the study is sufficient to enable initial proof of activity within a reasonable timeframe.

Additional New Changes in Version 2

The following changes have been newly implemented in this version of the protocol:

- The list of approved interleukin agents and sphingosine-1-phosphate receptor modulators for the treatment of ulcerative colitis (UC) has been updated to reflect recent health authority approvals (Section 1.1).
- Descriptions of a Phase II trial of vixarelimab and adverse events have been updated to align with the most recently available data (Section 1.2.2).
- Language in the Summary of Clinical Studies has been reduced, as the updated Vixarelimab Investigator's Brochure provides the most up-to-date and detailed information on vixarelimab (Section 1.2.2).
- Additional citations have been included to provide further evidence supporting the role of OSMR in the intestinal mucosa and in IBD (Sections 1.3 and 10).

- The partial Mayo Score (pMS) will not be collected for this study. All text regarding the pMS has been removed (Sections 3.1.1 and 4.5.7.2 and Appendix 3). All components of the Mayo Score, including the Physician's Global Assessment (PGA), will still be collected.
- The re-screen criteria have been revised to allow for—in exceptional cases—re-screening for screen failure due to an ineligible modified Mayo Score if driven by the endoscopy subscore <2 and not by the average stool frequency or rectal bleeding score (Section 3.1).
- Additional guidance has been provided on the re-screening process and required retesting (Section 3.1).
- In consultation with the Medical Monitor, an additional 7 days maximum may be added to the 35-day screening period for unforeseen events such as administrative or other logistical delays (Section 3.1).
- The exclusion criterion regarding previous treatment with JAK inhibitors has been revised to only exclude patients who have experienced inadequate response or loss of response to a JAK inhibitor for the treatment of UC (Sections 3.4.2 and 4.1.2).
- The inclusion criterion for permitted and prohibited UC therapies were revised to anchor to screening endoscopy date rather than screening date to reduce patient burden (Sections 4.1.1.1 and 4.4.2.2 and Table 2).
- Instruction has been added that women of childbearing potential must agree to refrain from donating eggs during the treatment period and for [redacted] after the final dose of study treatment (Section 4.1.1.1).
- Clarification has been provided regarding the definition of history of intolerance to AZA, 6-MP, or MTX (Section 4.1.1.3).
- The definition of corticosteroid dependence has been revised to align with global guidelines [1] (Section 4.1.1.3).
- CMV testing has been modified to be required only if clinical suspicion of infection is high during endoscopy, which aligns with clinical practice (Section 4.5.8).
- The language regarding single-patient emergency and non-emergency unblinding requested by the investigator has been updated to align with internal procedures (Section 4.2.2).
- Text has been modified to align with updates to the Roche Global Policy on Continued Access to Investigational Medicinal Products (Section 4.3.4).
- Short-term, intermittent use of topical (rectally administered) 5-ASA is now allowed during the optional active treatment extension (ATE) period up to [redacted] to reduce potential patient burden (Section 4.4.1 and Table 2).

---

[1] Stange EF, Travis SPL, Vermeire S, et al. European evidence-based Consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis. J Crohns Colitis 2008;2:1–23.

- The visit windows for the Week 1 and Week 2 timepoints have been expanded to reduce site and patient burden (Appendix 1).
- Additional guidance has been provided regarding the order of study assessments prior to performing ECG (Study 4.5.5, Appendix 1, and Appendix 2).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM 13

PROTOCOL SYNOPSIS 14

1. BACKGROUND 19
   - 1.1 Background on Ulcerative Colitis 19
   - 1.2 Background on Vixarelimab 20
   - 1.2.1 Summary of Nonclinical Safety 20
   - 1.2.2 Summary of Clinical Studies 21
   - 1.3 Study Rationale and Benefit–Risk Assessment 22

2. OBJECTIVES AND ENDPOINTS 23

3. STUDY DESIGN 26
   - 3.1 Description of the Study 26
   - 3.1.1 Overview of Study Design 26
   - 3.1.2 Patient Input into Study Design 30
   - 3.2 End of Study Definition 30
   - 3.3 Duration of Participation 30
   - 3.4 Rationale for Study Design 30
   - 3.4.1 Rationale for Vixarelimab Dose and Schedule 30
   - 3.4.2 Rationale for Patient Population 31
   - 3.4.3 Rationale for Placebo Control Group 32
   - 3.4.4 Rationale for Biomarker Assessments 33
   - 3.4.5 Rationale for Optional Active Treatment Extension 33

4. MATERIALS AND METHODS 33
   - 4.1 Patients 33
   - 4.1.1 Inclusion Criteria 33
   - 4.1.1.1 General Inclusion Criteria for All Patients 33
   - 4.1.1.2 Inclusion Criteria for Advanced Failures 35
   - 4.1.1.3 Inclusion Criteria for Conventional Failures 36
   - 4.1.2 Exclusion Criteria 37
   - 4.2 Method of Treatment Assignment and Blinding 40

4.2.1 Treatment Assignment 40
4.2.2 Blinding 40
4.3 Study Treatment and Other Treatments Relevant to the Study Design 41
4.3.1 Study Treatment Formulation and Packaging 41
4.3.1.1 Vixarelimab and Placebo 41
4.3.2 Study Treatment Dosage, Administration, and Compliance 42
4.3.2.1 Vixarelimab and Placebo 42
4.3.3 Investigational Medicinal Product Handling and Accountability 43
4.3.4 Continued Access to Vixarelimab 43
4.4 Concomitant Therapy 44
4.4.1 Permitted and Prohibited Therapy for Ulcerative Colitis (Including Background and Rescue Therapy) 44
4.4.2 Other Concomitant Therapy 48
4.4.2.1 Other Permitted Concomitant Therapy 48
4.4.2.2 Other Prohibited Concomitant Therapy 48
4.5 Study Assessments 49
4.5.1 Informed Consent Forms and Screening Records 49
4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data 49
4.5.3 Physical Examinations 50
4.5.4 Vital Signs 50
4.5.5 Electrocardiograms 50
4.5.6 Colonoscopy or Flexible Sigmoidoscopy with Colonic Biopsies 51
4.5.7 Clinical Outcome Assessments 52
4.5.7.1 Data Collection Methods for Clinical Outcome Assessments 52
4.5.7.2 Description of Clinical Outcome Assessment Instruments 53
4.5.8 Laboratory, Biomarker, and Other Biological Samples 55
4.5.9 Use of Screen-Fail Samples (Patients at Participating Sites) 58
4.5.10 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites) 58

4.5.11 Optional Samples for Research Biosample Repository 59
4.5.11.1 Overview of the Research Biosample Repository 59
4.5.11.2 Approval by the Institutional Review Board or Ethics Committee 59
4.5.11.3 Sample Collection 60
4.5.11.4 Data Protection, Use, and Sharing 60
4.5.11.5 Consent to Participate in the Research Biosample Repository 61
4.5.11.6 Withdrawal from the Research Biosample Repository 62
4.5.11.7 Monitoring and Oversight 62
4.6 Treatment, Patient, Study, and Site Discontinuation 62
4.6.1 Study Treatment Discontinuation 62
4.6.2 Patient Discontinuation from the Study 63
4.6.3 Study Discontinuation 64
4.6.4 Site Discontinuation 64
5. ASSESSMENT OF SAFETY 64
5.1 Safety Plan 64
5.1.1 Potential Risks Associated with Vixarelimab 64
5.1.2 Management of Patients Who Experience Adverse Events 65
5.1.2.1 Dose Modifications 66
5.1.2.2 Treatment Interruption 66
5.2 Safety Parameters and Definitions 66
5.2.1 Adverse Events 67
5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) 67
5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor) 68
5.3 Methods and Timing for Capturing and Assessing Safety Parameters 68
5.3.1 Adverse Event Reporting Period 69
5.3.2 Eliciting Adverse Event Information 69
5.3.3 Assessment of Severity of Adverse Events 69
5.3.4 Assessment of Causality of Adverse Events 70
5.3.5 Procedures for Recording Adverse Events 71

5.3.5.1 Injection Reactions and Anaphylactic Reactions 71
5.3.5.2 Diagnosis versus Signs and Symptoms 71
5.3.5.3 Adverse Events That Are Secondary to Other Events 72
5.3.5.4 Persistent or Recurrent Adverse Events 72
5.3.5.5 Abnormal Laboratory Values 73
5.3.5.6 Abnormal Vital Sign Values 73
5.3.5.7 Abnormal Liver Function Tests 74
5.3.5.8 Deaths 74
5.3.5.9 Preexisting Medical Conditions 75
5.3.5.10 Lack of Efficacy or Worsening of Ulcerative Colitis 75
5.3.5.11 Hospitalization or Prolonged Hospitalization 75
5.3.5.12 Patient-Reported Outcome Data 76
5.3.6 Special Situations (Accidental Overdose and/or Medication Error) 76
5.4 Immediate Reporting Requirements from Investigator to Sponsor 76
5.4.1 Emergency Medical Contacts 77
5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest 77
5.4.2.1 Events That Occur prior to Study Treatment Initiation 77
5.4.2.2 Events That Occur after Study Treatment Initiation 77
5.4.3 Reporting Requirements for Pregnancies 78
5.4.3.1 Pregnancies in Female Patients 78
5.4.3.2 Pregnancies in Female Partners of Male Patients 78
5.4.3.3 Abortions 79
5.4.3.4 Congenital Anomalies/Birth Defects 80
5.5 Follow-Up of Patients after Adverse Events 80
5.5.1 Investigator Follow-Up 80
5.5.2 Sponsor Follow-Up 80
5.6 Adverse Events That Occur after the Adverse Event Reporting Period 80
5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees 81
6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN 81

6.1 Determination of Sample Size 81
6.2 Summaries of Conduct of Study 82
6.3 Summaries of Demographic and Baseline Characteristics 82
6.4 Efficacy Analyses 82
6.4.1 Primary Efficacy Endpoint 82
6.4.2 Secondary Efficacy Endpoints 83
6.4.3 Exploratory Efficacy Endpoints 83
6.5 Safety Analyses 83
6.6 Pharmacokinetic Analyses 84
6.7 Immunogenicity Analyses 84
6.8 Biomarker Analyses 85
[redacted] 85
7. DATA COLLECTION AND MANAGEMENT 85
7.1 Data Quality Assurance 85
7.2 Electronic Case Report Forms 86
7.3 Electronic Patient- and Clinician-Reported Outcome Data 86
7.4 Source Data Documentation 87
7.5 Use of Computerized Systems 87
7.6 Retention of Records 87
8. ETHICAL CONSIDERATIONS 88
8.1 Compliance with Laws and Regulations 88
8.2 Informed Consent 88
8.3 Institutional Review Board or Ethics Committee 89
8.4 Confidentiality 90
8.5 Financial Disclosure 91
9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION 91
9.1 Study Documentation 91
9.2 Protocol Deviations 91
9.3 Management of Study Quality 91
9.4 Site Inspections 92
9.5 Administrative Structure 92

9.6 Dissemination of Data and Protection of Trade Secrets 92
9.7 Protocol Amendments 93
10. REFERENCES 94

LIST OF TABLES

Table 1 Objectives and Corresponding Endpoints 24
Table 2 Permitted and Prohibited Therapies for Ulcerative Colitis 45
Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events 66
Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in DAIDS Toxicity Grading Scale 70
Table 5 Causal Attribution Guidance 71

LIST OF FIGURES

Figure 1 Study Schema 29

LIST OF APPENDICES

Appendix 1 Schedule of Activities: Induction 98
Appendix 2 Schedule of Activities: Optional Active Treatment Extension 102
Appendix 3 Mayo Score 105
Appendix 4 Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS) 106
Appendix 5 Anaphylaxis Precautions 108
Appendix 6 Investigational and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom) 109
Appendix 7 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events 111
Appendix 8 Sampson Criteria for Diagnosing Potential Cases of Anaphylaxis 142
Appendix 9 Laboratory Sampling in China 143

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, MULTICENTER INDUCTION STUDY WITH AN ACTIVE TREATMENT EXTENSION TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF VIXARELIMAB IN PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS**
PROTOCOL NUMBER:	GA44839
VERSION NUMBER:	2
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 167385 EU CT Number: 2023-506655-19-00
TEST PRODUCT:	Vixarelimab (RO7622888; KPL-716)
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your Contract Research Associate..

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, MULTICENTER INDUCTION STUDY WITH AN ACTIVE TREATMENT EXTENSION TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF VIXARELIMAB IN PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS**
PROTOCOL NUMBER:	GA44839
VERSION NUMBER:	2
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 167385 EU CT Number: 2023-506655-19-00
SPONSOR:	Genentech, Inc.

PRIMARY AND SECONDARY OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of vixarelimab compared with placebo in patients with moderate to severe ulcerative colitis (UC) who have demonstrated inadequate response to, loss of response to, or intolerance to prior conventional or advanced therapy. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
• To evaluate the induction efficacy of vixarelimab compared with placebo • To evaluate the induction efficacy of vixarelimab compared with placebo in advanced failures	• Clinical remission at Week 12, with clinical remission defined as mMS [a] of ≤ 2, including: o Stool frequency subscore ≤ 1 o Rectal bleeding subscore $= 0$ o Endoscopy subscore ≤ 1 (score of 1 modified to exclude friability) [b]

mMS = modified Mayo Score.

[a] Modified Mayo Score is the composite of three Mayo Score assessments: stool frequency, rectal bleeding, and centrally read endoscopy.

[b] Endoscopy scores will be based on interpretation by a blinded central reader.

Secondary Objectives	Corresponding Endpoints
• To evaluate the induction efficacy of vixarelimab compared with placebo • To evaluate the induction efficacy of vixarelimab compared with placebo in advanced failures	• Clinical response at Week 12, with clinical response defined as meeting both of the following criteria: o Decrease from baseline in the mMS [a] of ≥2 and ≥30% reduction from baseline o Decrease in rectal bleeding subscore of ≥1 or absolute rectal bleeding subscore of ≤1 • Endoscopic improvement at Week 12, with endoscopic improvement defined as a Mayo endoscopy subscore of ≤ 1 (score of 1 modified to exclude friability) [b] • Endoscopic remission at Week 12, with endoscopic remission defined as a Mayo endoscopy subscore of 0 [b]
• To evaluate the safety of vixarelimab compared with placebo	• Incidence and severity of adverse events, with severity determined according to the DAIDS toxicity grading scale [c] • Change from baseline in selected vital signs • Change from baseline in selected clinical laboratory test results
• To characterize the pharmacokinetics of vixarelimab	• Serum concentration of vixarelimab at specified timepoints
• To evaluate the immune response to vixarelimab	• Prevalence of ADAs at baseline and incidence of ADAs during the study

ADA = anti-drug antibody; DAIDS = Division of AIDS; mMS = modified Mayo Score.

[a] Modified Mayo Score is the composite of three Mayo Score assessments: stool frequency, rectal bleeding, and centrally read endoscopy.

[b] Endoscopy scores will be based on interpretation by a blinded central reader.

[c] Adverse events will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, with slight modifications for clarity and for alignment with internal practices.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase II, multicenter, randomized, parallel-group, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and pharmacokinetics of vixarelimab compared with placebo in patients with active moderate to severe UC, including 1) patients who have demonstrated inadequate response to, loss of response to, or intolerance to prior advanced therapy which includes biologics and targeted small molecules (advanced failures), and 2) patients who have demonstrated inadequate response to, loss of response to, or intolerance to prior conventional therapies (corticosteroids and/or immunosuppressants) but have not failed advanced therapy (conventional failures).

Several key aspects of the study design and study population are summarized below.

Phase:	Phase II	**Population Type:**	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	Ulcerative colitis
Interventional Model:	Parallel group	**Population Age:**	≥ 18 years
Test Compound:	Vixarelimab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Randomized
Number of Arms:	3	**Number of Participants to Be Enrolled:**	Approximately 210

STUDY TREATMENT

Patients will be randomized to receive SC injections of either vixarelimab [redacted], vixarelimab [redacted], or placebo [redacted]) during the induction period [redacted]; all patients will receive SC injections of vixarelimab [redacted] during the optional active treatment extension (ATE) period ([redacted]).

DURATION OF PARTICIPATION

The total duration of study participation for each patient is expected to be approximately [redacted] who complete the optional ATE.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AD	atopic dermatitis
ADA	anti-drug antibody
ATE	active treatment extension
AUC	area under the concentration–time curve
AxMP	auxiliary medicinal product
AZA	azathioprine
BCG	Bacillus Calmette-Guérin
BEN	benign ethnic neutropenia
C. difficile	*Clostridium difficile*
ClinRO	clinician-reported outcome
Cmax	maximum serum concentration
CMV	cytomegalovirus
CRO	contract research organization
CRP	C-reactive protein
DAIDS	Division of AIDS (Table for Grading the Severity of Adult and Pediatric Adverse Events)
DAP	Data Analysis Plan
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
e-diary	electronic diary
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FeCal	fecal calprotectin
GLP	Good Laboratory Practice
gp130	glycoprotein 130
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
IGRA	*interferon-γ release assay*

Abbreviation	Definition
IL	interleukin
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
JAK	Janus kinase
LIFR	leukemia inhibitory factor receptor
mMS	modified Mayo Score
MTX	methotrexate
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
OSM	oncostatin M
OSMR	oncostatin M receptor
OSMRβ	oncostatin M receptor-beta
PD	pharmacodynamic
PGA	Physician's Global Assessment
PK	pharmacokinetic
PN	prurigo nodularis
PPD	purified protein derivative
PRO	patient-reported outcome
[redacted]	
QTcF	QT interval corrected through use of Fridericia's formula
QTL	quality tolerance limit
QW	weekly
RBR	Research Biosample Repository
SAE	serious adverse event
TB	tuberculosis
TNF	tumor necrosis factor
UC	ulcerative colitis
UC-PRO/SS	Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON ULCERATIVE COLITIS

Ulcerative colitis (UC) is a chronic inflammatory condition that affects the rectum and extends proximally to the colon in a diffuse, continuous, superficial pattern. UC is characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain and may be complicated by severe bloody diarrhea and toxic megacolon, requiring major and sometimes urgent surgery. One-third of patients with UC can also experience extra-intestinal complications affecting the skin, joints, eyes, mouth, liver, and lungs (Ungaro et al. 2017; Kobayashi et al. 2020). Although there are many risk factors associated with the development of UC, the disease fundamentally represents dysregulation of the mucosal immune system in a genetically susceptible individual in response to commensal microbiota and other environmental triggers.

The burden of UC is rising, with increasing worldwide incidence and prevalence over time (Unagaro et al. 2017). The highest incidence rates have been reported in Europe (0.6 to 24.3 per 100,000), North America (8.8 to 23.1 per 100,000), and Oceania (7.3 to 17.41 per 100,000) (Du and Ha 2020). While the incidence of UC is stabilizing in Western countries, the prevalence continues to rise, and incidence is increasing in many newly industrialized countries in South America, Asia, Africa, and the Middle East (Ng et al. 2017; Du and Ha 2020; Mak et al. 2020). This rise may be due in part to better detection and diagnosis as well as environmental factors such as improved hygiene and a Western diet. The disease can affect any age group, but onset peaks between the ages of 15 and 35 years.

Current pharmacologic management of UC includes conventional therapies: anti-inflammatory drugs (corticosteroids and aminosalicylates such as 5-aminosalicylic acid [5-ASA]), immunosuppressants (such as azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]); and advanced therapies: tumor necrosis factor (TNF) inhibitors, anti-integrin agents (e.g., vedolizumab), anti-interleukin agents (e.g., ustekinumab*, mirikizumab, risankizumab, guselkumab*), Janus kinase (JAK) inhibitors (e.g., tofacitinib, upadacitinib, filgotinib), and sphingosine-1-phosphate receptor modulators (e.g., ozanimod*, etrasimod*) (Ungaro et al. 2017; Aslam et al. 2022). Current treatment strategies are focused on disease modification via induction of mucosal healing, decreased dependence on corticosteroids, and reduction in the probability of progression to surgery, without significant compromise of immune competence (Danese et al. 2020; Cai et al. 2021; Le Berre et al. 2022).

Despite the availability of advanced therapies, a therapeutic ceiling remains in patients with moderate to severe UC, with remission rates of only 20%–30% in induction trials (Alsoud et al. 2021). Recent estimates of remission rates from an international survey are 37%–55% with current treatments; however, 22%–29% of patients have experienced a loss of response to current medications (i.e., anti-TNF therapy, anti-integrin, JAK inhibitor, or anti-IL-12/23) (Rubin et al. 2021), highlighting the need for more durable

treatment options for patients with UC. Additionally, available advanced therapies have been associated with serious infections, infusion reactions, cardiovascular events, thrombosis, and malignancies (Gordon et al. 2015; XELJANZ® [tofacitinib] U.S. Prescribing Information; RINVOQ® [upadacitinib] U.S. Prescribing Information; STELARA® [ustekinumab] U.S. Prescribing Information; HUMIRA® [adalimumab] U.S. Prescribing Information). Therefore, there remains an unmet need for additional safe UC treatments that are both well tolerated and have durable efficacy.

1.2 BACKGROUND ON VIXARELIMAB

Vixarelimab (also known as KPL-716 and RO7622888) is a first-in-class, fully human, monoclonal antibody that targets oncostatin M receptor-beta (OSMRβ). OSMRβ is a cytokine receptor subunit that heterodimerizes with interleukin (IL)-31 receptor-alpha or glycoprotein 130 (gp130) to form two distinct cytokine receptors, IL-31 and oncostatin M (OSM) receptors, which mediate signaling of the cytokines IL-31 and OSM, respectively. Both cytokines mediate signaling pathways implicated in inflammation and fibrosis (Mozaffarian et al. 2008; Marden et al. 2020; Yaseen et al. 2020; Kuzumi et al. 2021). Vixarelimab binds to the human and cynomolgus monkey cytokine-binding domain of OSMRβ with an equilibrium dissociation constant of [redacted], respectively, and does not bind to [redacted] OSMRβ. Vixarelimab does not inhibit signaling of OSM via the leukemia inhibitory factor receptor (LIFR) pathway, which is implicated in hematopoiesis and the synthesis of platelets (Qadi et al. 2016), therefore leaving this pathway unaltered.

1.2.1 Summary of Nonclinical Safety

The nonclinical toxicology program for vixarelimab was designed to support IV and SC administration in clinical studies and included a Good Laboratory Practice (GLP) in vitro study of hemolytic potential (Study WIL-793060), an ex vivo tissue cross-reactivity study in a full panel of human and cynomolgus monkey tissues (Study 20080123), and 7-week (Study WIL-793057) and 26-week (Study CRL-082322) repeat-dose toxicology studies in cynomolgus monkeys.

Vixarelimab did not cause hemolysis in vitro when tested at concentrations up to [redacted] in human blood.

In an ex vivo tissue cross-reactivity study, vixarelimab staining was observed [redacted]

There were no vixarelimab-related effects in male and female cynomolgus monkeys following weekly IV or SC administration of doses up to [redacted] (the highest dose

tested) for up to 26 weeks. Thus, the no-observed-adverse-effect level (NOAEL) was considered to be [redacted] IV/SC when administered weekly. The corresponding mean Day 176 area under the concentration–time curve from time 0 to the end of the dosing interval (AUC_{0-168h}) for both sexes was [redacted] for IV administration and [redacted] for SC administration; the corresponding mean last-dose maximum serum concentration (C_{max}) for both sexes was [redacted] for IV administration and [redacted] for SC administration.

In summary, the vixarelimab toxicology program supports the clinical program. Refer to the Vixarelimab Investigator's Brochure for additional details on nonclinical studies.

1.2.2 Summary of Clinical Studies

Results from previous Phase I and Phase II studies have produced robust safety and efficacy data in inflammatory, hyperkeratotic skin disorders. In completed studies as of *15 July 2024, a total of 327 healthy volunteers and patients were exposed to vixarelimab across all studies.* Thirty-seven healthy volunteers (Phase Ib Study KPL-716-C001, Part 3), 41 patients with atopic dermatitis (AD) (Phase Ib Study KPL-716-C001, Parts 1 and 4), 23 patients with prurigo nodularis (PN) (Phase IIa portion of Study KPL-716-C201), *187 patients with PN (Phase IIb portion of Study KPL-716-C201),* 14 patients with plaque psoriasis, 14 patients with chronic idiopathic pruritis, 4 patients with chronic idiopathic urticaria, 3 patients with lichen planus, and 4 patients with lichen simplex chronicus (Phase II Study KPL-716-C202) have been exposed to at least one dose of vixarelimab. *Evidence of clinical activity (i.e., significant improvements in pruritus, sleep loss, and skin lesions) have been demonstrated with varying doses of vixarelimab in patients with AD, PN, or other chronic pruritic conditions across the completed Phase I and Phase II trials.*

[redacted]

The ongoing Phase II clinical trial (GB44496) *is* evaluating the efficacy, safety, and pharmacokinetics of vixarelimab at [redacted] versus placebo in patients with idiopathic pulmonary fibrosis and in patients with systemic sclerosis–associated interstitial lung disease.

Overall, vixarelimab has been well tolerated with an acceptable safety profile in healthy volunteers and in patients with AD, PN, and other chronic pruritic conditions. Refer to the Vixarelimab Investigator's Brochure for additional details on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Despite the emergence of new agents to treat patients with UC, additional treatment options are needed to improve disease control and outcomes, particularly targeting novel mechanisms in the pathophysiology of UC. Vixarelimab is a first-in-class oncostatin M receptor (OSMR) inhibitor, blocking signaling via the OSM and IL-31 pathways implicated in fibrosis, inflammation, hyperplasia, and pruritis; while sparing OSM signaling via gp130/LIFR, which is involved in hematopoiesis (Hermanns 2015; West et al. 2018; Stawski and Trojanowska 2019). Study GA44839 is the first study of vixarelimab in patients with UC.

Genome-wide association studies have identified polymorphisms in both *OSM* and *OSMR* associated with UC and Crohn's disease (Jostins et al. 2012; Liu et al. 2015). Further, OSM and OSMR mRNA and protein are increased in patients with inflammatory bowel disease (IBD). OSMR protein expression was higher in colonic biopsies from patients with active UC compared with those from patients in remission, with the highest expression observed in the epithelial and lamina propria cells (Beigel et al. 2014). Both mRNA and protein expression of OSM and OSMR were upregulated in the intestinal mucosa of patients with IBD and active disease relative to healthy controls (West et al. 2017; *Bondensgaard et al. 2021;* Verstockt et al. 2021).

In the intestinal mucosa, OSMR is expressed in nonhematopoietic and nonepithelial stromal cells (West et al. 2017*; Bondensgaard et al. 2021*), notably in inflammatory fibroblasts. Emerging evidence suggests that intestinal stromal cells play a key role in IBD pathogenesis (Barnhoorn et al. 2020). Inflammatory fibroblasts are greatly expanded in areas of active disease in the colon of patients with UC compared with healthy individuals, indicating that increased expression of OSMR may be driven by cell population numbers rather than upregulation of *OSMR* (Smillie et al. 2019). Additional data have shown a higher abundance of inflammatory fibroblasts in IBD lesions compared with other fibroblast types (*Kokkotis et al. 2024; Toghi Eshghi et al. 2024*).

OSM is expressed by hematopoietic cells of the intestinal mucosa, including $CD4^+$ T cells and myeloid cells (West et al. 2017). [redacted]

Of note, increased mucosal *OSM* and *OSMR* expression is correlated with worse disease prognosis, and increased levels were predictive of the absence of response to anti-TNF therapy in patients with IBD (West et al. 2017; Verstockt et al. 2021). Similar findings have been observed with serum/plasma OSM and response to anti-TNF therapy (Minar et al. 2019; Bertani et al. 2020; Guo et al. 2022). Further, an anti-TNF drug resistance signature was identified in OSMR-expressing inflammatory fibroblasts and OSM-expressing inflammatory monocytes and myeloid cells from inflamed colon biopsies of patients with UC (Smillie et al. 2019). This suggests that inhibition of OSM signaling may be of particular benefit in patients with UC who fail anti-TNF therapy.

As a selective inhibitor of OSMRβ, vixarelimab is anticipated to confer clinical benefit in UC patients. Vixarelimab has already been evaluated in healthy volunteers and patients with inflammatory skin disorders, including AD and PN, in Phase I and Phase II trials (see Section 1.2.2). Results from these trials to date demonstrate that vixarelimab is well tolerated with no identified safety risks.

As with all protein therapies, there is a possibility that administration of vixarelimab may lead to the development of anti-vixarelimab antibodies, which could lead to adverse events and/or decreased vixarelimab exposure. However, the immunogenicity rates observed with vixarelimab in clinical studies thus far have generally been low and with no apparent relationship between anti-drug antibody (ADA) positivity and exposure or safety in these studies. Monoclonal antibodies also carry a potential risk of hypersensitivity reactions and anaphylaxis, or hypersensitivity-like reactions. Hypersensitivity reactions are less frequent with SC administration in comparison with IV use (Pintea et al. 2021). Nevertheless, several measures, including implementation of stringent inclusion and exclusion criteria, and close monitoring of hypersensitivity reactions, have been implemented in this protocol to ensure the safety of patients participating in this study (see Section 5.1).

In summary, given the well-tolerated safety profile demonstrated by nonclinical and clinical results, the risk mitigation measures for the study, and the scientific rationale supporting the potential benefit of vixarelimab in patients with IBD, there is strong support for conducting this Phase II study in patients with UC.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of vixarelimab compared with placebo in patients with moderate to severe UC who have demonstrated inadequate response to, loss of response to, or intolerance to prior conventional or advanced therapy. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the induction efficacy of vixarelimab compared with placebo • To evaluate the induction efficacy of vixarelimab compared with placebo in advanced failures	• Clinical remission at Week 12, with clinical remission defined as mMS [a] of ≤2, including: ○ Stool frequency subscore ≤1 ○ Rectal bleeding subscore =0 ○ Endoscopy subscore ≤1 (score of 1 modified to exclude friability) [b]
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the induction efficacy of vixarelimab compared with placebo • To evaluate the induction efficacy of vixarelimab compared with placebo in advanced failures	• Clinical response at Week 12, with clinical response defined as meeting both of the following criteria: ○ Decrease from baseline in the mMS [a] of ≥2 and ≥30% reduction from baseline ○ Decrease in rectal bleeding subscore of ≥1 or absolute rectal bleeding subscore of ≤1 • Endoscopic improvement at Week 12, with endoscopic improvement defined as a Mayo endoscopy subscore of ≤ 1 (score of 1 modified to exclude friability) [b] • Endoscopic remission at Week 12, with endoscopic remission defined as a Mayo endoscopy subscore of 0 [b]
• To evaluate the safety of vixarelimab compared with placebo	• Incidence and severity of adverse events, with severity determined according to the DAIDS toxicity grading scale [c] • Change from baseline in selected vital signs • Change from baseline in selected clinical laboratory test results
• To characterize the pharmacokinetics of vixarelimab	• Serum concentration of vixarelimab at specified timepoints
• To evaluate the immune response to vixarelimab	• Prevalence of ADAs at baseline and incidence of ADAs during the study

ADA=anti-drug antibody; DAIDS=Division of AIDS; mMS=modified Mayo Score.

[a] Modified Mayo Score is the composite of three Mayo Score assessments: stool frequency, rectal bleeding, and centrally read endoscopy (see Appendix 3).

[b] Endoscopy scores will be based on interpretation by a blinded central reader.

[c] Adverse events will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (HHS 2017), with slight modifications for clarity and for alignment with internal practices (see Section 5.3.3 and Appendix 7).

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• To evaluate the long-term efficacy of vixarelimab	• Sustained remission, defined as clinical remission at [redacted] Week 12 [redacted] • Clinical remission at [redacted] • Clinical response at [redacted] • Endoscopic improvement at [redacted] • Endoscopic remission at [redacted] • Change from baseline in UC bowel movement signs and symptoms at Week 12 and [redacted], as assessed by UC-PRO/SS score • Improvement in UC bowel movement signs and symptoms at Week 12 [redacted], as defined by the proportion of patients with a ≥6-point decrease in the UC-PRO/SS bowel domain score • Change from baseline in UC functional signs and symptoms at Week 12 and [redacted], as assessed by UC-PRO/SS score • Improvement in UC functional symptoms at Week 12 and [redacted], as defined by the proportion of patients with a ≥2-point decrease in the UC-PRO/SS functional domain score
• To evaluate potential relationships between vixarelimab exposure and the efficacy and safety of vixarelimab	• Relationship between PK parameters for vixarelimab and efficacy endpoints • Relationship between PK parameters for vixarelimab and safety endpoints
• To evaluate potential relationships between selected covariates and exposure to vixarelimab	• Relationship between selected covariates and PK parameters for vixarelimab
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints

ADA = anti-drug antibody; PK = pharmacokinetic; UC = ulcerative colitis; UC-PRO/SS = Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms.

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives (cont.)	Corresponding Endpoints
• To identify and/or evaluate biomarkers that are predictive of response to vixarelimab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to vixarelimab, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of vixarelimab activity or disease improvement (i.e., PD biomarkers), can serve as a useful surrogate endpoint, or can increase the knowledge and understanding of disease biology and drug safety or pharmacokinetics	• Relationship between biomarkers in blood, serum, stool, and colonic tissue (listed in Section 4.5.8) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
• To evaluate the use of automated assessment of endoscopic videos to infer the efficacy of vixarelimab	• Automated assessment of disease severity • Automated spatial assessment of mucosal features

PD = pharmacodynamic; PK = pharmacokinetic.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase II, multicenter, randomized, parallel-group, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and pharmacokinetics of vixarelimab compared with placebo in patients with active moderate to severe UC, including 1) patients who have demonstrated inadequate response to, loss of response to, or intolerance to prior advanced therapy which includes biologics and targeted small molecules (advanced failures), and 2) patients who have demonstrated inadequate response to, loss of response to, or intolerance to prior conventional therapies (corticosteroids and/or immunosuppressants) but have not failed advanced therapy (conventional failures).

The study consists of a screening period of up to 35 days, a [redacted] treatment period, and a safety follow-up period for [redacted] following the final dose of study treatment. The induction period [redacted] will test the induction of clinical remission. After completion of the induction period, all patients, irrespective of clinical response or remission, will be eligible to continue study treatment during an optional active treatment

extension (ATE) period [redacted] During the ATE period, all patients will receive vixarelimab, including patients who received placebo during the induction period, and the durability of clinical response and remission will be explored.

Approximately 210 patients, including advanced failures and conventional failures, will be enrolled across global investigational sites. [redacted] Randomization will be stratified by previous advanced or conventional therapy failure and baseline modified Mayo Score (mMS) [redacted] Restrictions regarding concomitant therapy are outlined in Section 4.4.1.

Eligible patients will be randomized in a [redacted] ratio to one of the following treatment arms for the induction period ([redacted]:

- Vixarelimab [redacted] arm [redacted]
- Vixarelimab [redacted] arm [redacted]
- Placebo [redacted] arm [redacted]

All patients who complete the induction period can receive SC injections of vixarelimab [redacted] during the optional ATE period [redacted]. Patients assigned to the vixarelimab [redacted] arm or vixarelimab [redacted] arm during the induction period will continue on their randomized treatment assignment during the optional ATE period:

- Patients in the vixarelimab [redacted] arm will receive vixarelimab [redacted].
- Patients in the vixarelimab [redacted] arm will receive vixarelimab [redacted] and placebo [redacted].
- Patients in the placebo arm during the induction period will receive vixarelimab [redacted] during the optional ATE period.

Patients will undergo an endoscopy with biopsy and a full Mayo Score assessment (see Appendix 3) at screening (baseline), [redacted]. Efficacy will be assessed using the modified Mayo Score (mMS; see Appendix 3), with the Mayo endoscopic subscore calculated on the basis of centrally read endoscopy. The mMS (see Appendix 3) will be derived from the Mayo Score (see Section 4.5.7).

Patients who complete the treatment period (induction and optional ATE) will enter the safety follow-up period and undergo assessments at [redacted] Patients who discontinue study treatment without entering the optional ATE period will enter the safety follow-up period and undergo assessments at [redacted] following the final dose of study treatment. Patients who discontinue study treatment prematurely for the reasons listed in Section 4.6.1 should return to the clinic for a treatment

discontinuation visit within 14 days of the event and will then enter the safety follow-up period.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. *In exceptional cases and in consultation with the Medical Monitor, a patient who screen fails because of an ineligible mMS may be re-screened if the screen fail is due to an ineligible endoscopy subscore (i.e., < 2) and not due to the average stool frequency and rectal bleeding score.* Patients who are classified as screen failures due to the presence of *Clostridium difficile* (*C. difficile*), cytomegalovirus (CMV), *or other intestinal pathogen* infection may be re-screened *30 days* after successful treatment*, per local practice*.

Patients are not required to re-sign the consent form if they are re-screened within 6 weeks after previously signing the consent form. The investigator will maintain a record of reasons for screen failure (see Section 4.5.1).

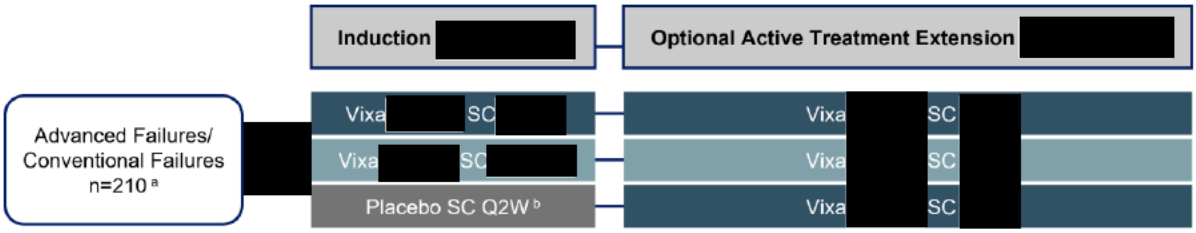
In the event the individual is re-screened, screening assessments should be repeated as follows:

- *If the individual is re-screened ≤6 weeks after the initial consent form is signed, only the assessments that triggered screen failure need to be repeated.*
  - *Screening endoscopy does not need to be repeated if the initial endoscopy was performed within 35 days prior to dosing on Day 1, and*
  - *Colonic biopsies as specified by the protocol have been obtained.*
- *If the individual is re-screened >6 weeks after the initial consent form is signed, all screening assessments must be repeated, with the following exceptions:*
  - *HIV and hepatitis B and C testing do not need to be repeated if re-screening occurs within 3 months after the initial consent form was signed.*
  - *The chest X-ray does not need to be repeated if results are available from a chest X-ray or chest CT scan performed within 3 months prior to re-screening.*
- *If a second ECG is required for re-screening purposes, it must be performed at least 30 minutes after the first ECG.*

The screening period is up to 35 days; however, if required because of unforeseen circumstances, the screening period may be extended up to 7 additional days, in consultation with the Medical Monitor.

An overview of the study design is presented in Figure 1. Schedules of activities are provided in Appendix 1 (induction period) and Appendix 2 (optional ATE period).

Figure 1 Study Schema



Rand = randomization; SC = subcutaneous; Vixa = vixarelimab.

a .

b .

c

Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor data on safety, efficacy, and study conduct on an ongoing basis. Members of the IMC will include Sponsor representatives from Clinical Science, Drug Safety, and Biostatistics, and may invite representatives from other functional areas (e.g., Statistical Programing, Clinical Pharmacology, Research) or external experts on an ad hoc basis when additional expertise is required. Further details regarding roles and responsibilities will be outlined in an IMC Charter.

The IMC will review cumulative unblinded data on a periodic basis as defined in the IMC charter. In addition, ad hoc reviews may be requested by the IMC or the Sponsor at any time to address potential safety concerns. The data will include, but will not be limited to, demographic data, concomitant medications, adverse events data (including serious adverse events and adverse events of special interest), ECG data, and relevant laboratory data.

After reviewing the data, the IMC may make recommendations such as the following:

- The trial will continue as planned
- The trial will continue with a reduction in dose level or frequency within a treatment arm
- The trial will stop for safety or futility reasons
- Additional analyses will need to be performed
- Enrollment will be held pending further safety evaluation

The IMC may also provide recommendations for amending the protocol after consideration of all available data. Final decisions will rest with the Sponsor's study team.

3.1.2 Patient Input into Study Design

This protocol was developed considering the perspective of individuals living with IBD and IBD patient organization representatives. Insights, lessons learned from prior studies, and examples of what individuals living with IBD consider to be a patient-friendly trial were previously generated through multiple interactions and collaborations with individuals in the IBD community (Roche IBD Patient Council).

3.2 END OF STUDY DEFINITION

The end of this study is defined as the date when the last patient has completed his or her last visit or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur [redacted] after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 DURATION OF PARTICIPATION

The total duration of study participation for each patient is expected to be approximately [redacted] who complete the optional ATE.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Vixarelimab Dose and Schedule

[redacted]:

- [redacted]
- [redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.4.2 Rationale for Patient Population

There is an ongoing high unmet medical need in the treatment of patients with moderate to severe UC. Despite advances in the range of therapeutic options from biologics to targeted small molecules, many patients have an inadequate response to therapy, lose response over time, or cannot tolerate available treatments. In addition to inadequate disease control, available treatments are associated with at least one or more risks such

as serious infections and thromboembolic, cardiovascular, and malignancy. Because of the limitations of currently available therapies, there exists a need for new safe and effective UC treatment options, especially in patients for whom prior therapies have failed. Vixarelimab is being developed as a novel therapeutic agent to achieve clinical remission in patients with moderate to severe UC who have demonstrated inadequate response to, loss of response to, or intolerance to prior conventional or advanced therapy.

[redacted]. All patients considered for participation will have a diagnosis of moderate to severe UC established at least 3 months prior to screening, with active disease confirmed by clinical and endoscopic evidence during screening. Patients must have demonstrated an inadequate response, loss of response, or intolerance to prior conventional UC therapies and/or to [redacted] approved advanced therapies (as defined in Section 4.1.1). [redacted]

Because OSMR mediates signal transduction of OSM via a signaling pathway involving JAKs, patients with inadequate response or loss of response to JAK inhibitors are less likely to benefit from treatment with vixarelimab, and therefore patients *who have experienced inadequate response or loss of response to a JAK inhibitor for treatment of UC* will be excluded. Additionally, patients who may be at increased risk and those who require intervention other than the standard-of-care therapies as defined in this protocol will be excluded (see Section 4.1.2).

3.4.3 Rationale for Placebo Control Group

In accordance with the International Council for Harmonisation (ICH) E10 guideline, the European Medicines Agency (EMA) "Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis" (EMA 2018), and the FDA draft "Ulcerative Colitis: Developing Drugs for Treatment" Guidance for Industry (FDA 2022), a placebo-treated control group will be used to provide optimal evaluation of the efficacy and safety of vixarelimab. Because observed placebo response and remission rates have been highly variable across prior UC clinical trials (Jairath et al. 2017), a placebo group controls for the variability in outcome measures associated with subjective assessments such as patient-reported outcomes and disease factors such as spontaneous remission and the inherent variability in disease flares. Patients in the placebo arm who complete the induction period at [redacted] will be provided the option to receive active treatment with vixarelimab in the optional ATE period of the study.

3.4.4 Rationale for Biomarker Assessments

Target engagement and pharmacodynamic biomarkers will be assessed in serum, stool, and colon biopsy tissue to demonstrate evidence of biologic activity of vixarelimab in patients to support interpretation of clinical endpoints and selection of recommended dose and dosing regimen. [redacted]

Disease biomarkers, including fecal calprotectin and serum CRP, are associated with active disease and are commonly used for disease monitoring. Therefore, levels of these biomarkers will be assessed for change to support the interpretation of clinical endpoints and selection of recommended dosing regimen.

UC is a heterogenous disease, with treatment response varying among patients due to factors that are not fully understood, highlighting the need for biomarkers that may predict treatment response and guide treatment decisions. Baseline biomarkers in serum, blood, tissue, and fecal samples will be assessed for any prognostic association with disease projection or trajectory and potential value in predicting response.

3.4.5 Rationale for Optional Active Treatment Extension

The optional ATE period will explore the durability of clinical response and remission and the long-term safety of vixarelimab over an extended treatment period of [redacted]. The design of the optional ATE period will allow all eligible patients who have completed the induction period to be treated with vixarelimab, regardless of initial treatment assignment.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 210 patients with moderate to severe UC will be enrolled in this study.

4.1.1 Inclusion Criteria

4.1.1.1 General Inclusion Criteria for All Patients

All patients must meet the following criteria for study entry, as well as additional criteria for advanced failures (Section 4.1.1.2) **or** conventional failures (Section 4.1.1.3):

- Signed Informed Consent Form
- Adults (≥18 years of age or per local standards) at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Diagnosis of UC established at least 3 months prior to screening, confirmed by clinical and endoscopic evidence during screening

The diagnosis of UC should be corroborated by histopathology and documented by a histopathology report. A histopathologic examination should be performed at screening if no prior report is readily available.

- [redacted]
- [redacted]
- Any permitted background UC therapy must be at stable doses, as outlined below:
  - May be receiving oral 5-ASA compounds at a dose that has been stable for ≥2 weeks immediately prior to screening *endoscopy*.
  - May be receiving oral corticosteroid therapy at a dose of ≤20 mg/day of prednisone (or equivalent) that has been stable for ≥2 weeks immediately prior to screening *endoscopy*.
  - May be receiving oral probiotic (e.g., Culturelle, *Saccharomyces boulardii*), at a dose has been stable for ≥2 weeks immediately prior to screening *endoscopy*.
  - May be receiving AZA, 6-MP, or MTX at a dose that has been stable for ≥12 weeks immediately prior to screening *endoscopy*.
- Must have received a colonoscopy within 2 years prior to screening or be willing to undergo a colonoscopy in lieu of a flexible sigmoidoscopy at screening. This colonoscopy must:
  - Confirm disease extent, defined as 1) left-sided colitis (inflammation up to the splenic flexure), 2) extensive colitis (inflammation beyond the splenic flexure but not involving the entire colon), or 3) pancolitis (inflammation of the entire colon)
  - Include removal of any adenomatous polyps
  - Include surveillance to detect dysplasia per local standard of care for all patients with left-sided colitis of >12 years' duration or extensive colitis or pancolitis of >8 years' duration
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, *and agreement to refrain from donating eggs,* as defined below:

  Women must remain abstinent or use <u>two</u> methods of contraception, including at least one method with a failure rate of <1% per year, during the treatment period and for [redacted] after the final dose of study treatment. *Women must refrain from donating eggs during this same period.*

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator

(e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

A barrier method may be used as the second contraceptive method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for [redacted] after the final dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.1.2 Inclusion Criteria for Advanced Failures

Advanced failure patients must meet the following criteria for study entry:

- Inadequate response, loss of response to, or intolerance to [redacted] of approved advanced therapies, which include biologics and targeted small molecules, as defined by the following:
  - Inadequate response is defined by persistent signs and symptoms of active disease despite at least one induction regimen of advanced therapy.
  - Loss of response is defined by the recurrence of symptoms during maintenance dosing of advanced therapy following prior clinical benefit (discontinuation despite clinical benefit or discontinuation due to loss of access does not qualify).
  - Intolerance is defined by history of adverse effect necessitating treatment discontinuation of advanced therapy (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection).

4.1.1.3 Inclusion Criteria for Conventional Failures

Conventional failure patients must meet the following criteria for study entry:

- Inadequate response, loss of response to, or intolerance to prior conventional UC therapies (immunosuppressant and/or corticosteroid treatment)

  Failure to only 5-ASA treatment is not sufficient.

  Inadequate response to, loss of response to, or intolerance to prior immunosuppressant treatment (i.e., AZA, 6-MP, or MTX), is defined as one or more of the following:

  – Persistent signs and symptoms of active disease despite treatment with at least one 12-week regimen of AZA (≥1.5 mg/kg/day) or 6-MP (≥0.75 mg/kg/day) and/or MTX ≥15 mg/week)

  – Persistent signs and symptoms of active disease despite a 6-thioguanine nucleotide level of ≥230 pmol/8×10^8 RBCs (as measured by quantitative high-performance liquid chromatography or liquid chromatography/tandem mass spectrometry) during at least one 12-week regimen of oral AZA or 6-MP at a stable or increasing dose

  – History of intolerance to, *or inability to titrate doses to levels listed above for,* AZA, 6-MP, or MTX *because of the risk of adverse effects* (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, TPMT genetic mutation, or infection)

  Inadequate response, loss of response, or intolerance to corticosteroid treatment is defined as one or more of the following:

  – Steroid refractory: persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included ≥30 mg/day of oral prednisone (or equivalent) for at least 2 weeks or ≥30 mg/day of IV prednisone (or equivalent) for at least 1 week

  – Steroid dependent: *one* failed attempt to taper *cortico*steroids below a dose equivalent to 10 mg/day of oral prednisone (or equivalent) *within 3 months, or disease relapse within 3 months after corticosteroid discontinuation*

  – Steroid intolerant: history of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection)

- Conventional failures who have received a prior advanced therapy but do not meet inclusion criteria for advanced failures (Section 4.1.1.2) may be enrolled, in consultation with the Medical Monitor

  Patients must have discontinued the biologic for reasons other than inadequate response, loss of response, or intolerance (e.g., change of insurance, well controlled disease), and must meet the criteria for inadequate response, loss of response, or intolerance to immunosuppressants and/or corticosteroids defined above.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnancy or breastfeeding or intention to become pregnant during the study or within [redacted] after the final dose of study treatment

  Women of childbearing potential must have a negative serum pregnancy test result at screening and a negative urine pregnancy test on Day 1 prior to initiation of study treatment.
- History of alcohol, drug, or chemical abuse ≤2 years prior to screening
- Prior extensive colonic resection, subtotal or total colectomy, or planned surgery for UC
- Past or present ileostomy or colostomy
- Diagnosis of Crohn's disease or indeterminate colitis
- Suspicion of ischemic colitis, radiation colitis, or microscopic colitis
- Diagnosis of toxic megacolon within 12 months of initial screening visit
- Past or present fistula or abdominal abscess
- History or current evidence of unresected adenomatous colonic polyps or colonic mucosal dysplasia
- Any stricture (stenosis) of the colon that precludes endoscopic evaluation
- Diagnosis or suspicion of primary sclerosing cholangitis
- History of *known or suspected* allergic reaction or anaphylactic reaction to a biologic agent*, including vixarelimab or its excipients*
- Previous treatment with vixarelimab or current participation in Study GB44496
- *Inadequate response or loss of response to* previous treatment *of UC* with tofacitinib, upadacitinib, or other systemic JAK inhibitor
- Treatment of UC with approved biologic agents within 8 weeks or 5 half-lives prior to screening *endoscopy*, whichever is longer

  If there is proper documentation of undetectable drug level measured by a commercially available assay for any of the approved biologics, there is no minimum washout prior to screening *endoscopy*.
- Treatment of UC with approved non-biologic therapies other than those specifically listed as permitted medications (Section 4.4) within *2 weeks* or 5 half-lives prior to screening *endoscopy*, whichever is longer
- Use of IV corticosteroids within 2 weeks prior to screening *endoscopy*
- Treatment with corticosteroid enemas or suppositories and/or topical (rectal) 5-ASA preparations within 2 weeks prior to screening *endoscopy*
- Apheresis (e.g., Adacolumn® apheresis) within 2 weeks prior to screening *endoscopy* or intent to receive during the study
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use

Occasional use of NSAIDs [e.g., headache, arthritis, myalgias, or menstrual cramps] and aspirin (up to 325 mg/day) is permitted.

- Participation in an investigational study involving non-biologic therapy within *4 weeks* or 5 half-lives of the investigational product (whichever is greater) prior to screening, or biologic therapy (including vaccines) within 8 weeks or 5 half-lives of the investigational product (whichever is greater) prior to screening
- Treatment with any live-attenuated vaccine within 4 weeks prior to screening or intended to receive such during the study.

  Uses of non-live (inactivated) vaccines are allowed.
- Treatment with immunoglobulin or blood products within 4 weeks prior to screening, or any condition that is likely to require such treatment during the course of the study, unless the treatment is deemed acceptable by the investigator, in consultation with the Medical Monitor
- Conditions other than UC that could require treatment with $>$20 mg/day of prednisone (or equivalent) during the course of the study*, per the investigator's assessment*
- Significant uncontrolled medical condition or comorbidity, such as cardiac (e.g., moderate to severe heart failure New York Heart Association Class III/IV or historical evidence of left ventricular ejection fraction $<$35%), pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders (excluding UC) that in the opinion of the investigator, would confound the study results or compromise patient safety
- Hospitalized (other than for elective reasons) during the screening period
- History of malignancy within the 5 years prior to screening, with the exception of basal cell or squamous cell skin neoplasms

  In addition, a malignant diagnosis or condition that occurred more than 5 years prior to screening, and any basal cell or squamous cell neoplasm must be considered cured, inactive, and not under treatment.
- History or presence of complete left bundle branch block, second- or third-degree atrioventricular heart block, *or other abnormal ECG finding during screening that is deemed clinically significant by the investigator*
- QT interval corrected through use of Fridericia's formula (QTcF) $>$450 ms if patient is male or QTcF $>$470 if patient is female

  For male or female patients with QRS $>$120: QTcF $>$480 ms
- Acquired or congenital immunodeficiency
- Positive HIV antibody test at screening
- Positive hepatitis C virus (HCV) antibody test result accompanied by a positive HCV RNA test at screening
- Positive test results for hepatitis B infection at screening, defined as meeting either of the following criteria:
  - Positive hepatitis B surface antigen (HBsAg) test at screening

- Quantitative HBV DNA ≥20 IU/mL in patients with a negative hepatitis B surface antibody (HBsAb) test and positive total hepatitis B core antibody (HBcAb) test

- Positive for tuberculosis (TB) during screening or within 3 months prior to screening, defined as a positive *interferon-γ release assay* (*IGRA; e.g.,* QuantiFERON®-TB Gold *or T-SPOT.TB), or* if not available, a positive purified protein derivative (PPD) skin test according to Centers for Disease Control and Prevention guidelines, with the following exceptions:
  - Patients with a history of Bacillus Calmette-Guérin (BCG) vaccination who have a positive PPD skin test will not be excluded if they have a negative *IGRA* at screening
  - Patients who have a positive or indeterminate *IGRA* and patients with no history of BCG vaccination who have a positive PPD skin test will not be excluded if they meet all of the following criteria:

    No symptoms consistent with TB

    Documented history of a completed course of adequate prophylaxis (completed treatment for latent TB) per local standard of care prior to screening, *or initiation of treatment for latent TB per local standard of care at least 3 weeks prior to randomization with intention to complete treatment while on study*

    For patients not currently on latent TB treatment, no known exposure to a case of active TB after most recent *completed* prophylaxis*, if applicable*

    No evidence of active TB on chest X-ray performed during screening or within 3 months prior to screening

- Evidence of *C. difficile* (as assessed by *C. difficile* toxin testing) or other intestinal pathogens (as assessed by stool culture and ova and parasite evaluation) at screening or within *30 days* prior to screening

- Colonic biopsy positive for CMV, as determined by histologic examination or immunohistochemistry per local standards, at screening or within *30 days* prior to screening

  Laboratory confirmation of CMV from a colon biopsy sample is required during screening evaluation only if clinical suspicion is high and to determine the need for CMV treatment.

- Clinically significant abnormality on laboratory tests during screening (hematology, serum chemistry, and urinalysis) that, in the opinion of the investigator, may pose an additional risk in administering study treatment to the patient

- ALT, AST, or ALP >2.5 × upper limit of normal (ULN), total bilirubin >2 × ULN, or presence of abnormalities in synthetic liver function tests judged to be clinically significant by the investigator

  Patients with known Gilbert syndrome who have unconjugated hyperbilirubinemia will not be excluded.

- ANC $< 1.5 \times 10^9$/L (1500/μL), with one exception:

  Patients with benign ethnic neutropenia (BEN): ANC $< 1.3 \times 10^9$/L (1300/μL)

  BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestations (Atallah-Yunes et al. 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.

- Absolute lymphocyte count $< 0.5 \times 10^9$/L (500/μL)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a three-arm randomized study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of three treatment arms: the vixarelimab [redacted] arm, vixarelimab [redacted] arm, or placebo arm in a [redacted] ratio. Randomization will occur through use of a permuted-block randomization method to ensure a [redacted]. Randomization will be stratified by advanced or conventional failure and baseline mMS [redacted] During the optional ATE period, patients assigned to the vixarelimab [redacted] arm or the vixarelimab [redacted] arm during the induction period will continue on the randomized treatment assignment; patients treated with placebo during the induction period will receive vixarelimab [redacted] (see Section 3.1.1 for further details).

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment *until database lock*. The Sponsor and its agents will also be blinded to treatment assignment *until the execution of the primary analyses*, with the exception of *a limited set of* individuals who *are not directly involved with study conduct and* require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and IMC members.

While PK and immunogenicity samples must be collected from patients assigned to the placebo arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the placebo arm will not be analyzed for study drug PK concentration except by request (e.g., to

evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all patients. Postbaseline immunogenicity samples from patients assigned to the placebo arm will not be analyzed for ADAs except by request.

If unblinding *becomes* necessary *because of* a medical emergency (e.g., serious adverse event for which management might be affected by knowledge of *the participant's* treatment assignment), the investigator will be able to break the treatment code *via* the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code *in an emergency situation*. However, the Medical Monitor *should be informed* that the treatment code has been broken.

The investigator will also be able to break the treatment code to determine the suitability of subsequent medical care for a participant. However, approval must be obtained from the Sponsor Medical Monitor if the investigator wants to break the treatment code to determine a participant's eligibility for a subsequent clinical trial testing investigational medicinal products or procedures. The investigator must contact the Sponsor Medical Monitor prior to breaking the treatment code for any reason other than a medical emergency. The investigator should document and provide an explanation for any non-emergency unblinding.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to drugs listed in Section 5.7). The investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is vixarelimab.

Appendix 6 identifies all investigational and non-investigational medicinal products for this study.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Vixarelimab and Placebo

Vixarelimab will be supplied by the Sponsor as sterile liquid in glass vials. For information on the vixarelimab formulation, see the pharmacy manual and Vixarelimab Investigator's Brochure.

Placebo will be supplied by the Sponsor as sterile liquid in glass vials indistinguishable from vials of blinded vixarelimab. For information on the placebo formulation, see the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

Refer to the pharmacy manual for detailed instructions on drug preparation.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.6.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

4.3.2.1 Vixarelimab and Placebo

Vixarelimab and matching placebo will be administered by SC injection.

Patients assigned to vixarelimab [redacted] arm will receive [redacted] vixarelimab at [redacted] throughout the induction period and optional ATE period. Patients assigned to vixarelimab [redacted] will receive [redacted] vixarelimab [redacted] throughout the induction period and optional ATE period. [redacted], patients assigned to vixarelimab [redacted] will also receive [redacted] through the induction period and optional ATE period. Patients assigned to placebo [redacted] in the induction period and [redacted] vixarelimab [redacted] in the optional ATE period. Study treatment should be administered after all other procedures have been completed at each visit, unless specifically indicated otherwise.

Administration of study treatment will be performed at the clinical site by trained personnel in a monitored setting where there is immediate access to adequate equipment and medications (e.g., IV solutions, epinephrine, antihistamines, corticosteroids) to manage potentially serious reactions.

Patients should be monitored during study treatment [redacted]

Investigators and healthcare professionals administering study treatment should recognize and manage the signs and symptoms of anaphylactic reactions according to 2006 National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network guidelines (Sampson et al. 2006; Appendix 8). Healthcare professionals should also instruct patients on how to recognize the symptoms of any such events and to contact a healthcare provider or seek emergency care in case of any such symptoms. All cases of suspected allergic or anaphylactic reactions will be documented through the

Anaphylaxis, Anaphylactoid, and Hypersensitivity Reaction eCRF. For anaphylaxis precautions, see Appendix 5.

Rules for treatment interruption are provided in Section 5.1.2.2. Dose modifications are not permitted.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Vixarelimab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Vixarelimab

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMP (vixarelimab) or any other study treatments to patients

who have completed the study. The Sponsor may evaluate whether to continue providing vixarelimab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from the start of the screening period to the study completion or discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medication eCRF.

Patients requiring a prohibited therapy (refer to Section 4.4.1 [Table 2] and Section 4.4.2.2) will be discontinued from study treatment (see Section 4.6.1) and will undergo follow-up assessments as described in Appendix 1 and Appendix 2.

4.4.1 Permitted and Prohibited Therapy for Ulcerative Colitis (Including Background and Rescue Therapy)

Permitted and prohibited concomitant therapies for UC, including background and rescue therapies, are outlined in Table 2.

Table 2 Permitted and Prohibited Therapies for Ulcerative Colitis

Therapy	Prior to Screening *Endoscopy* [a]	During Screening and Induction	During Optional ATE and Safety Follow-Up	Rescue Therapy
Anti-Inflammatories				
Topical (rectal) 5-ASA	• Must not have received topical (rectal) 5-ASA within 2 weeks prior to screening *endoscopy*	• Treatment with topical (rectal) 5-ASA is prohibited	• *Intermittent use of topical (rectal) 5-ASA is permitted up to 2 weeks of daily use; must be discontinued by* [redacted]	• Initiation of topical (rectal) 5-ASA is considered rescue therapy *and is permitted only during the optional ATE period*
Oral 5-ASA	• May be receiving oral 5-ASA if dose has been stable for at least 2 weeks prior to screening *endoscopy*	• Baseline level of oral 5-ASA must be maintained • Initiation or increase in dose of oral 5-ASA is prohibited	• *For patients on oral 5-ASA at baseline, the dose may be tapered until discontinuation, starting at* [redacted] • Initiation or increase in dose of oral 5-ASA is prohibited	• Initiation of oral 5-ASA or increase in dose of oral 5-ASA compared with baseline is considered rescue therapy *and is prohibited*
IV corticosteroids and rectal corticosteroids (i.e., enemas or suppositories)	• Must not have received IV corticosteroids within 2 weeks prior to screening *endoscopy* • Must not have received rectal corticosteroids within 2 weeks prior to screening *endoscopy*	• Treatment with IV or rectal corticosteroids is prohibited	• Treatment with IV or rectal corticosteroids is prohibited	• Initiation of IV or rectal corticosteroids is considered rescue therapy *and is prohibited*

5-ASA = 5-aminosalicylic acid; ATE = active treatment extension.

[a] See inclusion and exclusion criteria in Section 4.1.1 and Section 4.1.2 for additional details.

Table 2 Permitted and Prohibited Therapies for Ulcerative Colitis (cont.)

Therapy	Prior to Screening *Endoscopy* [a]	During Screening and Induction	During Optional ATE and Safety Follow-Up	Rescue Therapy
Anti-Inflammatories (cont.)				
Oral corticosteroids	• May be receiving oral corticosteroids *at doses* ≤20 mg/day prednisone (or equivalent) if dose has been stable for at least 2 weeks prior to screening *endoscopy* (baseline steroid level) [b, c]	• Baseline level of oral corticosteroids must be maintained (≤20 mg/day prednisone or equivalent) • Initiation or increase in dose of oral corticosteroids is prohibited	• For patients on oral corticosteroids at baseline, corticosteroid dose may be tapered until discontinuation, starting at [redacted] • For patients who cannot tolerate the corticosteroid taper without recurrence of UC symptoms or experience symptoms of corticosteroid withdrawal, the corticosteroid dose can be increased [d] • Initiation or increase in dose of oral corticosteroids above baseline steroid level is prohibited	• Initiation of oral corticosteroids or increase in dose of oral corticosteroids above baseline steroid level is considered rescue therapy *and is prohibited*
Immunosuppressants				
AZA, 6-MP, or MTX	• May be receiving AZA, 6-MP, or MTX if the dose has been stable for at least 12 weeks prior to screening *endoscopy* • *Discontinuation of AZA, 6-MP, or MTX must be for at least 2 weeks prior to screening endoscopy*	• Baseline level of AZA, 6-MP, or MTX must be maintained • Initiation or increase in dose of AZA, 6-MP, or MTX is prohibited	• For patients on AZA, 6-MP, or MTX at baseline, the dose may be tapered until discontinuation, starting at [redacted] • Initiation or increase in dose of AZA, 6-MP, or MTX is prohibited	• Initiation or increase in dose of AZA, 6-MP, or MTX is considered rescue therapy *and is prohibited*

6-MP = 6-mercaptopurine; ATE = active treatment extension; AZA = azathioprine; MTX = methotrexate.

[a] See inclusion and exclusion criteria in Section 4.1.1 and Section 4.1.2 for additional details.

[b] The equivalent dose of budesonide to prednisone has not been fully characterized; however, ≤6 mg/day budesonide is permitted .

[c] There is limited/no data on beclomethasone dipropionate equivalency in inflammatory bowel disease. Beclomethasone dipropionate should not be used for more than 4 weeks based on the Clipper Summary of Product Characteristics.

[d] If the corticosteroid dose has not been increased above the baseline level, these patients can re-initiate corticosteroid dose tapering. Treatment with corticosteroids above the baseline dose will be considered rescue therapy.

Table 2 Permitted and Prohibited Therapies for Ulcerative Colitis (cont.)

Therapy	Prior to Screening *Endoscopy* [a]	During Screening and Induction	During Optional ATE and Safety Follow-Up	Rescue Therapy
Advanced Therapies				
Biologics: • Anti-TNFs • Anti-integrin • Anti-interleukins Small molecules: • S1P receptor modulators	• Must not have received an advanced therapy within 8 weeks *for biologic therapy, 2 weeks for non-biologic therapy,* or 5-half-lives prior to screening *endoscopy*, whichever is longer	• Treatment with advanced therapy is prohibited	• Treatment with advanced therapy is prohibited	• Advanced therapies are prohibited as rescue therapy
JAK inhibitors	• *Inadequate response or loss of response to* prior treatment with JAK inhibitor is exclusionary • *Discontinuation of JAK inhibitor must be for at least 2 weeks prior to screening endoscopy*	• Treatment with JAK inhibitors is prohibited	• Treatment with JAK inhibitors is prohibited	• JAK inhibitors are prohibited as rescue therapy
Other Therapies				
Oral probiotics	• May be receiving oral probiotics (e.g., Culturelle, *S. boulardii*) if dose has been stable for at least 2 weeks at the time of screening *endoscopy*	• Initiation of oral probiotics is not permitted • Baseline usage of oral probiotics must remain stable during the study	—	—

ATE = active treatment extension; JAK = Janus kinase; TNF = tumor necrosis factor.

[a] See inclusion and exclusion criteria in Section 4.1.1 and Section 4.1.2 for additional details.

4.4.2 Other Concomitant Therapy

4.4.2.1 Other Permitted Concomitant Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of < 1% per year (see Section 4.1.1)
- Hormone-replacement therapy
- *Latent TB treatment per local standard of care, as described in Section 4.1.2*

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Premedication with antihistamines, anti-pyretics, and/or analgesics may be administered at the discretion of the investigator.

Patients may continue on stable regimens of drugs they are receiving as treatment for coexistent stable diseases (e.g., antihypertensives, cholesterol-lowering drugs, or bronchodilators).

Over-the-counter preparations deemed *necessary after taking into consideration prohibited concomitant therapies, as described in Section 4.4.2.2 and not expected to interfere with the study drug,* will be allowed during the study. Initiation of over-the-counter medications during the study will need to be approved by the investigator *in consultation with the Medical Monitor, if necessary*.

4.4.2.2 Other Prohibited Concomitant Therapy

Use of the following concomitant therapies during the study is prohibited as described below:

- Any treatment for UC other than those listed in Section 4.4.1
- Chronic use of NSAIDs is prohibited prior to and during the study.

  Occasional use of NSAIDs(e.g., headache, arthritis, myalgias, or menstrual cramps), and aspirin *(*up to 325 mg daily*)* is permitted.
- Apheresis (e.g., Adacolumn® apheresis) is prohibited within 2 weeks prior to screening *endoscopy* and during the study.
- Chronic use of anti-diarrheals (e.g., loperamide, diphenoxylate with atropine) is prohibited prior to and during the study.
- *Investigational biologic and non-biologic therapy use is prohibited within 8 weeks or 4 weeks, respectively, or 5 half-lives (whichever is greater) prior to screening and during the study.*
- *Live-attenuated vaccines are prohibited within 4 weeks prior to screening and during the study.*
- *Treatment with immunoglobulin or blood products within 4 weeks prior to screening and during the study.*

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 and Appendix 2. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and *recent* laboratory test values*, if available,* are acceptable.

4.5.1 Informed Consent Forms and Screening Records

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all patients screened, to document eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at screening. In addition, all concomitant therapy (see Section 4.4) used by the patient from the start of the screening period will be recorded. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded.

A UC-specific history including complications and surgeries related to UC, and a detailed history of UC medications used by the patient within 1 year prior to the screening visit will be recorded. In addition, a detailed history of advanced therapies used by the patient within 5 years prior to the screening visit (e.g., name and duration of previous biologic therapies and reason for discontinuation) will be recorded.

The extent and duration of the patient's disease, as recorded in the patient's medical record, will be captured in the eCRF. The extent of disease should be identified as one of the following:

- Left-sided colitis (inflammation up to the splenic flexure)
- Extensive colitis (inflammation beyond the splenic flexure but not involving the entire colon)
- Pancolitis (inflammation of the entire colon)

An interval medical history should be obtained at subsequent clinic visits, and any changes in medications and allergies should be recorded.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

Limited, symptom-directed physical examinations, including an abdominal examination, should be performed at specified visits and as clinically indicated. Changes from abnormalities identified at screening should be recorded in patient notes.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention; see Section 5.3.1). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints (see Appendix 1 and Appendix 2) and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed on a device that is equipped with reliable, automated algorithms for measuring heart rate and ECG intervals and capable of local printing. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine or semi-supine position for at least 10 minutes, and the patient should remain in a supine or semi-supine position during recording. The same positioning should be maintained for each patient throughout the study. ECG recordings should be performed prior to *invasive* procedures scheduled at that same time (e.g., blood draws) and should not be performed within

2.5 hours after any meal. *Vital sign measurements, physical examinations, and diary training may be conducted prior to performing the ECG.* Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

Paper copies of all ECG tracings must be reviewed, annotated to indicate any clinical findings, signed, and dated by a medically qualified member of the site staff. For each timepoint, heart rate, RR interval, PR interval, QRS interval, uncorrected QT interval, and QTcF based on machine readings of ECG tracings should be recorded on the appropriate eCRF. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

If at a particular postdose timepoint the mean QTcF is >500 ms or >60 ms longer than the baseline value (i.e., last value prior to initiation of study treatment), another ECG must be recorded, ideally within the next 5 minutes, and ECGs should be repeated at least hourly until two successive ECGs show resolution of the findings. A PK sample should be obtained if not already scheduled for that timepoint. The Medical Monitor should be notified, and standard-of-care treatment may be instituted at the discretion of the investigator. A decision on study treatment discontinuation should be made, as described in Section 5.1.2.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

4.5.6 Colonoscopy or Flexible Sigmoidoscopy with Colonic Biopsies

All patients will undergo either a colonoscopy or flexible sigmoidoscopy with collection of colonic biopsies at baseline/screening, at [redacted] or the treatment discontinuation visit. Patients without documentation of a colonoscopy within 2 years prior to screening must have a colonoscopy in lieu of a flexible sigmoidoscopy at screening. Every effort should be made to schedule on-treatment endoscopies on the same day as the protocol-specified study visit.

Bowel preparation prior to the colonoscopy and flexible sigmoidoscopy procedures should be done per local practice. Medications used for bowel preparation should be reported on the Concomitant Medications eCRF. Scheduled stool samples should be taken prior to bowel preparation.

For each patient, a video recording will be performed during the colonoscopy or flexible sigmoidoscopy procedure through use of high-definition video recording per the endoscopy manual.

Video recordings should be taken of the entire endoscopic procedure, starting from insertion into the bowel. Biopsies should be performed upon withdrawal of the

endoscope from the bowel. Technical instructions for video recording and biopsy collection will be provided in the endoscopy and/or laboratory manual.

The clinician who performs the endoscopy may take into account endoscopy findings when completing the Physician's Global Assessment (PGA) subscore of the Mayo Score (see Section 4.5.7.2).

All video recordings will be submitted to a central reading facility to be centrally reviewed for mucosal lesions and endoscopic severity by an independent gastroenterologist experienced in UC who is blinded to the patient's clinical activity, study visit, and treatment allocation. Endoscopic videos will be assessed to determine if patients meet the endoscopic inclusion criterion as well as to objectively document subsequent disease activity. For efficacy assessment of primary, secondary, and exploratory endpoints, Mayo endoscopy subscore will be calculated on the basis of centrally read patient videos. Locally read endoscopic videos will be used to inform investigator-determined clinical or treatment decisions. [redacted]

4.5.7 Clinical Outcome Assessments

Clinical outcome assessments of treatment benefit will be primarily collected through the Mayo Score, a composite endpoint incorporating both patient-reported outcome (PRO) and clinician-reported outcome (ClinRO) measures (Appendix 3).

PRO data will be collected through use of the following instruments: Mayo Score (Stool Frequency and Rectal Bleeding items; Appendix 3) and Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS; Appendix 4). PRO instruments will capture each patient's direct experience with vixarelimab.

ClinRO data will be collected *using* the Mayo Score Physician's Global Assessment item (*PGA;* Appendix 3).

4.5.7.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at home at specified timepoints during the study (see schedule of activities in Appendix 1 and Appendix 2).

PRO instruments (Rectal Bleeding/Stool Frequency Mayo Score items and UC-PRO/SS), translated into the local language as appropriate, will be completed through use of an electronic device, either the patient's own device or one provided by the Sponsor. The device will be preprogrammed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

Patients should be given the following instructions for completing instruments at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

The ClinRO instrument *(the* PGA *component of the Mayo Score)* will be completed at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1 and Appendix 2). *The PGA will be* completed prior to the administration of study treatment *and entered into the Mayo Clinic Score - Revised eCRF.*

4.5.7.2 Description of Clinical Outcome Assessment Instruments

Mayo Score and Modified Mayo Score

The Mayo Score (including mMS) will be assessed during the study at specified timepoints.

The Mayo Score is a composite of four assessments, each having a scoring range of 0–3: stool frequency, rectal bleeding, endoscopy (score of 1 modified to exclude friability), and PGA. The Mayo Score is the sum of these assessment subscores and has a range of 0–12, with higher scores indicating more severe disease (see Appendix 3).

The mMS is a composite of three assessments from the Mayo Score, each having a scoring range of 0–3: stool frequency, rectal bleeding, and centrally read endoscopy. The mMS has a range of 0–9, with higher scores indicating more severe disease (see Appendix 3).

Patients are to report their stool frequency and rectal bleeding, as described below.

Stool Frequency and Rectal Bleeding

Stool frequency and rectal bleeding are components of the Mayo Score and mMS.

At screening, the patient's normal number of stools, defined as the number of stools passed when a patient is in remission (i.e., not in flare), or prior to the onset of UC if a patient has never been in remission, will be documented.

Patients are to record stool frequency and rectal bleeding daily in their electronic diary (e-diary) during screening and induction, beginning with the first screening visit, and at specified timepoints throughout the study (see Appendix 1 and Appendix 2). The average stool frequency and rectal bleeding scores from the daily e-diary entries within the [redacted] will be used as efficacy baseline and for inclusion. [redacted]

[redacted] If the average stool frequency and rectal bleeding scores are not available from the [redacted] the average stool frequency and rectal bleeding scores from the [redacted] will be used as the baseline for efficacy assessment and for inclusion.

Because the endoscopy and associated bowel preparation can interfere with the assessment of PROs, e-diary entries on days of bowel preparation, endoscopy, and the day after endoscopy will not be used to calculate any stool frequency or rectal bleeding scores.

Physician's Global Assessment

PGA data will be collected through use of *the Mayo Clinic Score - Revised eCRF*. The PGA is a component of the Mayo Score. The PGA should reflect the clinician's assessment of the patient's current overall status, taking into account stool frequency and rectal bleeding scores, clinician endoscopy findings, patient-reported symptoms, clinician observations, physical examination findings, and other pertinent findings. If possible, the clinician who completes the PGA should not be the same clinician who assesses adverse events. If possible, the same clinician should complete the PGA at each timepoint.

Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms

Patients are to complete the UC-PRO/SS in the e-diary at specified timepoints throughout the study (see Appendix 1 and Appendix 2).

The UC-PRO/SS is a 9-item daily diary to quantify the effects of treatment on patient-reported signs and symptoms of UC. The UC-PRO/SS assesses the presence of UC symptoms and, in some cases, the severity or frequency of the symptoms (Higgins et al. 2017; Pulley et al. 2021). The UC-PRO/SS includes two domains, Bowel Signs and Symptoms (6 items) and Functional Symptoms (3 items), and yields two separate weekly average scores. Each scale is scored separately; there is no total score. Patients are instructed to complete the diary each evening, reflecting back on their experiences during the past 24 hours. The UC-PRO/SS takes approximately 3 minutes to complete. The UC-PRO/SS will be collected daily during screening and daily over at least a 7-day period before each specified study visit.

Because the endoscopy and associated bowel preparation can interfere with the assessment of PROs, e-diary entries on days of bowel preparation, endoscopy, and the day after endoscopy will not be used to calculate any stool frequency or rectal bleeding scores.

A copy of the UC-PRO/SS instrument is provided in Appendix 4.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Samples for Local Laboratory Tests

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Urine pregnancy test

  All women of childbearing potential will have urine pregnancy tests performed at specified visits during the study. Urine pregnancy tests will be reviewed prior to each study drug administration for confirmation of a negative result.
  If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test*, which will be sent to a central laboratory for analysis*.

- Analysis of colonic tissue obtained by biopsy performed during screening endoscopic procedure (flexible sigmoidoscopy or colonoscopy)
  - *Patients with clinical suspicion of CMV colitis:* CMV, as determined by histologic examination or immunohistochemistry per local standards
  - Patients without a prior histopathology report corroborating UC diagnosis: histopathologic examination
  - Patients with left-sided colitis of >12 years' duration or extensive colitis or pancolitis of >8 years' duration with no documentation of colonic cancer surveillance within 2 years prior to screening: evaluation for dysplasia per local standards

Samples for Local Laboratory Tests or Option for Analysis at Central Laboratory

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis, but may be sent to a central laboratory for analysis if local analysis is not available:

- Stool analysis: culture and sensitivity, ova and parasites, and *C. difficile* toxin
- Urinalysis: pH, specific gravity, glucose, protein, ketones, blood by dipstick

  Abnormalities should be confirmed by microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

Samples for Central Laboratory Tests

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Urine drug screening
- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and lactate dehydrogenase

- Coagulation: INR, aPTT, and PT
- HIV serology: HIV-1/2 antibody
- HBV serology: HBsAg, HBsAb, and total HBcAb for all patients

  If a patient has a negative HBsAg and HBsAb tests and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody for all patients

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- TB test: *IGRA* or, if *IGRA* is unavailable, PPD skin test

  Test may be performed locally.
- Serum pregnancy test

  All women of childbearing potential (defined in Section 4.1.1) will have a serum pregnancy test performed at screening. Urine pregnancy tests will be performed at specified subsequent visits at the site's local laboratory. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  Test for follicle-stimulating hormone may be performed at screening to confirm postmenopausal state, if required per local guidelines.
- Serum CRP
- Fecal calprotectin

The following PK and biomarker samples will be sent to the Sponsor or a designee for analysis:

- Serum samples for PK analysis
- Serum samples for immunogenicity analysis
- Serum samples for exploratory biomarker research and PK/PD analyses
- Stool samples for exploratory biomarker research that may include, but will not be limited to, microbiota analyses and inflammatory proteins

  Note: These samples will not be collected or analyzed in China (see Appendix 9).
- Colonic tissue samples obtained by biopsy performed during screening and subsequent endoscopic procedures (flexible sigmoidoscopy or colonoscopy) for histological assessment and exploratory biomarker research that may include, but will not be limited to, [redacted] and [redacted], and other molecular assessments

  Note: These samples will not be collected or analyzed in China (see Appendix 9).

Exploratory biomarker research may include, but will not be limited to, [redacted] gene signatures associated with IBD severity, treatment response, and

non-response; and analysis of immune response in blood and colonic tissue. Research may involve extraction of cells, DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling. Genomic research may include exploration of germline variants. Genomic profiling may include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, but only at participating sites (see Section 4.5.10). *These samples,* [redacted] *, will not be collected or analyzed in China (see Appendix 9).*

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- *Residual* serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation*, or may be used for exploratory biomarker research as described above*; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. *Samples collected in China will not be used for exploratory research.*
- Serum, plasma, stool, and colonic tissue samples collected for exploratory biomarker research, including biomarker assay development, will be destroyed no later than 15 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with applicable laws (e.g., health authority requirements) and the Informed Consent Form approved by the Institutional Review Board or Ethics Committee (IRB/EC).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.9 Use of Screen-Fail Samples (Patients at Participating Sites)

At participating sites, screening blood and tissue from colon biopsy samples collected from patients who do not enroll in the study (screen-fail samples) may be used for research related to the disease under study and the development of disease-related tests or tools.

If a site does not permit research on screen-fail samples, this section of the protocol (Section 4.5.9) will not be applicable at that site.

4.5.10 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will include exploration of germline variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.10) will not be applicable at that site.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.8 for details on use of samples after patient withdrawal and confidentiality standards for data.

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not

been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to vixarelimab, diseases, or drug safety:

- Leftover blood, serum, stool, and colon biopsy tissue samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Confirmed anaphylaxis *related* to study treatment
- Pregnancy
- Use of a prohibited therapy*, including rescue therapy for worsening UC* (see Section 4.4.1 and Section 4.4.2)

- Significant laboratory abnormalities, confirmed on repeat laboratory collection and*, if applicable, confirmed after holding or discontinuation of concomitant medications with known relevant toxicities (e.g., latent TB infection treatments), and* determined to be related to study drug:
  - ALT, AST, or ALP $>2.5\times$ULN, total bilirubin $>2\times$ULN, or presence of abnormalities in synthetic liver function tests judged to be clinically significant by the investigator
  - ANC $<1.5\times10^9$/L (1500/μL), with one exception:

    Patients with BEN: ANC $<1.3\times10^9$/L (1300/μL)
  - Absolute lymphocyte count $<0.5\times10^9$/L (500/μL)

For cases of active TB or reactivation of TB, permanent discontinuation should be considered.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit within 14 ($\pm$3) days after the final dose of study treatment.

Refer to the schedule of activities (see Appendix 1 and Appendix 2) for details on follow-up assessments to be performed for patients who permanently discontinue study treatment. If a patient requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request

must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Vixarelimab is not approved by health authorities, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with vixarelimab in completed and ongoing studies. There are currently no identified risks. The potential risks associated with vixarelimab are outlined below. Please refer to the Vixarelimab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for adverse events. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing specific adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Potential Risks Associated with Vixarelimab

Hypersensitivity Reactions

Monoclonal antibodies carry a potential risk of hypersensitivity reactions and anaphylaxis (allergic reactions), or hypersensitivity-like reactions (pseudoallergic reactions). In

[redacted] Differentiating allergic reactions from pseudoallergic reactions is important because it may impact the understanding of the risk profile of the drug. In instances where the reaction occurs with the first study drug administration without any suspicion of prior sensitization, it is less likely to be an allergic reaction. When a new reaction is seen with the second or subsequent injections, or if there is an atypical presentation (e.g., rapid onset or increase in severity when compared with previous reactions), there is a higher likelihood that the reaction is allergic.

Patients with a history of severe allergic reaction or anaphylactic reaction to a biologic agent are excluded from this study.

Hypersensitivity reactions, including injection-site reactions, will be closely monitored during the study. [redacted]

Investigators and healthcare professionals administering study treatment should recognize and manage the signs and symptoms of such reactions and should be familiar with Sampson's criteria for defining anaphylaxis events (Sampson et al. 2006; Appendix 8). All potential cases of anaphylaxis should be captured on the Adverse Event eCRF as instructed in Section 5.2 and Section 5.3. Investigators and healthcare professionals should accurately report these events immediately to the Sponsor as serious adverse events if appropriate. Healthcare professionals should also instruct patients on how to recognize the symptoms of any such events and to contact a healthcare provider or seek emergency care in case of any such symptoms.

5.1.2 Management of Patients Who Experience Adverse Events

Guidelines for management of patients who experience specific adverse events are outlined in Table 3.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Acute allergic reaction or ISR, Grade 1	• Observe. • Capture signs and symptoms per appropriate eCRF. • Administer non-systemic symptomatic treatment (topical corticosteroids, antihistamines).
Acute allergic reaction or ISR, Grades 2 and 3	• Capture signs and symptoms per appropriate eCRF. • Administer symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • For subsequent doses, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for ISRs or systemic symptoms.
Acute allergic reaction or ISR, Grade 4	• Capture signs and symptoms per appropriate eCRF. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue study treatment and contact Medical Monitor.

eCRF = electronic Case Report Form; ISR = injection-site reaction.

5.1.2.1 Dose Modifications

Dose modifications are not permitted.

5.1.2.2 Treatment Interruption

Study treatment may be interrupted (withheld) for patients who experience a treatment-emergent adverse event considered to be related to study treatment. If study treatment has been withheld for >2 consecutive doses because of an ongoing adverse event related to study treatment, the patient should be permanently discontinued from study treatment, unless resumption of treatment is approved by the investigator following consultation with the Medical Monitor. Study treatment may be withheld for reasons other than a treatment-emergent adverse event (e.g., surgical procedures) at the investigator's discretion following consultation with the Medical Monitor. The investigator should consult with the Medical Monitor to determine the acceptable length of treatment interruption.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and

conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated mild, moderate, severe, life-threatening, or according or according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- Suspected angioedema, anaphylactic, or hypersensitivity reactions (DAIDS Grade 3 or greater)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until [redacted] after the final dose of study treatment.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The investigator will use the DAIDS toxicity grading scale (HHS 2017), with slight modifications for clarity and for alignment with internal practices (see Appendix 7), for assessing the severity of each adverse event reported during the study. The investigator will use the grading scale in Table 4 for assessing the severity of adverse events that are not specifically listed in the DAIDS toxicity grading scale.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in DAIDS Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

DAIDS = Division of AIDS.

Notes: Developed by the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with the study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions and Anaphylactic Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment injection should be captured as a diagnosis (e.g., "injection-related reaction", "injection-site reaction," or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF or Anaphylaxis, Anaphylactoid, and Hypersensitivity Reaction eCRF, as appropriate. If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded as a separate diagnosis on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the Injection Reaction and Anaphylaxis, Anaphylactoid and Hypersensitivity Reaction eCRFs. Investigators may use the Sampson criteria as a guideline to identify and report anaphylaxis events (see Appendix 8).

5.3.5.2 Diagnosis versus Signs and Symptoms

For all adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded

on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ ULN) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Ulcerative Colitis

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of ulcerative colitis on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of ulcerative colitis"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the Mayo Score, which includes endoscopic disease evaluation. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.3.6 Special Situations (Accidental Overdose and/or Medication Error)

Accidental overdose and medication error **(hereafter collectively referred to as "special situations"), are defined as follows:**

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)

After initiation of study treatment, special situations associated with vixarelimab or matching placebo and any associated adverse events will be reported until [redacted] after the final dose of study treatment.

Special situations, regardless of whether they result in an adverse event, should be recorded on the Special Situations eCRF. If there are any associated adverse events, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated adverse events should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section 5.4.2.2.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator becomes aware of the event. The following is a list of events that the investigator must report to the Sponsor within

24 hours after the investigator becomes aware of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until [redacted] after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF

and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur [redacted] after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within [redacted] after the final dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within [redacted] after the final dose of study treatment. The investigator should report the

pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion in a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as [redacted] after the final dose of study treatment), if the event is believed to be related to prior exposure to study treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Vixarelimab	Vixarelimab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An Internal Monitoring Committee (IMC) will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analyses of efficacy and safety data will be performed after all enrolled patients have either completed the [redacted] visit or have discontinued from the study prior to [redacted], and all data from this period are in the database and have been cleaned and verified. The final analyses of complete data for the study will be performed when all enrolled patients have either completed the safety follow-up period or discontinued early from the study, all data from the study are in the database, and the database is locked. Detailed specifications of the statistical methods will be described in the Data Analysis Plan (DAP).

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 210 patients will be enrolled in this study. [redacted] Eligible patients will be randomized in a [redacted] to vixarelimab [redacted] arm, vixarelimab [redacted] arm, or placebo [redacted] arm during the induction period [redacted]

[redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), or complete the study will be summarized. Reasons for premature treatment discontinuation or early termination from the study will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including, but not limited to, age, sex, race/ethnicity) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will be the modified intent-to-treat population defined as all patients who received at least one dose of study treatment and have at least one postbaseline efficacy measurement, with patients grouped according to their assigned treatment.

Because the study is hypothesis-generating in nature, hypothesis testing will be carried out in an exploratory fashion, at a two-sided 0.20 significance level. [redacted]. A separate DAP will contain more details on the statistical analyses.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is clinical remission at Week 12 (see definition of clinical remission in Section 2). A comparison between the vixarelimab arms and the placebo arm will be carried out. The difference between vixarelimab arms versus placebo arm in the proportion of patients with clinical remission at Week 12 will be evaluated by the Cochran-Mantel-Haenszel test, stratified by advanced or conventional failure and baseline mMS [redacted] The non-responder imputation method, where subjects with missing data at scheduled assessment visits will be considered as "not achieved" for the clinical remission, will be used for primary analysis. A subgroup (advanced failure) analysis for the primary efficacy endpoint will be conducted *using the same methods outlined above, except that the Cochran-Mantel-Haenszel test will be stratified by baseline mMS* [redacted].

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are defined in Section 2. The secondary efficacy endpoints will be summarized by descriptive statistics based on the following calculations:

- Proportion of patients with clinical response at Week 12
- Proportion of patients with endoscopic improvement at Week 12
- Proportion of patients with endoscopic remission at Week 12

Data will be summarized by treatment arms. In addition, the secondary endpoints will be analyzed in the advanced failure subgroup.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are defined in Section 2. The exploratory efficacy endpoints will be summarized by descriptive statistics based on the following calculations:

- Proportion of patients with sustained remission at [redacted] Week 12 [redacted]
- Proportion of patients with clinical remission [redacted]
- Proportion of patients with clinical response [redacted]
- Proportion of patients with endoscopic improvement [redacted]
- Proportion of patients with endoscopic remission [redacted]
- Change from baseline in UC bowel movement signs and symptoms at Week 12 [redacted] as assessed by UC-PRO/SS score
- Improvement in UC bowel movement signs and symptoms at Week 12 [redacted] as defined by the proportion of patients with a ≥6-point decrease in the UC-PRO/SS bowel domain score
- Change from baseline in UC functional signs and symptoms at Week 12 [redacted], as assessed by UC-PRO/SS score
- Improvement in UC functional symptoms at Week 12 [redacted], as defined by the proportion of patients with a ≥2-point decrease in the UC-PRO/SS functional domain score

Data will be summarized by treatment arms.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study treatment, with patients grouped according to treatment received.

Safety will be assessed by adverse events, clinical laboratory evaluations, vital signs, and ECGs.

Separate summaries of adverse events will be provided for the screening period, the induction period, and optional ATE period. Adverse events will be summarized by treatment arms.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to DAIDS toxicity grading scale.

Relevant laboratory, vital sign (e.g., pulse rate), and ECG data will be displayed by time, with grades identified where appropriate.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with at least one postdose serum PK sample in which vixarelimab concentration is evaluable, unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred which may interfere with PK evaluation, with patients grouped according to treatment arm.

Serum vixarelimab concentration data will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum) at relevant timepoints. Inter-participant variability and drug accumulation will be evaluated.

Exploratory analyses may be conducted to evaluate potential relationships between drug exposure and efficacy/safety endpoints and to evaluate potential relationships between selected covariates and exposure to vixarelimab. Additional exploratory PK analyses (e.g., using PK data from this study in a population PK analysis) may be conducted as appropriate, and the results may be reported separately from this study report.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one postdose ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not

have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

The PD biomarker analyses will include all patients with one pretreatment and at least one post-treatment biomarker assessment, with patients grouped according to the treatment received. PD biomarker analyses will include examination of changes from baseline (pretreatment) with post-treatment timepoints. PD biomarkers will be assessed as an absolute increase over time, and/or as a percent change relative to original baseline for each patient. In addition, efforts will be made to perform PK/PD analyses based on PD and PK exposure data. Results will be summarized through use of summary statistics and or other graphs as required. Descriptive statistics will be listed by dose, treatment arm, and response status. Additional PD analyses will be conducted as appropriate.

Additional (e.g., predictive, prognostic, pathway) biomarker analyses will include all patients with one pretreatment biomarker assessment, with patients grouped according to the treatment received, provided there are sufficient data in each biomarker arm to facilitate a meaningful analysis. Baseline values may be used to evaluate predictive biomarkers in the context of activity (clinical and/or pharmacological), drug levels, safety, and/or immunogenicity endpoints. Results will be summarized descriptively.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data, endoscopy scores, electronic diary data, and some ClinRO and PRO data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO and ClinRO data will be collected through the use of an electronic device/portal provided by a vendor (see Section 7.3 for details).

ClinRO data may be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT- AND CLINICIAN-REPORTED OUTCOME DATA

An electronic device/portal will be used to capture PRO and ClinRO data. The device/portal is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure method. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO and ClinRO data (if applicable), Informed Consent Forms, laboratory test results, medication inventory records, and images, must be retained by the investigator for 15 years after completion or

discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include imaging data and data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, data may be disseminated as described in Section 9.6.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a risk-based quality management approach to ensure the quality of the study, focusing on processes and data that are critical to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify and evaluate potential risks associated with critical study processes and data, and will implement appropriate mitigation plans for evaluating and controlling these risks. Details regarding the applied approach for the study will be provided in an Integrated Quality Risk Strategy.

Risk control will include the selection of risk-based parameters and an evaluation for quality tolerance limits (QTLs). For studies applying QTLs, details on the management and review of QTLs will be provided in a separate Quality Tolerance Limit Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately [redacted] will participate to enroll approximately 210 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to health care professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Alsoud D, Verstockt B, Fiocchi C, et al. Breaking the therapeutic ceiling in drug development in ulcerative colitis. Lancet Gastroenterol Hepatol 2021;6:589–95.

Aslam N, Lo SW, Sikafi R, et al. A review of the therapeutic management of ulcerative colitis. Therap Adv Gastroenterol 2022;15:17562848221138160.

Atallah-Yunes SA, Ready A, Newburger PE. Benign ethnic neutropenia. Blood Reviews 2019;37:100586.

Barnhoorn MC, Hakuno SK, Bruckner RS, et al. Stromal cells in the pathogenesis of inflammatory bowel disease. J Crohns Colitis 2020;14:995–1009.

Beigel F, Friedrich M, Probst C, et al. Oncostatin M mediates STAT3-dependent intestinal epithelial restitution via increased cell proliferation, decreased apoptosis and upregulation of SERPIN family members. PLoS One 2014;9:e93498.

Bertani L, Fornai M, Fornili M, et al. Serum oncostatin M at baseline predicts mucosal healing in Crohn's disease patients treated with infliximab. Aliment Pharmacol Ther 2020;52:284–91.

Bondensgaard K, Qiu J, Carvajal L, et al. Th81. Vixarelimab, an anti-OSMR-beta fully human monoclonal antibody, inhibits OSM-induced activation of intestinal fibroblasts in TNF-refractory ulcerative colitis [abstract]. Federation of Clinical Immunology Societies, Virtual Annual Meeting, June 8–11, 2021:79–80.

Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology 2015;149:350-5.e2.

Cai Z, Wang S, Li J. Treatment of Inflammatory Bowel Disease: A Comprehensive Review. Front Med (Lausanne) 2021;8:765474.

Danese S, Roda G, Peyrin-Biroulet L. Evolving therapeutic goals in ulcerative colitis: towards disease clearance. Nat Rev Gastroenterol Hepatol 2020;17:1–2.

Du L, Ha C. Epidemiology and pathogenesis of ulcerative colitis. Gastroenterol Clin North Am 2020;49:643–54.

[EMA] European Medicines Agency. Development of new medicinal products for the treatment of ulcerative colitis – Scientific guideline [resource on the Internet]. 2018 [cited 8 May 2023]. Available from: https://www.ema.europa.eu/en/development-new-medicinal-products-treatment-ulcerative-colitis-scientific-guideline.

[FDA] U.S. Food and Drug Administration. Draft Guidance Document. Ulcerative Colitis: Developing Drugs for Treatment [resource on the Internet]. April 2022 [cited 8 May 2023]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ulcerative-colitis-developing-drugs-treatment.

Gordon JP, McEwan PC, Maguire A, et al. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. Eur J Gastroenterol Hepatol 2015;27:804–12.

Guo A, Ross C, Chande N, et al. High oncostatin M predicts lack of clinical remission for patients with inflammatory bowel disease on tumor necrosis factor α antagonists. Sci Rep 2022;12:1185.

Hermanns HM. Oncostatin M and interleukin-31: Cytokines, receptors, signal transduction and physiology. Cytokine Growth Factor Rev 2015;26:545–58.

Higgins PDR, Harding G, Revicki DA, et al. Development and validation of the Ulcerative Colitis patient-reported outcomes signs and symptoms (UC-pro/SS) diary. J Patient Rep Outcomes 2017;2:26.

[HHS] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1 [resource on the Internet]. 2017 [cited: 31 March 2023]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

Hua F, Ribbing J, Reinisch W, et al. A pharmacokinetic comparison of anrukinzumab, an anti-IL-13 monoclonal antibody, among healthy volunteers, asthma and ulcerative colitis patients. Br J Clin Pharmacol 2015;80:101–9.

Jairath V, Zou GY, Parker CE, et al. Cochrane Database Syst Rev 2017;9:CD011572.

Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 2012;491:119–24.

Kobayashi T, Siegmund B, Le Berre C, et al. Ulcerative colitis. Nat Rev Dis Primers 2020;6:74.

Kokkotis G, Filidou E, Tarapatzi G, et al. Oncostatin M induces a pro-inflammatory phenotype in intestinal subepithelial myofibroblasts. Inflamm Bowel Dis 2024 May 8:izae098.

Kuzumi A, Yoshizaki A, Matsuda KM, et al. Interleukin-31 promotes fibrosis and T helper 2 polarization in systemic sclerosis. Nat Commun 2021;12:5947.

Le Berre C, Ricciuto A, Peyrin-Biroulet L, et al. Evolving short- and long-term goals of management of inflammatory bowel diseases: getting it right, making it last. Gastroenterology 2022;162:1424–38.

Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet 2015;47:979–86.

Mak WY, Zhao M, Ng SC, et al. The epidemiology of inflammatory bowel disease: East meets west. J Gastroenterol Hepatol 2020;35:380–9.

Marden G, Wan Q, Wilks J, et al. The role of the oncostatin M/OSM receptor β axis in activating dermal microvascular endothelial cells in systemic sclerosis. Arthritis Res Ther 2020;22:179.

Minar P, Lehn C, Tsai YT, et al. Elevated pretreatment plasma oncostatin M Is associated with poor biochemical response to infliximab. Crohns Colitis 360 2019;1:otz026.

Mozaffarian A, Brewer AW, Trueblood ES, Luzina IG, Todd NW, Atamas SP, Arnett HA. Mechanisms of oncostatin M-induced pulmonary inflammation and fibrosis. J Immunol 2008;181:7243–53.

Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017;390:2769–78.

Pintea I, Petricau C, Dumitrascu D, et al. Hypersensitivity reactions to monoclonal antibodies: Classification and treatment approach (Review). Exp Ther Med 2021;22:949.

Pulley J, Galloway D, Oh Y, et al. P103 Minimal clinically important difference (MCID) for the Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS) Tool. Journal Crohns Colitis 2021;15.

Qadi AA, Taberlay PC, Phillips JL, Young A, West AC, Brettingham-Moore KH, Dickinson JL, and Holloway AF. The leukemia inhibitory factor receptor gene is a direct target of RUNX1. J Cell Biochem 2016;117:49–58.

Rubin DT, Sninsky C, Siegmund B, et al. International perspectives on management of inflammatory bowel disease: opinion differences and similarities between patients and physicians from the IBD GAPPS Survey. Inflamm Bowel Dis 2021;27:1942–53.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117:391–7.

Sedano R, Hogan M, Nguyen TM, et al. Systematic review and meta-analysis: clinical, endoscopic, histological and safety placebo rates in induction and maintenance trials of ulcerative colitis. J Crohns Colitis 2022;16:224–43.

Smillie CS, Biton M, Ordovas-Montanes J, et al. Intra- and inter-cellular rewiring of the human colon during ulcerative colitis. Cell 2019;178:714–730.e22.

Stawski L, Trojanowska M. Oncostatin M and its role in fibrosis. Connect Tissue Res 2019;60:40–9.

Toghi Eshghi S, Gubatan JM, Mazrooei P, et al. Molecular characterization of response to etrolizumab and anti-TNF reveals treatment resistance in ulcerative colitis is associated with the abundance of residual neutrophil subsets and inflammatory fibroblast populations. bioRxiv 2024.07.02.601267.

Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. Lancet 2017;389:1756–70.

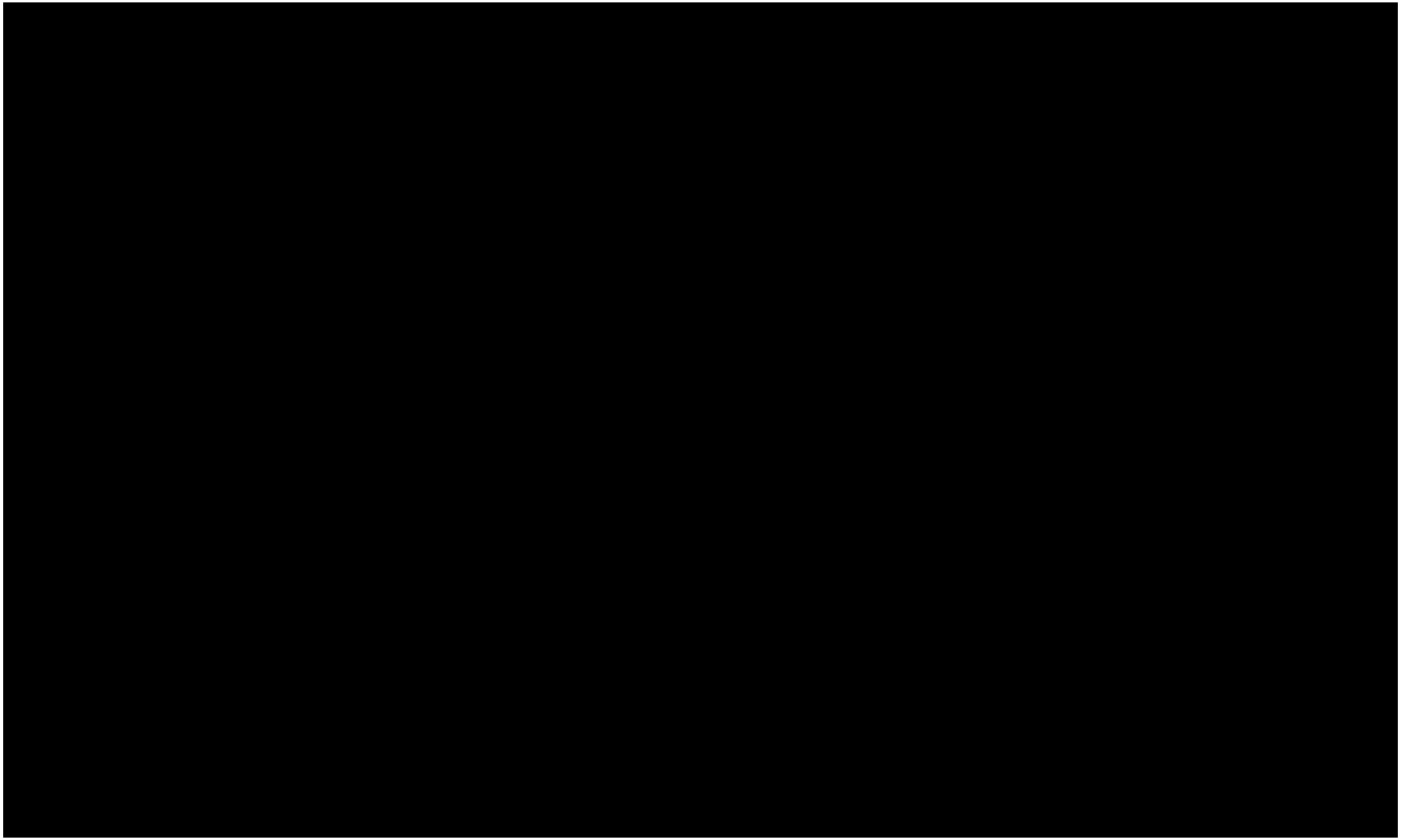
Verstockt S, Verstockt B, Machiels K, et al. Oncostatin M is a biomarker of diagnosis, worse disease prognosis, and therapeutic nonresponse in inflammatory bowel disease. Inflamm Bowel Dis 2021;27:1564–75.

West NR, Hegazy AN, Owens BMJ, et al. Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor-neutralizing therapy in patients with inflammatory bowel disease. Nat Med 2017;23:579–89.

West NR, Owens BMJ, Hegazy AN. The oncostatin M-stromal cell axis in health and disease. Scand J Immunol 2018;88:e12694.

Yaseen B, Lopez H, Taki Z, et al. Interleukin-31 promotes pathogenic mechanisms underlying skin and lung fibrosis in scleroderma. Rheumatology (Oxford) 2020;59:2625–36.

Appendix 1
Schedule of Activities: Induction



Appendix 1: Schedule of Activities for Induction

ADA = anti-drug antibody; ATE = active treatment extension; CMV = cytomegalovirus; CRP = C-reactive protein; FeCal = fecal calprotectin; IxRS = interactive voice or web-based response system; PK = pharmacokinetic; PRO = patient-reported outcome; TB = tuberculosis; TD = treatment discontinuation; UC-PRO/SS = Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms; UV = unscheduled visit; WES = whole exome sequencing; WGS = whole genome sequencing.

Notes: On treatment days, all assessments should be performed prior to study treatment administration, unless otherwise specified.

Assessments shaded in gray are not applicable for sites in China.

Appendix 1: Schedule of Activities for Induction

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within 35 days prior to Day 1 may be used; such assessments do not need to be repeated for screening. Patients who do not meet the criteria for participation in this study may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion, as described in Section 3.1.1.

[b] Patients may continue to the optional ATE period (Appendix 2) following completion of the [redacted] visit. For patients who do not continue to the optional ATE period, the [redacted] visit will also serve as the treatment completion visit; these patients will then enter the safety follow-up period.

[c] Patients who discontinue study treatment prematurely during the induction period will return to the clinic for a treatment discontinuation visit within 14 days after their final dose of study treatment and will then enter the safety follow-up period.

[d] Patients will undergo follow-up assessments at [redacted] after their final dose of study treatment.

[e] Unscheduled visits may be performed if clinically indicated (e.g., for evaluation of an adverse event). The specified assessments are required at each unscheduled visit. Assessments listed in parentheses are not required, but may be performed for patients who receive rescue therapy or experience persistent or worsening disease for which rescue therapy is indicated, as determined by the investigator. Additional assessments may be performed if clinically indicated, as determined by the investigator.

[f] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 35 days before initiation of study treatment.

[g] Stool samples should be obtained prior to bowel preparation for endoscopy (colonoscopy or sigmoidoscopy), if applicable.

[h] Samples will be analyzed for culture and sensitivity, ova and parasites, and *C. difficile*.

[i] Patients assigned to the vixarelimab [redacted] arm will receive [redacted] vixarelimab at [redacted]. Patients assigned to the vixarelimab [redacted] arm will receive [redacted] vixarelimab at [redacted] to maintain blind, these patients will also receive [redacted]. Patients assigned to placebo [redacted] will receive placebo at [redacted]

[j] Study treatment should not be administered at the [redacted] visit if the patient elects not to continue to the optional ATE period.

[k] Record medications used by a patient from the start of the screening period to initiation of study treatment.

[l] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until [redacted] after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6).

[m] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[n] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated.

[o] ECG recordings should be performed prior to *invasive* procedures scheduled at that same time (e.g., blood draws). *Vital sign measurements, physical examinations, and diary training may be conducted prior to performing the ECG.* See Section 4.5.5.

[p] All women of childbearing potential will have a serum pregnancy test performed at screening. Urine pregnancy tests will be performed at specified subsequent visits during treatment, at the treatment discontinuation visit, and at [redacted] after the final dose of study treatment. Urine pregnancy tests will be reviewed prior to each study drug administration for confirmation of a negative result. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] All patients will undergo either a colonoscopy or a flexible sigmoidoscopy at specified timepoints. Patients without documentation of a colonoscopy within 2 years prior to screening must undergo a colonoscopy in lieu of a flexible sigmoidoscopy at screening. The screening endoscopy will be used as efficacy baseline and for inclusion. Video recordings should be taken of the entire endoscopic procedure (colonoscopy or flexible sigmoidoscopy), starting from insertion into the bowel. Biopsies should be performed upon withdrawal of the endoscope from the bowel. Technical instructions for video recording and biopsy collection will be provided in the endoscopy and/or laboratory manual.

[r] Tissue collected at screening will be analyzed for CMV, *if required (see Section 4.1.2),* as determined by histologic examination or immunohistochemistry per local standards, and will undergo histopathologic examination for patients without a prior histopathology report. Tissue collected at screening and subsequent timepoints will also be used for histologic assessments and exploratory biomarker research *at participating sites, excluding China (see Appendix 9). For endoscopy assessments after screening for sites located in China, endoscopy will be performed but no biopsy will be collected.*

[s] See Appendix 3. *The Mayo Score will be calculated by the Sponsor.*

[t] Clinician-reported outcome instruments will be completed after the physical examination, prior to the administration of study treatment.

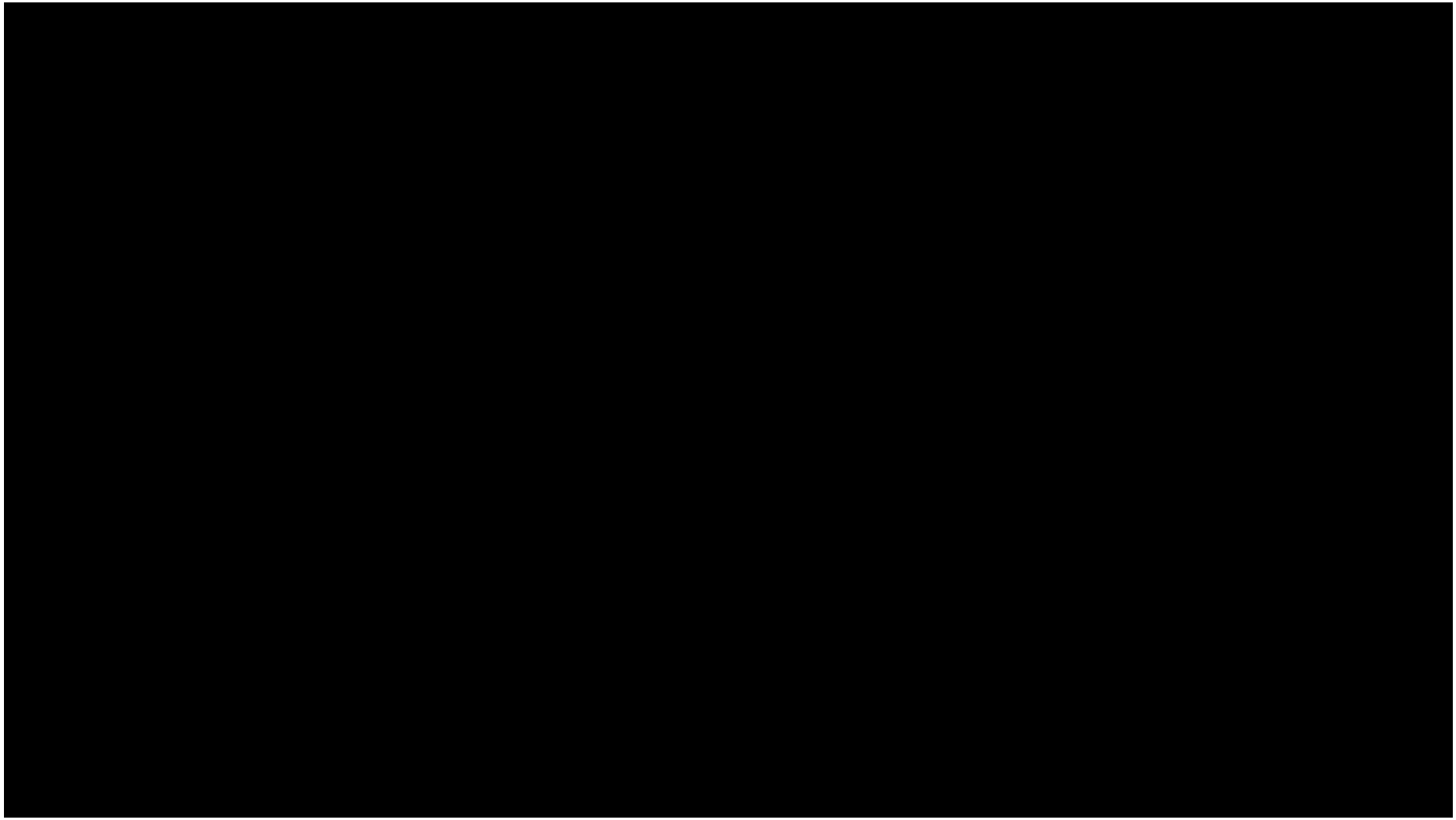
[u] An electronic diary will be used to collect PRO data, including stool frequency/rectal bleeding and the UC-PRO/SS instrument (see Section 4.5.7.2). Stool frequency and rectal bleeding will be recorded daily; UC-PRO/SS will be collected daily during screening and daily over at least a 7-day period before each specified study visit.

[v] On treatment days, all samples should be collected prior to dosing.

[w] Additional ADA samples should be collected in patients with signs and symptoms of injection-related reactions.

[x] Not applicable for a site that has not been granted approval for WGS/WES. If a sample is not collected at the randomization visit (Day 1), it may be collected at any subsequent visit.

Appendix 2
Schedule of Activities: Optional Active Treatment Extension



Appendix 2: Schedule of Activities for Optional Active Treatment Extension

[redacted]

ADA = anti-drug antibody; ATE = active treatment extension; CRP = C-reactive protein; FeCal = fecal calprotectin; NA = not applicable; PK = pharmacokinetic; PRO = patient-reported outcome; [redacted] SC = study completion; TD = treatment discontinuation; UC-PRO/SS = Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms; UV = unscheduled visit.

Notes: On treatment days, all assessments should be performed prior to study treatment administration, unless otherwise specified.

Patients must complete induction treatment and assessments through [redacted] to continue into active treatment extension.

Assessments shaded in gray are not applicable for sites in China.

[a] Patients who complete the active treatment extension period will return to the clinic for a study completion visit at [redacted]

[b] Patients who discontinue study treatment prematurely will return to the clinic for a treatment discontinuation visit within 14 days after their final dose of study treatment and will then enter the safety follow-up period.

[c] Patients who complete the active treatment extension period and patients who discontinue study treatment prior to [redacted] will undergo follow-up assessments at [redacted] after their final dose of study treatment.

[d] Unscheduled visits may be performed if clinically indicated (e.g., for evaluation of an adverse event). The specified assessments are required at each unscheduled visit, unless otherwise specified. Assessments listed in parentheses are not required, but may be performed for patients who receive rescue therapy or experience persistent or worsening disease for which rescue therapy is indicated, as determined by the investigator. Additional assessments may be performed if clinically indicated, as determined by the investigator.

[e] Samples will be analyzed for culture and sensitivity, ova and parasites, and *C. difficile*.

[f] Stool samples should be obtained prior to bowel preparation for endoscopy (colonoscopy or sigmoidoscopy), if applicable.

[g] Patients assigned to the vixarelimab [redacted] arm or to the placebo arm during induction will receive [redacted] vixarelimab [redacted] during ATE. Patients assigned to the vixarelimab [redacted] arm will continue to receive [redacted] vixarelimab Q4W during ATE. To maintain blind, patients assigned to receive vixarelimab [redacted] during ATE will also receive placebo [redacted] (see Section 3.1.1).

[h] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until [redacted] the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6).

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[j] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated.

[k] ECG recordings should be performed prior to *invasive* procedures scheduled at that same time (e.g., blood draws). *Vital sign measurements, physical examinations, and diary training may be conducted prior to performing the ECG.* See Section 4.5.5.

[l] Urine pregnancy tests will be reviewed prior to each study drug administration for confirmation of a negative result. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[m] Video recordings should be taken of the entire endoscopic procedure, starting from insertion into the bowel. Biopsies should be performed upon withdrawal of the endoscope from the bowel. Technical instructions for video recording and biopsy collection will be provided in the endoscopy and/or laboratory manual.

[n] Tissue collected will be used for histologic assessments and exploratory biomarker research *at participating sites, excluding China (see Appendix 9). For endoscopy assessments after screening for sites located in China, endoscopy will be performed but no biopsy will be collected.*

[o] See Appendix 3. *The Mayo Score will be calculated by the Sponsor.*

[p] Clinician-reported outcome instruments will be completed after the physical examination, prior to the administration of study treatment.

[q] An electronic diary will be used to collect PRO data, including stool frequency/rectal bleeding and the UC-PRO/SS instrument (see Section 4.5.7.2). Stool frequency, rectal bleeding, and UC-PRO/SS will be collected daily over at least a 7-day period before each specified study visit.

[r] On treatment days, all samples should be collected prior to dosing.

[s] Additional ADA samples should be collected in patients with signs and symptoms of injection-related reactions.

Appendix 3
Mayo Score

The Mayo Score is a composite endpoint consisting of patient-reported outcomes (stool frequency, rectal bleeding), endoscopy, and clinician-reported outcome (Physician's Global Assessment) components. Each component is scored on a scale from 0 to 3, and totaled for a maximum score of 12.

The modified Mayo Score (mMS) is a composite of stool frequency, rectal bleeding, and centrally read endoscopy. Maximum total score of 9.

1. **Stool frequency** [a]
   0 = Normal number of stools for this patient
   1 = 1–2 more stools than normal
   2 = 3–4 more stools than normal
   3 = 5 or more stools than normal

2. **Rectal bleeding** [b]
   0 = No blood seen or no bowel movement
   1 = Stool with streaks of blood
   2 = Stool with more than streaks of blood
   3 = Blood alone passed

3. **Endoscopy**
   0 = Normal appearance of mucosa
   1 = Mild disease (erythema, decreased vascular pattern), no friability
   2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
   3 = Severe disease (spontaneous bleeding, ulceration)

4. **Physician's Global Assessment**
   0 = Normal
   1 = Mild
   2 = Moderate
   3 = Severe

[a] Each patient provides own baseline against which to compare the degree of abnormality in stool frequency.

[b] Represents the worst bleeding score for that day.

Appendix 4
Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS)

You and Your Ulcerative Colitis

The following questions ask about your bowel movements in the **past 24 hours**.

For these questions, a ***bowel movement*** is defined as any time you pass solid or liquid including stool, blood, mucus (white material), or water. Passing gas alone is not considered a bowel movement.

1. In the past 24 hours, how many bowel movements did you have? *Please select one response.*	0 ☐ 0 1 ☐ 1-2 2 ☐ 3-4 3 ☐ 5-6 4 ☐ 7-9 5 ☐ 10-12 6 ☐ 13-17 7 ☐ 18 or more
2. In the past 24 hours, how often were your bowel movements **mostly or completely liquid?** *Please select one response.*	0 ☐ Never 1 ☐ Rarely 2 ☐ Sometimes 3 ☐ Often 4 ☐ Always

Appendix 4: Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS)

The following questions ask about the presence and how often you experienced your ulcerative colitis symptoms in the **past 24 hours**.

Please answer each question by selecting yes or no.		**If Yes, how often did you experience this symptom?** *Please select one response.*
3. In the past 24 hours, did you have blood in your bowel movements?	☐ Yes 0☐ No	1☐ Rarely 2☐ Sometimes 3☐ Often 4☐ Always
4. In the past 24 hours, did you have mucus (white material) in your bowel movements?	☐ Yes 0☐ No	1☐ Rarely 2☐ Sometimes 3☐ Often 4☐ Always
5. In the past 24 hours, did you have stool, blood, or liquid leak out before you reached a toilet?	☐ Yes 0☐ No	1☐ Rarely 2☐ Sometimes 3☐ Often 4☐ Always
6. In the past 24 hours, did you pass gas?	☐ Yes 0☐ No	1☐ Rarely 2☐ Sometimes 3☐ Often 4☐ Very Often

The following questions ask about the presence and severity of your ulcerative colitis symptoms in the **past 24 hours**.

Please answer each question by selecting yes or no.		**If Yes, how severe was this symptom at its worst?** *Please select one response.*
7. In the past 24 hours, did you feel the need to have a bowel movement right away?	☐ Yes 0☐ No	1☐ Mild 2☐ Moderate 3☐ Severe 4☐ Very Severe
8. In the past 24 hours, did you feel pain in your belly?	☐ Yes 0☐ No	1☐ Mild 2☐ Moderate 3☐ Severe 4☐ Very Severe
9. In the past 24 hours, did you feel bloating in your belly?	☐ Yes 0☐ No	1☐ Mild 2☐ Moderate 3☐ Severe 4☐ Very Severe

Appendix 5
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), SC, IV, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

- Stop the study treatment administration, if possible.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
- Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
- Continue to observe the patient and document observations.
- Collect serum samples for immunogenicity testing.
- Ask the patient to return for immunogenicity sample collection at the time of washout, if appropriate.

Appendix 6
Investigational and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Vixarelimab (RO7622888)	IMP (test product)	Not approved	Not applicable
Vixarelimab placebo	IMP (placebo)	Not approved	Not applicable
Topical 5-ASA	AxMP (rescue therapy)	Approved	Yes
Oral 5-ASA	AxMP (other [a])	Approved	Yes
IV corticosteroids and rectal corticosteroids (i.e., enemas or suppositories)	AxMP (rescue therapy)	Approved	Yes
Oral corticosteroids	AxMP (other [a])	Approved	Yes
AZA	AxMP (other [a])	Approved	Yes
6-MP	AxMP (other [a])	Approved	Yes
MTX	AxMP (other [a])	Approved	Yes

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AxMP = auxiliary medicinal product; AZA = azathioprine; EEA = European Economic Area; IMP = investigational medicinal product; MTX = methotrexate.

[a] Used as a background or rescue therapy; will differ patient to patient.

Table 2 Investigational and Non-Investigational Medicinal Product Designations for United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in U.K.	Used within Marketing Authorization
Vixarelimab (RO7622888)	IMP (test product)	Not Approved	Not applicable
Vixarelimab placebo	IMP (placebo)	Not Approved	Not applicable
Topical 5-ASA	NIMP (rescue therapy)	Approved	Yes
Oral 5-ASA	NIMP (other [a])	Approved	Yes
IV corticosteroids and rectal corticosteroids (i.e. enemas or suppositories)	NIMP (rescue therapy)	Approved	Yes
Oral corticosteroids	NIMP (other [a])	Approved	Yes
AZA	NIMP (other [a])	Approved	Yes
6-MP	NIMP (other [a])	Approved	Yes
MTX	NIMP (other [a])	Approved	Yes

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; EEA = European Economic Area; IMP = investigational medicinal product; MTX = methotrexate; NIMP = non-investigational medicinal product.

[a] Used as a background or rescue therapy; will differ patient to patient.

Appendix 7
Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

The investigator will use the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (HHS 2017), with slight modifications for clarity and for alignment with internal practices, for assessing the severity of each adverse event reported during the study.

Table 1 Severity Grading for Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Cardiovascular				
Arrhythmia (by ECG or physical examination) (Specify type if applicable)	No symptoms and no intervention indicated	No symptoms and non-urgent intervention indicated	Non–life-threatening symptoms and non-urgent intervention indicated	Life-threatening arrhythmia or urgent intervention indicated
Hypertension (with the lowest reading taken after repeat testing during a visit): ≥ 18 years of age	140 to < 160 mmHg systolic or 90 to < 100 mmHg diastolic [a]	≥ 160 to < 180 mmHg systolic or ≥ 100 to < 110 mmHg diastolic [a]	≥ 180 mmHg systolic or ≥ 110 mmHg diastolic [a]	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) or hospitalization indicated
Hypertension (with the lowest reading taken after repeat testing during a visit): < 18 years of age [b]	> 120 mmHg systolic or > 80 mmHg diastolic, but systolic and diastolic < 95th percentile adjusted for age, height, and sex	≥ 95th to < 5 mmHg above the 99th percentile adjusted for age, height, and sex (systolic and/or diastolic) [a]	≥ 5 mmHg above the 99th percentile adjusted for age, height, and sex (systolic and/or diastolic) [a]	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) or hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms and IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

[a] When systolic and diastolic blood pressures meet criteria for different grades, the higher grade should be used.

[b] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128(Suppl 5):S213–56.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Cardiovascular (cont.)				
Cardiac ischemia or infarction (Report the most appropriate term)	—	—	New symptoms with ischemia (stable angina) or new testing consistent with ischemia	Unstable angina or acute myocardial infarction
Heart failure	No symptoms and laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) or intervention indicated (e.g., oxygen)	Life-threatening consequences or urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	—	Symptoms and no transfusion indicated	Symptoms and transfusion of $\leq$2 units packed RBCs (for children, packed RBCs $\leq$10 cc/kg) indicated	Life-threatening hypotension or transfusion of $>$2 units packed RBCs (for children, packed RBCs $>$10 cc/kg) indicated
Prolonged PR interval or AV block: $>$16 years of age (Report the most appropriate term)	PR interval 0.21 to $<$0.25 seconds	PR interval $\geq$0.25 seconds or Type I second-degree AV block	Type II second-degree AV block or ventricular pause $\geq$3.0 seconds	Complete AV block
Prolonged PR interval or AV block: $\leq$16 years of age (Report the most appropriate term)	First-degree AV block (PR interval $>$normal for age and rate)	Type I second-degree AV block	Type II second-degree AV block or ventricular pause $\geq$3.0 seconds	Complete AV block
Prolonged QTc interval (corrected per Bazett's formula)	0.45 to 0.47 seconds	$>$0.47 to 0.50 seconds	$>$0.50 seconds or $\geq$0.06 seconds above baseline	Life-threatening consequences (e.g., torsade de pointes, other associated serious ventricular dysrhythmia)

AV = atrioventricular.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Cardiovascular (cont.)				
Thrombosis or embolism (Report the most appropriate term)	—	Symptoms and no intervention indicated	Symptoms and intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
Dermatologic				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing greater than minimal interference with usual social and functional activities	—	—
Bruising	Localized to one area	Localized to more than one area	Generalized	—
Cellulitis	—	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social and functional activities	Marked or generalized causing greater than minimal interference with usual social and functional activities	—	—
Hypopigmentation	Slight or localized causing no or minimal interference with usual social and functional activities	Marked or generalized causing greater than minimal interference with usual social and functional activities	—	—

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Dermatologic (cont.)				
Petechiae	Localized to one area	Localized to more than one area	Generalized	—
Pruritus [c] (without skin lesions)	Itching causing no or minimal interference with usual social and functional activities	Itching causing greater than minimal interference with usual social and functional activities	Itching causing inability to perform usual social and functional activities	—
Rash (Specify type, if applicable)	Localized rash	Diffuse rash or target lesions	Diffuse rash and vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions or ulceration of mucous membrane involving two or more distinct mucosal sites or Stevens-Johnson syndrome or toxic epidermal necrolysis
Endocrine and Metabolic				
Diabetes mellitus	Controlled without medication	Controlled with medication or modification of current medication regimen	Uncontrolled despite treatment modification or hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing pain with greater than minimal interference with usual social and functional activities	Disfiguring changes and symptoms requiring intervention or causing inability to perform usual social and functional activities	—

[c] For pruritus associated with injections or infusions, see "Site Reactions to Injections and Infusions."

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Endocrine and Metabolic (cont.)				
Hyperthyroidism	No symptoms and abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities or thyroid suppression therapy indicated	Symptoms causing inability to perform usual social and functional activities or uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms and abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities or thyroid replacement therapy indicated	Symptoms causing inability to perform usual social and functional activities or uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (disorder characterized by fat loss in the face, extremities, and buttocks)	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing greater than minimal interference with usual social and functional activities	Disfiguring changes	—
Lipohypertrophy (disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen)	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing greater than minimal interference with usual social and functional activities	Disfiguring changes	—

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Gastrointestinal				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences or aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms and intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or distension (Report the most appropriate term)	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	—
Cholecystitis	—	Symptoms and medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	—	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Gastrointestinal (cont.)				
Diarrhea: ≥1 year of age	Transient or intermittent episodes of unformed stools or increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools or increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools over baseline per 24-hour period or IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Diarrhea: <1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools or mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or odynophagia (Report the most appropriate term and specify location)	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or stomatitis (Report the most appropriate term and specify location)	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations or mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) or tissue necrosis or diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent nausea and no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for >48 hours or rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	—	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Gastrointestinal (cont.)				
Perforation (colon or rectum)	—	—	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social and functional activities or medical intervention indicated	Symptoms causing inability to perform usual social and functional activities or operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal discharge	Visible discharge	Discharge requiring the use of pads	—	—
Vomiting	Transient or intermittent vomiting and no or minimal interference with oral intake	Frequent vomiting episodes and no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Musculoskeletal				
Arthralgia	Joint pain causing no or minimal interference with usual social and functional activities	Joint pain causing greater than minimal interference with usual social and functional activities	Joint pain causing inability to perform usual social and functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Joint stiffness or swelling causing no or minimal interference with usual social and functional activities	Joint stiffness or swelling causing greater than minimal interference with usual social and functional activities	Joint stiffness or swelling causing inability to perform usual social and functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Musculoskeletal (cont.)				
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social and functional activities	Muscle pain causing greater than minimal interference with usual social and functional activities	Muscle pain causing inability to perform usual social and functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	—	No symptoms but with radiographic findings and no operative intervention indicated	Bone pain with radiographic findings or operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia: ≥ 30 years of age	BMD t-score −2.5 to −1	—	—	—
Osteopenia: < 30 years of age	BMD z-score −2 to −1	—	—	—
Osteoporosis: ≥ 30 years of age	—	BMD t-score < −2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Osteoporosis: < 30 years of age	—	BMD z-score < −2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

BMD = bone mineral density.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neurologic				
Acute CNS ischemia	—	—	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered mental status (for dementia, see cognitive, behavioral, or attentional disturbance below)	Changes causing no or minimal interference with usual social and functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities	Delirium or obtundation or coma
Ataxia	Symptoms causing no or minimal interference with usual social and functional activities or no symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, behavioral, or attentional disturbance (includes dementia and attention deficit disorder) (Specify type, if applicable)	Disability causing no or minimal interference with usual social and functional activities or specialized resources not indicated	Disability causing greater than minimal interference with usual social and functional activities or specialized resources on part-time basis indicated	Disability causing inability to perform usual social and functional activities or specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions or institutionalization indicated

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neurologic (cont.)				
Developmental delay < 18 years of age (Specify type, if applicable)	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions or hospitalization indicated or headache with significant impairment of alertness or other neurologic function
Neuromuscular weakness (includes myopathy and neuropathy) (Specify type, if applicable)	Minimal muscle weakness causing no or minimal interference with usual social and functional activities or no symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social and functional activities	Muscle weakness causing inability to perform usual social and functional activities	Disabling muscle weakness causing inability to perform basic self-care functions or respiratory muscle weakness impairing ventilation

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neurologic (cont.)				
Neurosensory alteration (includes paresthesia and painful neuropathy) (Specify type, if applicable)	Minimal paresthesia causing no or minimal interference with usual social and functional activities or no symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure, new onset: ≥ 18 years of age	—	—	1–3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) or difficult to control (e.g., refractory epilepsy)
Seizure, new onset: < 18 years of age (includes new or preexisting febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes or ≥ 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) or difficult to control (e.g., refractory epilepsy)
Seizure, preexisting (excludes preexisting febrile seizures)	—	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) or difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness and hospitalization or intervention required	—
Pregnancy, Puerperium, and Perinatal				
Stillbirth	—	—	Fetal death occurring at ≥ 20 weeks gestational age	—

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Pregnancy, Puerperium, and Perinatal (cont.)				
Preterm birth	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous abortion (a pregnancy loss occurring at < 20 weeks gestational age; also known as miscarriage)	Chemical pregnancy	Uncomplicated spontaneous abortion	Complicated spontaneous abortion	—
Psychiatric				
Insomnia	Mild difficulty falling asleep or staying asleep or mild difficulty caused by early morning awakening, causing no or minimal interference with usual social and functional activities	Moderate difficulty falling asleep or staying asleep, or moderate difficulty caused by early morning awakening, causing greater than minimal interference with usual social and functional activities	Severe difficulty falling asleep or staying asleep or severe difficulty caused by early morning awakening, causing inability to perform usual social and functional activities and requiring intervention or hospitalization	—
Psychiatric disorder (includes anxiety, depression, mania, and psychosis) (Specify disorder)	Symptoms with intervention not indicated or behavior causing no or minimal interference with usual social and functional activities	Symptoms with intervention indicated or behavior causing greater than minimal interference with usual social and functional activities	Symptoms with hospitalization indicated or behavior causing inability to perform usual social and functional activities	Threatens harm to self or others or acute psychosis or behavior causing inability to perform basic self-care functions

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Psychiatric (cont.)				
Suicidal ideation or suicide attempt (Report the most appropriate term)	Preoccupied with thoughts of death and no wish to kill oneself	Preoccupied with thoughts of death and wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so or hospitalization indicated	Suicide attempted
Respiratory				
Acute bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% of predicted or mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50% to < 70% of predicted or symptoms with intervention indicated or symptoms causing greater than minimal interference with usual social and functional activities	Forced expiratory volume in 1 second or peak flow 25% to < 50% of predicted or symptoms causing inability to perform usual social and functional activities	Forced expiratory volume in 1 second or peak flow < 25% of predicted or life-threatening respiratory or hemodynamic compromise or intubation
Dyspnea or respiratory distress (Report the most appropriate term)	Dyspnea on exertion with no or minimal interference with usual social and functional activities or wheezing or minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social and functional activities or nasal flaring or intercostal retractions or pulse oximetry 90% to < 95%	Dyspnea at rest causing inability to perform usual social and functional activities or pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Sensory				
Hearing loss (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram): ≥ 12 years of age	—	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) or non-serviceable hearing (i.e., > 50 dB audiogram and < 50% speech discrimination)
Hearing loss (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram): < 12 years of age	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) or hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language–related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social and functional activities and intervention not indicated	Symptoms causing greater than minimal interference with usual social and functional activities or intervention indicated	Symptoms causing inability to perform usual social and functional activities	—
Uveitis	No symptoms and detectable uveitis on examination	Anterior uveitis with symptoms or medical intervention indicated	Posterior uveitis or panuveitis or operative intervention indicated	Uveitis with disabling visual loss in affected eye(s)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Sensory (cont.)				
Vertigo	Vertigo causing no or minimal interference with usual social and functional activities	Vertigo causing greater than minimal interference with usual social and functional activities	Vertigo causing inability to perform usual social and functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social and functional activities	Visual changes causing greater than minimal interference with usual social and functional activities	Visual changes causing inability to perform usual social and functional activities	Visual changes with disabling visual loss in affected eye(s)
Systemic				
Acute allergic reaction	Localized urticaria (wheals) with no intervention indicated	Localized urticaria with intervention indicated or mild angioedema with no intervention indicated	Generalized urticaria or angioedema with intervention indicated or symptoms of mild bronchospasm	Acute anaphylaxis or life-threatening bronchospasm or laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	—

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Systemic (cont.)				
Cytokine-release syndrome (disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath)	Mild signs and symptoms and therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated and responds promptly to symptomatic treatment or prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms or recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or malaise (Report the most appropriate term)	Symptoms of fatigue or malaise causing no or minimal interference with usual social and functional activities	Symptoms of fatigue or malaise causing greater than minimal interference with usual social and functional activities	Symptoms of fatigue or malaise causing inability to perform usual social and functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to <38.6°C or 100.4 to <101.5°F	≥38.6 to <39.3°C or ≥101.5 to <102.7°F	≥39.3 to <40.0°C or ≥102.7 to <104.0°F	≥40.0°C or ≥104.0°F
Pain (not associated with study agent injections and not specified elsewhere) (Specify location)	Pain causing no or minimal interference with usual social and functional activities	Pain causing greater than minimal interference with usual social and functional activities	Pain causing inability to perform usual social and functional activities	Disabling pain causing inability to perform basic self-care functions or hospitalization indicated
Serum sickness (disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea)	Mild signs and symptoms	Moderate signs and symptoms and intervention indicated (e.g., antihistamines)	Severe signs and symptoms and higher level intervention indicated (e.g., corticosteroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Systemic (cont.)				
Underweight: > 5 to 19 years of age	WHO BMI z-score [d] < −1 to −2	WHO BMI z-score [d] < −2 to −3	WHO BMI z-score [d] < −3	WHO BMI z-score [d] < −3 with life-threatening consequences
Underweight: 2 to 5 years of age	WHO weight-for-height z-score [e] < −1 to −2	WHO weight-for-height z-score [e] < −2 to −3	WHO weight-for-height z-score [e] < −3	WHO weight-for-height z-score [e] < −3 with life-threatening consequences
Underweight: < 2 years of age	WHO weight-for-length z-score [e] < −1 to −2	WHO weight-for-length z-score [e] < −2 to −3	WHO weight-for-length z-score [e] < −3	WHO weight-for-length z-score [e] < −3 with life-threatening consequences
Unintentional weight loss (excludes postpartum weight loss)	—	5% to < 9% loss in body weight from baseline	≥ 9% to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline or aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Urinary				
Urinary tract obstruction	—	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

BMI = body mass index; WHO = World Health Organization.

[d] WHO reference tables for participants > 5 to 19 years of age: http://www.who.int/growthref/who2007_bmi_for_age/en/.

[e] WHO reference tables for participants ≤ 5 years of age: http://www.who.int/childgrowth/standards/chart_catalogue/en/.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Site Reactions to Injections and Infusions [f]				
Injection-site pain or tenderness [f]	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social and functional activities	Pain or tenderness causing inability to perform basic self-care function or hospitalization indicated
Injection-site erythema, redness, induration, or swelling: [f] >15 years of age (Report the most appropriate term; report multiple events if appropriate)	2.5 to <5 cm in diameter or 6.25 to <25 cm^2 surface area [g] and symptoms causing no or minimal interference with usual social and functional activities	≥5 to <10 cm in diameter or ≥25 to <100 cm^2 surface area [g] or symptoms causing greater than minimal interference with usual social and functional activities	≥10 cm in diameter or ≥100 cm^2 surface area [g] or ulceration or secondary infection or phlebitis or sterile abscess or drainage or symptoms causing inability to perform usual social and functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection-site erythema, redness, induration, or swelling: [f] ≤15 years of age (Report the most appropriate term; report multiple events if appropriate)	≤2.5 cm in diameter [g]	>2.5 cm in diameter with <50% surface area [g] of the extremity segment involved (e.g., upper arm or thigh)	≥50% surface area [g] of the extremity segment involved (e.g., upper arm or thigh) or ulceration or secondary infection or phlebitis or sterile abscess or drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

[f] Refer to Section 5.3.5.1 for instructions on reporting injection-site reactions to study treatment (if applicable). For reactions to drugs other than study treatment, report the most appropriate term and report multiple events, if applicable.

[g] Grading should be based on the greatest single diameter or measured surface area.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Site Reactions to Injections and Infusions (cont.) [f]				
Injection-site pruritus [f]	Itching localized to the injection site that is relieved spontaneously or requires treatment for < 48 hours	Itching beyond the injection site that is not generalized or itching localized to the injection site that requires treatment for ≥ 48 hours	Generalized itching causing inability to perform usual social and functional activities	—
Chemistries				
Acidosis	—	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, low	3.0 g/dL to < LLN (30 g/L to < LLN)	≥ 2.0 to < 3.0 g/dL (≥ 20 to < 30 g/L)	< 2.0 g/dL (< 20 g/L)	—
Alkaline phosphatase, high	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Alkalosis	—	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, high (Report the most appropriate term)	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Amylase (pancreatic) or amylase (total), high (Report the most appropriate term)	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN

LLN = lower limit of normal; ULN = upper limit of normal.

[f] Refer to Section 5.3.5.1 for instructions on reporting injection-site reactions to study treatment (if applicable). For reactions to drugs other than study treatment, report the most appropriate term and report multiple events, if applicable.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
AST or SGOT, high (Report the most appropriate term)	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Bicarbonate, low	16.0 mEq/L to < LLN (16.0 mmol/L to < LLN)	11.0 to < 16.0 mEq/L (11.0 to < 16.0 mmol/L)	8.0 to < 11.0 mEq/L (8.0 to < 11.0 mmol/L)	< 8.0 mEq/L (< 8.0 mmol/L)
Bilirubin (direct), high: > 28 days of age	—	—	> ULN with other signs and symptoms of hepatotoxicity	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Bilirubin (direct), high: ≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL [h]	> 2 mg/dL [h]
Bilirubin (total), high: > 28 days of age	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN
Bilirubin (total), high: ≤ 28 days of age	See Table 2			
Calcium, high: ≥ 7 days of age	10.6 to < 11.5 mg/dL (2.65 to < 2.88 mmol/L)	11.5 to < 12.5 mg/dL (2.88 to < 3.13 mmol/L)	12.5 to < 13.5 mg/dL (3.13 to < 3.38 mmol/L)	≥ 13.5 mg/dL (≥ 3.38 mmol/L)
Calcium, high: < 7 days of age	11.5 to < 12.4 mg/dL (2.88 to < 3.10 mmol/L)	12.4 to < 12.9 mg/dL (3.10 to < 3.23 mmol/L)	12.9 to < 13.5 mg/dL (3.23 to < 3.38 mmol/L)	≥ 13.5 mg/dL (≥ 3.38 mmol/L)
Calcium (ionized), high	> ULN to < 6.0 mg/dL (> ULN to < 1.5 mmol/L)	6.0 to < 6.4 mg/dL (1.5 to < 1.6 mmol/L)	6.4 to < 7.2 mg/dL (1.6 to < 1.8 mmol/L)	≥ 7.2 mg/dL (≥ 1.8 mmol/L)

LLN = lower limit of normal; ULN = upper limit of normal.

[h] Direct bilirubin > 1.5 mg/dL in a participant ≤ 28 days of age should be graded as Grade 2, if < 10% of the total bilirubin.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
Calcium, low: ≥ 7 days of age	7.8 to < 8.4 mg/dL (1.95 to < 2.10 mmol/L)	7.0 to < 7.8 mg/dL (1.75 to < 1.95 mmol/L)	6.1 to < 7.0 mg/dL (1.53 to < 1.75 mmol/L)	< 6.1 mg/dL (< 1.53 mmol/L)
Calcium, low: < 7 days of age	6.5 to < 7.5 mg/dL (1.63 to < 1.88 mmol/L)	6.0 to < 6.5 mg/dL (1.50 to < 1.63 mmol/L)	5.50 to < 6.0 mg/dL (1.38 to < 1.50 mmol/L)	< 5.50 mg/dL (< 1.38 mmol/L)
Calcium (ionized), low	< LLN to 4.0 mg/dL (< LLN to 1.0 mmol/L)	3.6 to < 4.0 mg/dL (0.9 to < 1.0 mmol/L)	3.2 to < 3.6 mg/dL (0.8 to < 0.9 mmol/L)	< 3.2 mg/dL (< 0.8 mmol/L)
Cardiac troponin I, high	—	—	—	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine kinase, high	3 to < 6 × ULN	6 to < 10 × ULN	10 to < 20 × ULN	≥ 20 × ULN
Creatinine, high	1.1 to 1.3 × ULN	> 1.3 to 1.8 × ULN or increase to 1.3 to < 1.5 × baseline [i]	> 1.8 to < 3.5 × ULN or increase to 1.5 to < 2.0 × baseline [i]	≥ 3.5 × ULN or increase to ≥ 2.0 × baseline [i]
Creatinine clearance or eGFR, low (Report the most appropriate term)	—	< 90 to 60 mL/min or mL/min/1.73 m^2 or 10% to < 30% decrease from baseline [j]	< 60 to 30 mL/min or mL/min/1.73 m^2 or 30% to < 50% decrease from baseline [j]	< 30 mL/min or mL/min/1.73 m^2 or ≥ 50% decrease from baseline [j] or dialysis needed

eGFR = estimated glomerular filtration rate; LLN = lower limit of normal; ULN = upper limit of normal.

[i] For participant with normal baseline value, grade should be based on current value relative to ULN. For participant with elevated baseline value, grade should be based on current value relative to baseline value.

[j] For participant with normal baseline value, grade should be based on current value. For participant with elevated baseline value, grade should be based on current value relative to baseline value.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
Glucose (fasting), high	110 to 125 mg/dL (6.11 to < 6.95 mmol/L)	> 125 to 250 mg/dL (6.95 to < 13.89 mmol/L)	> 250 to 500 mg/dL (13.89 to < 27.75 mmol/L)	≥ 500 mg/dL (≥ 27.75 mmol/L)
Glucose (non-fasting), high	116 to 160 mg/dL (6.44 to < 8.89 mmol/L)	> 160 to 250 mg/dL (8.89 to < 13.89 mmol/L)	> 250 to 500 mg/dL (13.89 to < 27.75 mmol/L)	≥ 500 mg/dL (≥ 27.75 mmol/L)
Glucose, low: ≥28 days of age	55 to 64 mg/dL (3.05 to < 3.55 mmol/L)	40 to < 55 mg/dL (2.22 to < 3.05 mmol/L)	30 to < 40 mg/dL (1.67 to < 2.22 mmol/L)	< 30 mg/dL (< 1.67 mmol/L)
Glucose, low: < 28 days of age	50 to 54 mg/dL (2.78 to < 3.00 mmol/L)	40 to < 50 mg/dL (2.22 to < 2.78 mmol/L)	30 to < 40 mg/dL (1.67 to < 2.22 mmol/L)	< 30 mg/dL (< 1.67 mmol/L)
Lactate, high	ULN to < 2.0 × ULN without acidosis	≥ 2.0 × ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, high	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN
Lipid disorder: cholesterol (fasting), high: ≥ 18 years of age	200 to < 240 mg/dL (5.18 to < 6.19 mmol/L)	240 to < 300 mg/dL (6.19 to < 7.77 mmol/L)	≥ 300 mg/dL (≥ 7.77 mmol/L)	—
Lipid disorder: cholesterol (fasting), high: < 18 years of age	170 to < 200 mg/dL (4.40 to < 5.15 mmol/L)	200 to < 300 mg/dL (5.15 to < 7.77 mmol/L)	≥ 300 mg/dL (≥ 7.77 mmol/L)	—
Lipid disorder: LDL (fasting), high: ≥ 18 years of age	130 to < 160 mg/dL (3.37 to < 4.12 mmol/L)	160 to < 190 mg/dL (4.12 to < 4.90 mmol/L)	≥ 190 mg/dL (≥ 4.90 mmol/L)	—

ULN = upper limit of normal.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
Lipid disorder: LDL (fasting), high: >2 to <18 years of age	110 to <130 mg/dL (2.85 to <3.34 mmol/L)	130 to <190 mg/dL (3.34 to <4.90 mmol/L)	≥190 mg/dL (≥4.90 mmol/L)	—
Lipid disorder: triglycerides (fasting), high	150 to 300 mg/dL (1.71 to 3.42 mmol/L)	>300 to 500 mg/dL (>3.42 to 5.7 mmol/L)	>500 to <1,000 mg/dL (>5.7 to 11.4 mmol/L)	>1,000 mg/dL (>11.4 mmol/L)
Magnesium, low	1.2 to <1.4 mEq/L (0.60 to <0.70 mmol/L)	0.9 to <1.2 mEq/L (0.45 to <0.60 mmol/L)	0.6 to <0.9 mEq/L (0.30 to <0.45 mmol/L)	<0.6 mEq/L (<0.30 mmol/L)
Phosphate, low: >14 years of age	2.0 mg/dL to <LLN (0.65 mmol/L to <LLN)	1.4 to <2.0 mg/dL (0.45 to <0.65 mmol/L)	1.0 to <1.4 mg/dL (0.32 to <0.45 mmol/L)	<1.0 mg/dL (<0.32 mmol/L)
Phosphate, low: 1 to 14 years of age	3.0 to <3.5 mg/dL (0.97 to <1.13 mmol/L)	2.5 to <3.0 mg/dL (0.81 to <0.97 mmol/L)	1.5 to <2.5 mg/dL (0.48 to <0.81 mmol/L)	<1.5 mg/dL (<0.48 mmol/L)
Phosphate, low: <1 year of age	3.5 to <4.5 mg/dL (1.13 to <1.45 mmol/L)	2.5 to <3.5 mg/dL (0.81 to <1.13 mmol/L)	1.5 to <2.5 mg/dL (0.48 to <0.81 mmol/L)	<1.5 mg/dL (<0.48 mmol/L)
Potassium, high	5.6 to <6.0 mEq/L or mmol/L	6.0 to <6.5 mEq/L or mmol/L	6.5 to <7.0 mEq/L or mmol/L	≥7.0 mEq/L or mmol/L
Potassium, low	3.0 to <3.4 mEq/L or mmol/L	2.5 to <3.0 mEq/L or mmol/L	2.0 to <2.5 mEq/L or mmol/L	<2.0 mEq/L or mmol/L
Sodium, high	146 to <150 mEq/L or mmol/L	150 to <154 mEq/L or mmol/L	154 to <160 mEq/L or mmol/L	≥160 mEq/L or mmol/L
Sodium, low	130 to <135 mEq/L or mmol/L	125 to <130 mEq/L or mmol/L	121 to <125 mEq/L or mmol/L	<121 mEq/L or mmol/L
Uric acid, high	7.5 to <10.0 mg/dL (0.45 to <0.59 mmol/L)	10.0 to <12.0 mg/dL (0.59 to <0.71 mmol/L)	12.0 to <15.0 mg/dL (0.71 to <0.89 mmol/L)	≥15.0 mg/dL (≥0.89 mmol/L)

LLN = lower limit of normal.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Hematology				
Absolute $CD4^+$ count, low (not HIV infected): >5 years of age	300 to <400 cells/mm^3 (0.300×10^9 to $<0.400 \times 10^9$ cells/L)	200 to <300 cells/mm^3 (0.200×10^9 to $<0.300 \times 10^9$ cells/L)	100 to <200 cells/mm^3 (0.100×10^9 to $<0.200 \times 10^9$ cells/L)	<100 cells/mm^3 (0.100×10^9 cells/L)
Absolute lymphocyte count, low (not HIV infected): >5 years of age	600 to <650 cells/mm^3 (0.600×10^9 to $<0.650 \times 10^9$ cells/L)	500 to <600 cells/mm^3 (0.500×10^9 to $<0.600 \times 10^9$ cells/L)	350 to <500 cells/mm^3 (0.350×10^9 to $<0.500 \times 10^9$ cells/L)	<350 cells/mm^3 ($<0.350 \times 10^9$ cells/L)
Absolute neutrophil count, low: >7 days of age	800 to 1000 cells/mm^3 (0.800×10^9 to 1.000×10^9 cells/L)	600 to 799 cells/mm^3 (0.600×10^9 to 0.799×10^9 cells/L)	400 to 599 cells/mm^3 (0.400×10^9 to 0.599×10^9 cells/L)	<400 cells/mm^3 ($<0.400 \times 10^9$ cells/L)
Absolute neutrophil count, low: 2 to 7 days of age	1250 to 1500 cells/mm^3 (1.250×10^9 to 1.500×10^9 cells/L)	1000 to 1249 cells/mm^3 (1.000×10^9 to 1.249×10^9 cells/L)	750 to 999 cells/mm^3 (0.750×10^9 to 0.999×10^9 cells/L)	<750 cells/mm^3 ($<0.750 \times 10^9$ cells/L)
Absolute neutrophil count, low: ≤1 day of age	4000 to 5000 cells/mm^3 (4.000×10^9 to 5.000×10^9 cells/L)	3000 to 3999 cells/mm^3 (3.000×10^9 to 3.999×10^9 cells/L)	1500 to 2999 cells/mm^3 (1.500×10^9 to 2.999×10^9 cells/L)	<1500 cells/mm^3 ($<1.500 \times 10^9$ cells/L)
Fibrinogen, decreased	100 to <200 mg/dL (1.00 to <2.00 g/L) or 0.75 to $<1.00 \times$ LLN	75 to <100 mg/dL (0.75 to <1.00 g/L) or ≥0.50 to $<0.75 \times$ LLN	50 to <75 mg/dL (0.50 to <0.75 g/L) or 0.25 to $<0.50 \times$ LLN	<50 mg/dL (<0.50 g/L) or $<0.25 \times$ LLN or associated with gross bleeding

LLN = lower limit of normal.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Hematology (cont.)				
Hemoglobin, low: ≥13 years of age (male only) [k]	10.0 to 10.9 g/dL (6.19 to 6.76 mmol/L)	9.0 to <10.0 g/dL (5.57 to <6.19 mmol/L)	7.0 to <9.0 g/dL (4.34 to <5.57 mmol/L)	<7.0 g/dL (<4.34 mmol/L)
Hemoglobin, low: ≥13 years of age (female only) [k]	9.5 to 10.4 g/dL (5.88 to 6.48 mmol/L)	8.5 to <9.5 g/dL (5.25 to <5.88 mmol/L)	6.5 to <8.5 g/dL (4.03 to <5.25 mmol/L)	<6.5 g/dL (<4.03 mmol/L)
Hemoglobin, low: 57 days to <13 years of age (male and female) [k]	9.5 to 10.4 g/dL (5.88 to 6.48 mmol/L)	8.5 to <9.5 g/dL (5.25 to <5.88 mmol/L)	6.5 to <8.5 g/dL (4.03 to <5.25 mmol/L)	<6.5 g/dL (<4.03 mmol/L)
Hemoglobin, low: 36 to 56 days of age (male and female) [k]	8.5 to 9.6 g/dL (5.26 to 5.99 mmol/L)	7.0 to <8.5 g/dL (4.32 to <5.26 mmol/L)	6.0 to <7.0 g/dL (3.72 to <4.32 mmol/L)	<6.0 g/dL (<3.72 mmol/L)
Hemoglobin, low: 22 to 35 days of age (male and female) [k]	9.5 to 11.0 g/dL (5.88 to 6.86 mmol/L)	8.0 to <9.5 g/dL (4.94 to <5.88 mmol/L)	6.7 to <8.0 g/dL (4.15 to <4.94 mmol/L)	<6.7 g/dL (<4.15 mmol/L)
Hemoglobin, low: 8 to 21 days of age (male and female) [k]	11.0 to 13.0 g/dL (6.81 to 8.10 mmol/L)	9.0 to <11.0 g/dL (5.57 to <6.81 mmol/L)	8.0 to <9.0 g/dL (4.96 to <5.57 mmol/L)	<8.0 g/dL (<4.96 mmol/L)
Hemoglobin, low: ≤7 days of age (male and female) [k]	13.0 to 14.0 g/dL (8.05 to 8.72 mmol/L)	10.0 to <13.0 g/dL (6.19 to <8.05 mmol/L)	9.0 to <10.0 g/dL (5.59 to <6.19 mmol/L)	<9.0 g/dL (<5.59 mmol/L)

[k] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, hemoglobin grade should be based on values for the gender with which they identify (e.g., grade for a transgender female should be based on hemoglobin laboratory values for females).

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Hematology (cont.)				
INR, high (not on anticoagulation therapy)	1.1 to $<1.5\times$ ULN	1.5 to $<2.0\times$ ULN	2.0 to $<3.0\times$ ULN	$\geq 3.0\times$ ULN
Methemoglobin (% hemoglobin)	5.0% to $<10.0\%$	10.0% to $<15.0\%$	15.0% to $<20.0\%$	$\geq 20.0\%$
PTT, high (not on anticoagulation therapy)	1.1 to $<1.66\times$ ULN	1.66 to $<2.33\times$ ULN	2.33 to $<3.00\times$ ULN	$\geq 3.00\times$ ULN
Platelets, decreased	100,000 to $<125{,}000$ cells/mm^3 (100.000×10^9 to $<125.000\times10^9$ cells/L)	50,000 to $<100{,}000$ cells/mm^3 (50.000×10^9 to $<100.000\times10^9$ cells/L)	25,000 to $<50{,}000$ cells/mm^3 (25.000×10^9 to $<50.000\times10^9$ cells/L)	$<25{,}000$ cells/mm^3 ($<25.000\times10^9$ cells/L)
PT, high (not on anticoagulation therapy)	1.1 to $<1.25\times$ ULN	1.25 to $<1.50\times$ ULN	1.50 to $<3.00\times$ ULN	$\geq 3.00\times$ ULN
WBC, decreased: >7 days of age	2000 to 2499 cells/mm^3 (2.000×10^9 to 2.499×10^9 cells/L)	1500 to 1999 cells/mm^3 (1.500×10^9 to 1.999×10^9 cells/L)	1000 to 1499 cells/mm^3 (1.000×10^9 to 1.499×10^9 cells/L)	<1000 cells/mm^3 ($<1.000\times10^9$ cells/L)
WBC, decreased: ≤ 7 days of age	5500 to 6999 (5.500×10^9 to 6.999×10^9 cells/L)	4000 to 5499 (4.000×10^9 to 5.499×10^9 cells/L)	2500 to 3999 (2.500×10^9 to 3.999×10^9 cells/L)	<2500 ($<2.500\times10^9$ cells/L)

ULN = upper limit of normal.

Table 1 Severity Grading for Adult and Pediatric Adverse Events (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Urinalysis				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	—
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots or with RBC casts or intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	—

Table 2 Severity Grading for Elevated Total Bilirubin in Neonates

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neonates ≥35 Weeks Gestational Age				
<24 hours of age	4 to <7 mg/dL (68.4 to <119.7 μmol/L)	7 to <10 mg/dL (119.7 to <171 μmol/L)	10 to <17 mg/dL (171 to <290.7 μmol/L)	≥17 mg/dL (≥290.7 μmol/L)
24 to <48 hours of age	5 to <8 mg/dL (85.5 to <136.8 μmol/L)	8 to <12 mg/dL (136.8 to <205.2 μmol/L)	12 to <19 mg/dL (205.2 to <324.9 μmol/L)	≥19 mg/dL (≥324.9 μmol/L)
48 to <72 hours of age	8.5 to <13 mg/dL (145.35 to <222.3 μmol/L)	13 to <15 mg/dL (222.3 to <256.5 μmol/L)	15 to <22 mg/dL (256.5 to <376.2 μmol/L)	≥22 mg/dL (≥376.2 μmol/L)
72 hours to <7 days of age	11 to <16 mg/dL (188.1 to <273.6 μmol/L)	16 to <18 mg/dL (273.6 to <307.8 μmol/L)	18 to <24 mg/dL (307.8 to <410.4 μmol/L)	≥24 mg/dL (≥410.4 μmol/L)
7 to 28 days of age (breast feeding)	5 to <10 mg/dL (85.5 to <171 μmol/L)	10 to <20 mg/dL (171 to <342 μmol/L)	20 to <25 mg/dL (342 to <427.5 μmol/L)	≥25 mg/dL (≥427.5 μmol/L)
7 to 28 days of age (not breast feeding)	1.1 to <1.6× ULN	1.6 to <2.6× ULN	2.6 to <5.0× ULN	≥5.0× ULN

ULN = upper limit of normal.

Table 2 Severity Grading for Elevated Total Bilirubin in Neonates (cont.)

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neonates < 35 Weeks Gestational Age				
32 to < 35 weeks gestational age and < 7 days of age	—	—	10 to < 14 mg/dL (171 to < 239.4 μmol/L)	≥ 14 mg/dL (≥ 239.4 μmol/L)
28 to < 32 weeks gestational age and < 7 days of age	—	—	6 to < 10 mg/dL (102.6 to < 171 μmol/L)	≥ 10 mg/dL (≥ 171 μmol/L)
< 28 weeks gestational age and < 7 days of age	—	—	5 to < 8 mg/dL (85.5 to < 136.8 μmol/L)	≥ 8 mg/dL (≥ 136.8 μmol/L)
7 to 28 days of age (breast feeding)	5 to < 10 mg/dL (85.5 to < 171 μmol/L)	10 to < 20 mg/dL (171 to < 342 μmol/L)	20 to < 25 mg/dL (342 to < 427.5 μmol/L)	≥ 25 mg/dL (≥ 427.5 μmol/L)
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN

ULN = upper limit of normal.

Table 3 Severity Grading for Events Not Specifically Listed in Tables 1 and 2

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

REFERENCE

[HHS] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1 [resource on the Internet]. 2017 [cited: 16 May 2023]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

Appendix 8
Sampson Criteria for Diagnosing Potential Cases of Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

   b) Reduced blood pressure (BP) or associated symptoms of end organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a) Adults: Systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

REFERENCE

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117:391–7.

Appendix 9
Laboratory Sampling in China

Testing, Analysis, and Biosample Destruction in China

The Sponsor delegates the testing, analysis, and destruction of samples for Study GA44839 from China sites to the following China domestic companies:

Testing Items	*Central Laboratory for Testing and Analysis*	*Biosample Destruction Provider*
Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)	*Labcorp Pharmaceutical Research & Development (Shanghai)Co, Ltd.*	*Shanghai Solid Waste Disposal, Co., Ltd.*

Clarification of Laboratory Sample Collection in China

The following table describes laboratory samples that will not be collected in China:

*Samples that will **not** be collected in China:*
• *Colonic tissue samples for histologic biomarker assessment and for exploratory biomarker research*
• *Genomic research (analysis or mutations, single nucleotide polymorphisms, or other genomic variants) or genomic profiling (WGS or WES) samples*
• *Stool sample for exploratory biomarker research*
• *Samples for Research Biosample Repository*

WES =whole exome sequencing; WGS =whole genome sequencing.

Signature Page for Protocol - GA44839 - VIXARELIMAB - v2 - Global/Core - Publish
System identifier: RIM-CLIN-733320

Approval Task	[redacted] Company Signatory 29-Oct-2024 20:52:56 GMT+0000