A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rosnilimab in Subjects with Moderate to Severe Ulcerative Colitis

Protocol Number: ANB030-204
Investigational New Drug Number: 167977
European Union Clinical Trial Number: 2023-508679-34

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Senior Director, Medical Development

Protocol Amendment 2.0 (Version 3.0)
12 December 2023

SPONSOR SIGNATURE PAGE

I confirm that I have read and approved this protocol amendment in its entirety and will comply with the obligations as detailed in all applicable regulations and guidelines (e.g., International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH], Good Clinical Practice [GCP] guidelines), and the protocol amendment.

DocuSigned by:
Zurab Machaidze
Signer Name: Zurab Machaidze
Signing Reason: I approve this document
Signing Time: 13-Dec-2023 | 3:02 PM CST
5C5DA1A6D11E46F89551DCB39B6CAB2F

13-Dec-2023 | 3:02 PM CST

Zurab Machaidze, MD
Senior Director, Medical Development
AnaptysBio, Inc.

Date

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rosnilimab in Subjects with Moderate to Severe Ulcerative Colitis

PROTOCOL NO: ANB030-204

VERSION: Protocol Amendment 2.0 (Version 3.0)

This protocol amendment is a confidential communication of AnaptysBio, Inc (AnaptysBio). I confirm that I have read this protocol amendment; I understand it; and I will work according to this protocol amendment. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from AnaptysBio.

Instructions to the Investigator: Please SIGN and DATE (DD-MMM-YYYY) this signature page. PRINT your name, title, and the name of the study site in which the study will be conducted. Return the signed copy to AnaptysBio or designee.

I have read this protocol amendment in its entirety and agree to conduct the study accordingly:

Investigator Signature: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

_____

DOCUMENT HISTORY

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment 2.0 (Version 3.0)	12 December 2023
Protocol Amendment 1.1 (Version 2.1)	19 October 2023
Protocol Amendment 1 (Version 2.0)	14 September 2023
Original Protocol (Version 1.0)	30 June 2023

SUMMARY OF CHANGE FROM PREVIOUS VERSION

Amendment 2.0 (12 December 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU).

Overall Rationale for the Amendment:

The purpose of this amendment is to exclude subjects with prior malignancies within 5 years before Randomization and expand the criteria for convening ad hoc Safety Monitoring Team meetings.

Amendment 2.0 Summary of Changes		
Section	**Description of Change**	**Rationale**
Title Page Sponsor Signature Page	Update Sponsor Medical Expert and Signatory.	Updated because of a change in responsibilities.
Section 5.2, Exclusion Criteria	Exclusion Criterion 15 updated to exclude subjects with prior malignancies within 5 years before Randomization (except for squamous and basal cell carcinomas of the skin or carcinoma *in situ* of the cervix).	The criteria for subjects with prior malignancy was narrowed by removing the subjective component of the criterion.
Section 7.1, Discontinuation Study Treatment	Expanded the criteria for convening an ad hoc Safety Monitoring Team meeting to include 2 or more subjects with severe infection, malignancy or lymphoproliferative disorder, or anaphylaxis.	Increased safety oversight.
Section 10.2.2 Amendment Policy	Minor revisions made to the text to clarify the intention of this section.	Clarified that this section describes the expedited approval of a protocol amendment.

Amendment 2.0 Summary of Changes		
Section	**Description of Change**	**Rationale**
Throughout	Minor editorial and document formatting revisions.	These editorial and formatting revisions have not been summarized because they do not alter the content of the protocol.

Amendment 1.1 (19 October 2023)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 2(13) of Regulation EU 536/2014 of the European Parliament and the Council of the European Union (EU) because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The purpose of this amendment is to update the European Union Clinical Trial Number.

Amendment 1.1 Summary of Changes		
Section	**Description of Change**	**Rationale**
Title Page	Update the European Union Clinical Trial Number from 2023-507750-32-00 to 2023-508679-34-00.	The study had to be entered under a new European Union Clinical Trial Number because the original European Union Clinical Trial Number was not working.
Throughout	Minor editorial and document formatting revisions.	These editorial and formatting revisions have not been summarized because they do not alter the content of the protocol.

Amendment 1 (14 September 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU).

Overall Rationale for the Amendment:

The purpose of this amendment is to update the study design to comply with study design recommendations from the United States Food and Drug Administration, to clarify safety monitoring plans, and to simplify blood sample collection procedures.

Amendment 1 Summary of Changes		
Section	**Description of Change**	**Rationale**
Statement of Compliance	Added reference to Clinical Trials Regulation (EU 536/2014)	Comply with Clinical Trials Regulation (EU 536/2014).
Section 1.1, Synopsis Section 4.1, Overall Design Section 5.1, Inclusion Criteria	Removed requirement for rectal bleeding score (RBS) ≥ 1 and stool frequency score (SFS) ≥ 2 from the definition of moderate to severe ulcerative colitis (UC).	Updated to agree with FDA Draft Guidance for Industry - Ulcerative Colitis: Developing Drugs for Treatment (April 2022)
Section 1.1, Synopsis Section 5.1, Inclusion Criteria	Inclusion Criterion 4 was revised to state that the subject has had a surveillance colonoscopy that did not detect potential dysplasia or colon cancer with 1 year of Day 1.	Revised for clarity.
Section 1.3, Schedule of Activities	Deleted blood biomarker samples at Week 8 visit.	Biomarker assessment at Week 8 are not needed and removed to reduce subject burden.
Section 1.3, Schedule of Activities	Deleted “daily” from “daily eDiary training.”	Clarify frequency of eDiary training.
Section 1.3, Schedule of Activities, footnote j	Added that blood biomarkers include collections for serum cytokines, transcriptomic analysis, and immunophenotyping.	Clarify what biomarkers will be assessed.
Section 2.1.3, Rosnilimab	Added that rosnilimab is not approved or marketed in any region or country	Clarify that rosnilimab has not been approved to comply with Clinical Trials Regulation (EU 536/2014).
Section 2.3.1, Known Potential Risks Section 6.1.2, Dosing and Administration	Moved guidance on monitoring for allergic reactions to dose administration section.	Guidance added to ensure subject safety.
Section 7.1, Discontinuation of Study Treatment	Added drug-induced liver injury criteria for discontinuing study treatment and follow-up instructions. Also added criterion for ad hoc formation of a Safety Monitoring Team if 2 or more subjects meet the drug-induced liver injury criteria for discontinuing study treatment.	Ensure subject safety.
Section 8.2.1.6, Serious Adverse Event Reporting	Added reference to notify EudraVigilance of SAEs	Comply with Clinical Trials Regulation (EU 536/2014).
Section 8.2.6, 12-Lead Electrocardiogram	Deleted reference to a separate ECG manual.	Correct text since a separate manual is not needed for ECG.
Section 10.1.3, Confidentiality and Privacy	Added information about what to do in case of a data breach.	Provide instructions for what to do in case of a data breach in accordance with the Clinical Trials Regulation (EU 536/2014).

Amendment 1 Summary of Changes		
Section	**Description of Change**	**Rationale**
Section 10.1.9.1, Data Collection and Management Responsibilities	Remove reference to subject's legal representative.	Reference removed because Inclusion Criterion 13 requires that the subject be capable of giving voluntary written informed consent.
Section 10.1.11, Publication and Data Sharing Policy	Added that results will be posted to the Clinical Trials Information System (CTIS) within 1 year of study completion.	Comply with requirements of the Clinical Trials Regulation (EU 536/2014) Annex IV.
Throughout	Minor editorial and document formatting revisions.	These editorial and formatting revisions have not been summarized because they do not alter the content of the protocol.
Abbreviations: EU: European Union: SAE: serious adverse event		

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

TABLE OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-amino salicylic acid
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC System	Anatomical Therapeutic Chemical System
$AUC_{0\text{-}168}$	AUC from time 0 to 168 hours postdose
$AUC_{0\text{-}inf}$	Area under the concentration time curve time 0 to infinity
AUC_{τ}	Area under the concentration-time curve over the dosing interval
BTLA	B- and T-lymphocyte attenuator
CD28	Cluster of differentiation 28
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease of 2019
CRF	Case Report Form
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
CT	Computerized tomography
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
C_{trough}	Predose (trough) concentration
CV	Coefficient of variation
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EOS	End of study
EOT	End of treatment
ET	Early termination

EU	European Union
FDA	Food and Drug Administration
FSH	Follicular stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GvHD	Graft-versus-host disease
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICOS	Inducible T-cell costimulator
IFNγ	Interferon γ
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous(ly)
JAK	Janus kinase
K_D	Dissociation constant
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
mMS	Modified Mayo Score

MS	Mayo Score
N	Population sample size
n	Number of subjects with available data
NOAEL	No-observed-adverse-effect level
PD	Pharmacodynamic(s)
PD1	Programmed cell death protein 1
PD1-L1	Programmed cell death protein ligand 1
PD1-L2	Programmed cell death protein ligand 2
PGA	Physician's Global Assessment
PK	Pharmacokinetic(s)
pmMS	Partial modified Mayo score
PP	Per protocol
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QC	Quality control
RBS	Rectal bleeding subscore
S1P	Sphingosine-1-phosphate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SFS	Stool frequency subscore
SoA	Schedule of Assessments
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TB	Tuberculosis
TDAR	T-cell-dependent antibody response
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum observed concentration
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor α
TT	Tetanus toxin
UC	Ulcerative colitis

ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Women of childbearing potential

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the protocol and protocol amendments, applicable ICH GCP guidelines, and applicable local laws and regulations (including the Clinical Trials Regulation [EU 536/2014]). The Investigator will assure that no planned deviation from or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) application Sponsor and documented approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard to the study subjects. All personnel involved in the conduct of this study have completed ICH GCP Training.

The protocol, informed consent forms (ICFs), recruitment materials, and all subject materials will be submitted to the IRB/EC for review and approval. Approval of the protocol and ICFs must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes to the study are implemented. In addition, all changes to the ICFs will be IRB/EC approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent using previously approved ICFs.

1 PROTOCOL SUMMARY

1.1 Synopsis

Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rosnilimab in Subjects with Moderate to Severe Ulcerative Colitis
Short Title:	Efficacy and Safety of Rosnilimab in Subjects with Ulcerative Colitis
Product:	Rosnilimab (ANB030)
Phase:	2
Study Centers:	Approximately 90 study centers globally are expected to participate in this study.
Study Description:	This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of rosnilimab in subjects with moderate to severe ulcerative colitis (UC). To be eligible for this study, a subject must be ≥ 18 years old, have a clinical diagnosis of active UC for ≥ 90 days prior to Day 1, have moderate to severe active UC (defined as a Modified Mayo score [mMS] at Baseline of ≥ 5 points with an endoscopic subscore (based on a central reader review) ≥ 2 with no evidence of current infection, colonic dysplasia, and/or malignancy. (The mMS is the Mayo score [MS] excluding the Physician's Global Assessment [PGA].) Appropriate documentation of biopsy results that are consistent with the diagnosis of UC, as assessed by the Investigator, must be available before Day 1. If suitable documentation is not available from a prior biopsy, it may be obtained from the Screening endoscopy. A subject with prior exposure to a programmed cell death protein 1 (PD1) or programmed cell death ligand 1 (PD-L1) agonist, antagonist, or modulator, or with a history of colectomy (total or subtotal), ileoanal pouch, Kock pouch, or ileostomy will be excluded from the study. In addition, a subject who failed (i.e., had an inadequate response, loss of response, or intolerance to) any combination of 3 or more advanced UC therapy classes will be excluded from the study. For this study, advanced UC therapy classes include, but are not limited to, 1) anti-tumor necrosis factor (TNF) antibodies (e.g., adalimumab, golimumab, infliximab), 2) other biologics (e.g., ustekinumab, vedolizumab), 3) oral Janus kinase

(JAK) inhibitors (e.g., tofacitinib, upadacitinib), and 4) oral sphingosine-1-phosphate (S1P) receptor modulators (e.g., ozanimod).

Subjects may be taking oral corticosteroids (prednisone ≤ 20 mg/day or equivalent) before and during the study but must have been at a stable dosage of oral corticosteroids for ≥ 4 weeks prior to Day 1 and must remain on that stable steroid dosage during the first 12 weeks of study drug treatment. Concurrent steroid therapy may be tapered beginning after assessment of the primary endpoint at Week 12.

At Screening, each subject will be provided an electronic diary (eDiary) to track daily stool frequency and rectal bleeding throughout the Screening, Blinded Treatment, and Follow-up Periods.

All subjects will undergo colonoscopies/sigmoidoscopies during Screening. The Screening endoscopy should not be performed until the majority of Screening activities have been completed and the corresponding inclusion and exclusion criteria have been confirmed. Sigmoidoscopies will be performed during Week 12 (the primary endpoint) and Week 24 (the End of Treatment [EOT] visit). Colon biopsies will be collected during each endoscopy.

The maximum study duration per subject will be up to 39 weeks consisting of a Screening Period of up to 35 days (5 weeks), a 24-week Blinded Treatment Period consisting of an initial 12-week Placebo-Controlled Treatment Period followed by a 12-week Continued Treatment Period, and a 10-week- Follow-up Period.

Approximately 132 subjects will be randomized in a 1:1:1 ratio to 3 treatment groups (n = 44 in each group): rosnilimab 800 mg administered subcutaneously (SC) every 2 weeks (Q2W), rosnilimab 400 mg SC every 4 weeks (Q4W), or placebo SC Q2W. All subjects will receive 4 SC injections every 2 weeks to protect the blind. Each subject will receive double-blind treatment during the 12-week Placebo-Controlled Treatment Period.

At the Week-12 visit,

- Subjects originally randomized to rosnilimab will continue their assigned treatment through the 12-week Continued Treatment Period
- Subjects originally randomized to placebo who achieve Responder status (defined as a decrease from Baseline to Week 12 of ≥ 2 points and ≥ 30% in the Partial Modified Mayo score [pmMS] with a decrease from baseline in rectal bleeding subscore (RBS) ≥ 1 point or an

absolute RBS ≤ 1) will continue their assigned placebo treatment through the 12-week Continued Treatment Period.

- Subjects originally randomized to placebo who do not achieve Responder status (i.e., nonresponders) will cross-over to active treatment (rosnilimab 800 mg SC Q2W) in a blinded manner and continue active treatment through the 12-week Continued Treatment Period

Therefore, all subjects initially randomized to rosnilimab, and those subjects initially randomized to placebo who are Responders will continue to receive their originally assigned study treatments (rosnilimab or placebo, respectively) for a total of up to 24 weeks. Subjects initially randomized to placebo who are nonresponders will receive placebo for 12 weeks and rosnilimab 800 mg SC Q2W for up to 12 weeks.

Enrollment of approximately 50% to 70% of the total study population by subjects who have prior treatment experience with advanced UC therapies is desired. Randomization will be stratified by prior experience with advanced UC therapies (experience with advanced UC therapy versus no prior advanced UC therapies) and concurrent oral steroid use (steroid use versus no steroid use).

An overview of the study design is presented in Figure 1. Safety and efficacy assessments and study procedures are outlined in the Schedule of Assessments (SoA) (Table 1).

After a Screening Period of up to 35 days, eligible subjects will be randomized, and the first dose of study treatment will be administered on Day 1. Subjects will return for study visits during the Blinded Placebo-Controlled Treatment Period at Weeks 2, 4, 6, 8, 10 and 12 for protocol-defined assessments and administration of study treatment. All subjects will continue into the 12-week Continued Treatment Period and return for study visits at Weeks 14, 16, 18, 20, and 22 for protocol-defined assessments and administration of study treatment. After the last dose of study treatment at the Week 22 visit, subjects will return for the EOT visit at Week 24 and for Follow-up visits at Weeks 26, 30, and 34 to complete protocol-defined assessments.

Clinical efficacy and outcomes will be assessed using the mMS, the pmMS, Geboes score (Geboes 2000), and Inflammatory Bowel Disease Questionnaire (IBDQ).

Safety assessments will include incidence, type, and severity of all adverse events (AEs), including serious AEs (SAEs) and AEs that lead to treatment discontinuation and study withdrawal; and changes in concomitant medications, vital signs, physical examination findings, and clinical laboratory tests.

Blood samples will be collected to assess the PK, immunogenicity (presence of anti-drug antibodies [ADA]), and PD (i.e., biomarkers) of rosnilimab predose on Day 1 and at the time points specified in the SoA (Table 1). Circulating blood PD biomarkers may include, but are not limited to, immunophenotyping, tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), Interleukin (IL)-6, and IL-12. Fecal samples will be collected for fecal calprotectin analysis. Tissue biomarkers include gene expression panels reflective of UC disease activity and cytokine levels including the same cytokines measured in peripheral blood.

Subjects may choose to stop study treatment and/or participation in the study at any time. Subjects who permanently discontinue study treatment before or at the Week-22 visit should complete all study assessments specified in the SoA (Table 1) for the visit at which the decision is made to permanently discontinue study treatment and then return for a final Early Termination (ET) Follow-up visit approximately 12 weeks after their last dose of study treatment.

Interim analyses may be performed during the study for internal decision making. No adjustment for Type I error will be performed.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary Efficacy Objective • To assess the clinical efficacy of rosnilimab versus placebo in subjects with moderate to severe UC	***Primary Efficacy Endpoint*** • Mean change from Baseline in mMS at Week 12 ***Secondary Efficacy Endpoints*** • Proportion of subjects achieving clinical remission (defined as a mMS ≤ 2, with a stool frequency subscore (SFS) ≤ 1, RBS = 0, and endoscopic subscore ≤ 1 without friability) at Week 12

	• Proportion of subjects showing endoscopic improvement (defined as an endoscopy subscore ≤ 1 without friability) at Week 12 • Proportion of subjects achieving a clinical response (defined as a decrease from Baseline in mMS ≥ 2 points and ≥ 30% with a decrease from Baseline in RBS ≥ 1 point or an absolute RBS ≤ 1) at Week 12
	Exploratory Efficacy Endpoints • Proportion of subjects achieving endoscopic remission (defined as an endoscopy subscore = 0) at Week 12 • Proportion of subjects achieving histologic-endoscopic mucosal improvement (defined as an endoscopic subscore of 0 and a Geboes score < 2) at Week 12 • Mean change from Baseline in the following assessments at each time point indicated in the SoA (Table 1): o mMS o pmMS o IBDQ o Individual mMS subscores (RBS, SFS, and endoscopy subscore) o Geboes score

Safety Objective • To evaluate the safety and tolerability of rosnilimab versus placebo in subjects with moderate to severe UC	***Safety Endpoints*** • Incidence, type, and severity of AEs, SAEs, and AEs leading to treatment discontinuation and study withdrawal • Change from Baseline in vital signs and clinical laboratory parameters
PK Objectives • To evaluate the PK of rosnilimab in subjects with moderate to severe UC	***Exploratory PK Endpoints*** • Mean observed predose (trough) rosnilimab concentration (C_{trough}) at each time point indicated in the SoA (Table 1)
PD Objectives • To evaluate the PD of rosnilimab in subjects with moderate to severe UC	***Exploratory PD Endpoints*** • Mean change from Baseline in biomarkers at each time point indicated in the SoA (Table 1)
Immunogenicity Objective • To evaluate the immunogenicity of rosnilimab in subjects with moderate to severe UC	***Exploratory Immunogenicity Endpoints*** • Number and percentage of subjects at each time point indicated in the SoA (Table 1) with confirmed positive ADA status and corresponding titer
Abbreviations: ADA: anti-drug antibody; AE: Adverse event; C_{trough}: Predose (trough) serum concentration; IBDQ: Inflammatory Bowel Disease Questionnaire; PD: pharmacodynamic; PK: Pharmacokinetic; RBS: Rectal bleeding subscore; SAE: Serious adverse event; SFS: Stool frequency subscore; SoA: Schedule of Assessments; UC: Ulcerative colitis.	

Description of Study Treatment: Rosnilimab is a humanized immunoglobulin (Ig) G1/kappa monoclonal antibody that binds to PD-1 and triggers PD-1 signaling, resulting in suppression of T-cell proliferation and effector function. Rosnilimab drug product will be provided as a sterile, colorless to brown-yellow, clear to opalescent solution for injection in glass vials containing a nominal volume

of 1 mL of 100 mg/mL rosnilimab. Rosnilimab will be administered in 2 dosages:

- Rosnilimab 800 mg SC Q2W
- Rosnilimab 400 mg SC Q4W

The placebo will be formulated to be identical in composition to the rosnilimab drug product, except that it lacks the active ingredient, rosnilimab. Placebo will be provided as a sterile, colorless to brown-yellow, clear to opalescent solution for injection in glass vials containing a nominal volume of 1 mL.

- For subjects in the Placebo group, placebo will be administered during the Blinded Treatment Period.
- For subjects in the Rosnilimab 400-mg Q4W SC group, placebo will alternate with active treatment Q2W starting 2 weeks after the first dose of rosnilimab on Day 1.

To maintain the blind, all subjects will receive 4 SC 2-mL injections Q2W of either active drug or placebo depending on treatment assignment.

Statistical Methods: The primary efficacy endpoint, change in the mMS from Baseline to Week 12, will be analyzed using a mixed-effects model for repeated measures (MMRM) with restricted maximum likelihood estimation. The change from baseline in the mMS will be the dependent variable, with treatment arm, baseline mMS, categorical time point, and treatment × time point interaction as fixed effects along with the stratification factors (prior experience with advanced UC therapies [experience with advanced UC therapy versus no prior advanced UC therapies] and steroid use [steroid use versus no steroid use]). The Kenward-Roger method will be used to calculate the denominator degrees of freedom and adjust standard errors for the test of fixed effects. The MMRM uses all available data and assumes that missing data because of dropouts are missing at random.

Sensitivity analyses using multiple imputation under missing-at-random and not missing-at-random assumptions may be performed.

Given the exploratory nature of this study, no Type 1 error adjustments for multiplicity will be used.

Sample Size: Approximately 132 subjects will be randomized into 3 treatment groups (44 subjects/treatment group). Assuming a dropout rate of 9% by Week 12, approximately 120 evaluable subjects (40 subjects/treatment group) will

complete the primary efficacy endpoint at the end of Week 12. Tests of both high and low doses of rosnilimab versus placebo will have 80.8% power to detect a between-group treatment difference of 0.59 in the mean change in mMS from Baseline to Week 12, using a 2-sided, equal variance, t-test at a significance level of $\alpha = 0.10$, with the assumption of a common standard deviation of 1.04 based on the QUASAR trial (Dignass 2022).

For the mMS-based clinical remission secondary endpoint, if we assume that the placebo rate for the trial proposed in this protocol will be similar to the rates reported in similar Phase 3 clinical trials, then tests of both high and low doses of rosnilimab versus placebo will have 81.9% power to detect a difference of 21.5 percentage points in mMS remission rate (29.6% versus 8.1%) at Week 12. This power calculation used unpooled variance estimates for a 2-sided test at a significance level of $\alpha = 0.10$.

Study Population:

Adult male and female subjects (age ≥18 years) with moderate to severe UC will be enrolled in this study. Subjects must meet all the inclusion criteria and none of the exclusion criteria to be enrolled in the study.

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

Key Inclusion Criteria:

- Male or female who is ≥18 years
- Clinical diagnosis of UC for ≥ 90 days prior to Day 1, including appropriate documentation of biopsy results that are consistent with UC, based on the assessment of the Investigator
- Moderate to severe active UC defined as a mMS ≥ 5 with an endoscopy subscore ≥ 2 (based on a central reader review) at Baseline.
- Surveillance colonoscopy did not detect potential dysplasia or colon cancer performed within 1 year of Day 1
- Subject has completed at least 3 consecutive or 4 nonconsecutive eDiary entries within 7 days before Day 1 (excluding days during bowel preparation for endoscopy)

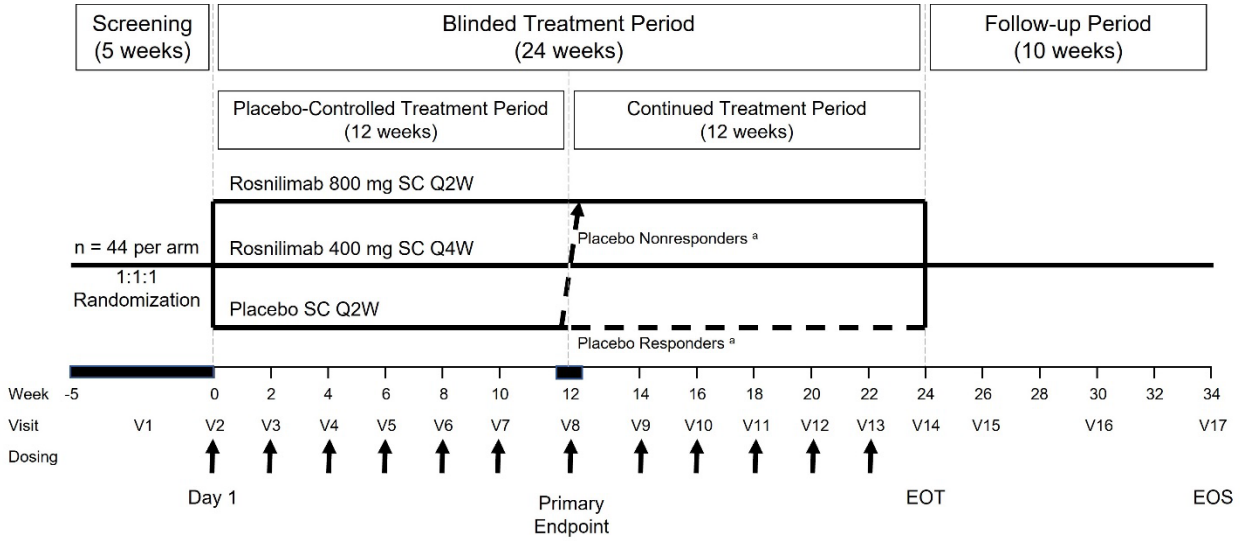
Key Exclusion Criteria:

- Clinical diagnosis of Crohn's disease, indeterminate colitis, fulminant colitis, and/or toxic megacolon
- Disease limited to the rectum (ulcerative proctitis) during the Screening endoscopy
- History of colectomy, ileoanal pouch, Kock pouch, or ileostomy or is planning bowl surgery

- Prior exposure to a PD-1 or PD-L1 agonist, antagonist, or modulator
- *Clostridioides difficile* infection within 30 days before Screening or a positive *C. difficile* toxin stool assay result at Screening, or infection with other intestinal pathogens within the 30 days before Screening
- Prior or current gastrointestinal (GI) dysplasia in any biopsy performed before or during the Screening endoscopy
- Evidence of colonic infection during Screening
- History of an inadequate response, loss of response, or intolerance to any combination of 3 or more advanced UC therapy classes defined as, but not limited to, 1) anti-TNF antibodies (e.g., adalimumab, golimumab, infliximab), 2) other biologics (e.g., ustekinumab, vedolizumab), 3) oral JAK inhibitors (e.g., tofacitinib, upadacitinib), and 4) oral S1P receptor modulators (e.g., ozanimod)
- Current treatment with any of the following:
  - Oral corticosteroids equivalent to prednisone > 20 mg per day
  - Oral corticosteroids equivalent to prednisone ≤ 20 mg per day that have been at a stable dose for < 4 weeks before Day 1
  - Methotrexate or azathioprine
  - Immunomodulatory biologic agents (including investigational biologics) received within 12 weeks or 5 half-lives (whichever is longer) immediately before Randomization.
  - Live or live-attenuated vaccines within 12 weeks before the first dose of study drug.
  - Fecal-microbial transplantation within 30 days prior to Day 1

1.2 Schema

Figure 1 ANB030-204 Study Schema



Primary endpoint: mean change from Baseline in Modified Mayo score at Week 12.

[a] At Week 12, subjects initially randomized to placebo who are placebo nonresponders will be re-assigned to receive rosnilimab 800 mg SC Q2W, and subjects initially randomized to placebo who are placebo responders will continue taking placebo SC Q2W.

Abbreviations: EOS: End of Study; EOT: End-of-Treatment; Q2W: Every 2 weeks: Q4W: Every 4 weeks; SC: Subcutaneously; V: Visit

1.3 Schedule of Activities

The screening evaluation will only be performed after the subject has agreed to participate in the study and has signed and dated the informed consent form (ICF). No treatment or study-related procedures will be initiated before the ICF is signed. All subjects will be assigned a unique Screening Number when the ICF is signed. The screening evaluation will be performed according to the SoA (Table 1). If the subject meets all inclusion criteria and none of the exclusion criteria, the subject may be randomized and assigned a unique randomization/subject identification number.

The first dose of study treatment will be administered on Day 1. The Day-1 visit must be performed no later than 35 days after the Screening Visit.

Table 1 provides a list of the procedures to be performed at each visit during the study. The primary endpoint will be evaluated at Week 12.

Unless specified otherwise, the study assessments scheduled on Day 1 and subsequent visits must be performed before administration of the study treatment.

The recommended order for performing the study assessments (applicable to all visits) is:

- Subject-reported questionnaires
- Efficacy assessments
- Vital signs
- Physical examination
- 12-lead electrocardiograms (ECG)
- Collection of blood samples for safety laboratories, PK/PD, ADA, and biomarkers

The coronavirus disease of 2019 (COVID-19) (or similar) pandemic may impact the ability to adhere to the study procedures described in the SoA (Table 1) due to challenges that include, but are not limited to, subject preferences, site closures, travel restrictions, and quarantines. Details of allowable modifications to protocol-specified visits and procedures because of pandemic restrictions are provided in Section 4.5.

Table 1 Schedule of Activities

Period	Screening	Blinded Treatment Period													Follow-up			
Period Description		**Placebo-Controlled Treatment Period**							**Continued Treatment Period**									
Visit	**V1**	**V2 Day 1**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14 EOT**	**V15**	**V16**	**V17 EOS**	**ET**
Week	**W(-5) to W(-1)**	**NA**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**	**W30**	**W34**	**NA**
Day	**-35 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**211**	**239**	**NA**
Test/Procedure **Window**	**NA**	**NA**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**(± 3)**	**NA**
Informed Consent	X																	
Screening Assessments																		
Demographics	X																	
Medical history	X																	
Prior medications	X																	
Chest X-rays/Chest CT scan [a]	X																	
Viral serology [b]	X																	
TB test (QuantiFERON®-TB Gold test) [c]	X																	
FSH [d]	X																	
Clostridioides difficile toxin stool assay	X																	
Randomization and Dosing																		
Inclusion/Exclusion Criteria	X	X																
Randomization		X																
Study treatment administration		X	X	X	X	X	X	X [e]	X	X	X	X	X					

Table 1 Schedule of Activities

Period	Screening	Blinded Treatment Period													Follow-up			
Period Description		Placebo-Controlled Treatment Period							Continued Treatment Period									
Visit	V1	V2 Day 1	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 EOT	V15	V16	V17 EOS	ET
Week	W(-5) to W(-1)	NA	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W30	W34	NA
Day	-35 to -1	1	15	29	43	57	71	85	99	113	127	141	155	169	183	211	239	NA
Test/Procedure / Window	NA	NA	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	NA
Safety Assessments																		
Routine safety laboratories (Hematology, serum chemistry)	X	X		X		X		X		X		X		X		X	X	X
Urinalysis	X	X		X		X		X		X		X		X		X	X	X
Serum pregnancy test [f]	X																	
Urine pregnancy test [f,g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																	
Weight and BMI	X																X	
Physical examination	X	X						X						X			X	
12-lead ECG [i]	X																	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD/ADA Assessments																		
Blood sample for PK [j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for biomarkers [j]		X	X					X						X			X	
Blood samples for ADA [j]		X	X			X		X			X			X			X	X

Table 1 Schedule of Activities

Period	Screening	Blinded Treatment Period													Follow-up			
Period Description		Placebo-Controlled Treatment Period							Continued Treatment Period									
Visit	V1	V2 Day 1	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 EOT	V15	V16	V17 EOS	ET
Week	W(-5) to W(-1)	NA	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W30	W34	NA
Day	-35 to -1	1	15	29	43	57	71	85	99	113	127	141	155	169	183	211	239	NA
Test/Procedure Window	NA	NA	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	NA
Training and distribution of kits for fecal calprotectin	X																	
Fecal calprotectin		X						X						X				
Efficacy Assessments																		
mMS [k]		X						X						X				
eDiary Training [l]	X																	
Daily eDiary Review [l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy [m]	X [n]							X [o]						X [o]				
Colon biopsies for Geboes Score and Tissue biomarkers [m]	X							X						X				
pmMS [k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IBDQ		X		X		X		X		X		X		X	X	X	X	X

[a] Chest X-rays (posterior anterior and lateral views) or a chest CT scan do not need to be performed if they have been performed within 6 months before Randomization and a report of the findings from a qualified radiologist is available before Randomization. If chest X-rays or a chest CT scan obtained within 6 months before Randomization are not available, chest X-rays or a chest CT scan must be obtained during the Screening Period and read by a qualified radiologist before Randomization.

[b] Blood screen for hepatitis C antibody and hepatitis C RNA; HBcAb, HBsAg, HBsAb with reflex hepatitis B DNA testing in subjects that are $HBcAb^{+}$, $HBsAg^{-}$; and $HBsAb^{-}$; and HIV1 and HIV2 antibodies

[c] QuantiFERON-TB Gold test. At sites where the tuberculin skin test is mandated by local health authorities, the tuberculin skin test may also be performed. Only the QuantiFERON-TB result(s) will be considered for subject eligibility.

Table 1 Schedule of Activities

Period		Screening	Blinded Treatment Period													Follow-up			
Period Description			Placebo-Controlled Treatment Period							Continued Treatment Period									
Visit		V1	V2 Day 1	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 EOT	V15	V16	V17 EOS	ET
Week		W(-5) to W(-1)	NA	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W30	W34	NA
Day		-35 to -1	1	15	29	43	57	71	85	99	113	127	141	155	169	183	211	239	NA
Test/Procedure	Window	NA	NA	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	NA

[d] To confirm postmenopausal status in postmenopausal female subjects

[e] Subjects originally randomized to placebo who do not achieve Responder status (i.e., nonresponders) will cross-over to active treatment (rosnilimab 800 mg SC Q2W) in a blinded manner and continue active treatment through the 12-week Continued Treatment Period.

[f] Pregnancy testing is required only for women of childbearing potential.

[g] The urine pregnancy test result must be read prior to the administration of study treatment at each visit.

[h] Vital signs assessment: body temperature, pulse rate, blood pressure, and respiratory rate

[i] A single 12-lead ECG will be obtained and interpreted by the Investigator and kept with the subject's source documentation.

[j] Blood samples for PK, PD, ADA, and blood biomarkers will be collected predose (right before study treatment administration) at visits when study treatment is administered. Blood biomarkers include collections for serum cytokines, transcriptomic analysis, and immunophenotyping. The specific timepoints for each biomarker assessment will be detailed in the Study Laboratory Manual.

[k] The mMS and pmMS will be calculated using the SFS and RBS from the subject's eDiary, and the centrally read endoscopy score, as applicable.

[l] At the Screening visit, trained staff will distribute and train subjects on the use of the eDiary and provide instructions for determining the daily SFS and RBS. At each subsequent visit, trained staff will review the subject's eDiary for completeness, and retrain the subject as necessary on the use of the eDiary, determining daily SFS and RBS, and the importance of completing the eDiary daily.

[m] Biopsies will be collected at each endoscopy for the Geboes score and tissue biomarkers.

[n] The Screening endoscopy should not be performed until the majority of Screening activities have been completed and the corresponding inclusion and exclusion criteria have been confirmed. During Screening, sigmoidoscopies will be performed unless a subject does not have a surveillance colonoscopy to rule out malignancy and lesions suspicious for colonic dysplasia within 1 year of Day 1. Subjects who do not have a surveillance colonoscopy within 1 year of Day 1 must undergo a colonoscopy during Screening. Endoscopy during Screening should be scheduled within 1 week before Day 1 unless extenuating circumstances preclude it.

[o] Only sigmoidoscopies will be performed following randomization. Each sigmoidoscopy should be scheduled within 1 week before or at the indicated visit.

Abbreviations: ADA: Anti-drug antibody; BMI: Body mass index; CT: Computed tomography; ECG: Electrocardiogram; eDiary: electronic diary; EOS: End of Study; EOT: End of Treatment; ET: Early Termination; FSH: Follicle-stimulating hormone; HBcAb: Hepatitis B core antibody; HBsAg: Hepatitis B surface antigen; HBsAb: Hepatitis B surface antibody; HIV: human immunodeficiency virus; IBDQ: Inflammatory bowel disease questionnaire; mMS: Modified Mayo Score; NA: Not

Table 1 Schedule of Activities

Period		Screening	Blinded Treatment Period													Follow-up			
Period Description			Placebo-Controlled Treatment Period							Continued Treatment Period									
Visit		V1	V2 Day 1	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 EOT	V15	V16	V17 EOS	ET
Week		W(-5) to W(-1)	NA	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W30	W34	NA
Day		-35 to -1	1	15	29	43	57	71	85	99	113	127	141	155	169	183	211	239	NA
Test/Procedure	Window	NA	NA	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	NA

applicable; PD: Pharmacodynamics; PK: Pharmacokinetics; pmMS: Partial modified Mayo Score; Q2W: every 2 weeks; RBS: Rectal bleeding subscore; TB: tuberculosis; SFS: Stool frequency subscore; V: Visit; W: Week

2 INTRODUCTION

2.1 Study Rationale

This study is designed to evaluate the efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of rosnilimab (also known as ANB030) as treatment in subjects with moderate to severe ulcerative colitis (UC).

2.1.1 Ulcerative Colitis

Ulcerative colitis is a common phenotype of inflammatory bowel disease (IBD). UC is an idiopathic gastrointestinal (GI) disease that causes irritation, inflammation, and ulcers in the colon and rectum, which, if a patient is refractory to medical treatment, may result in colorectal dysplasia and colon cancer (Gajendran 2019; Kobayashi, 2020; Reznicek 2021). Inflammation in the colon leads to symptoms such as abdominal pain, diarrhea, fatigue, and rectal bleeding that can negatively impact quality of life. Additionally, patients with UC may experience extraintestinal manifestations involving multiple organs resulting in conjunctivitis, iritis, mouth ulcers, hepatic steatosis, liver abscess, venous thrombosis, large joint arthritis, erythema nodosum, and pyoderma gangrenosum. Symptoms of UC typically wax and wane with random episodes of varying severity. Ulcerative colitis affects 1.2 to 20.3 patients per 100,000 persons/year. UC can affect people at any age, but peak onset occurs from age 20 to 39 years, followed by a second peak from 50 to 80 years (Gajendran 2019).

Treatment strategies in mild to severe patients can involve a combination of immune modification, microbiota manipulation, and environmental modification. Dietary changes to improve symptoms are recommended. Treatment to reduce inflammation and induce or maintain remission includes 5-amino salicylic acid (5-ASA) with or without topical therapy followed by thiopurines, corticosteroids, cyclosporine, advanced therapy (i.e., anti-tumor necrosis factor [TNF] therapy, integrin α4β7 antibodies, Janus Kinase (JAK) inhibitors, sphingosine-1-phosphate (S1P) receptor modulators), and surgery (Kaur 2020; Kobayashi 2020). UC can only be cured with a colectomy or proctocolectomy. Patients with medically refractory UC, a low drug tolerance, and UC-associated neoplasia are optimal surgical candidates. However, these procedures permanently alter the GI tract, require an ileostomy or ileoanal anastomosis, and may not resolve chronic diarrhea. A sizable proportion (20% to 25%) of patients with UC are at risk of surgical intervention within 20 years of diagnosis (Kobayashi 2020). Despite the availability of a number of non-surgical treatments, there is a clear need for additional therapeutic options with better safety tolerability and ability to maintain disease remission long term.

2.1.2 Programmed Cell Death Protein 1

Programmed cell death protein 1 (PD-1) is an integral membrane protein expressed primarily on the surface of activated T cells. It is a critical inhibitory immune checkpoint receptor used by the immune system to naturally down-regulate immune responses. Upon ligation with programmed cell death ligand 1 (PD-L1) or programmed cell death ligand 2 (PD-L2) of an antigen-presenting cell, PD-1 signaling contributes to the down-modulation of T-cell activation, thereby "turning off" T cells. (Okazaki 2007; Okazaki 2013; Bardhan 2016). PD-L1 expression is normally upregulated during inflammation to prevent overt tissue damage (Keir 2008). The importance of this molecule in regulating immune responses in the intestinal tract and maintaining tolerance was established in animal models using PD-L1 and/or PD-1 knockouts and transgenic mice (Keir 2008). Abnormal expression of PD-L1 and/or PD-L1/PD-1 signaling have been observed in IBD (Cassol 2020, Pinchuk 2008, Beswick 2018).

Triggering PD-1 signaling with a functional modulator of PD-1 that is not an antagonist has the potential to down-regulate activated T-cells in inflammatory diseases such as UC.

2.1.3 Rosnilimab

Rosnilimab is a humanized immunoglobulin (Ig)G1, kappa anti-PD-1 antibody that triggers PD-1 signaling and down-regulates T-cell-mediated immune responses, reduces inflammatory cytokine secretion from Type 1 and Type 2 T_{helper} cells and T_{helper} 17 cells, and depletes PD-1^{+} T cells via effector function. Rosnilimab has the potential as a therapeutic agent in autoimmune and inflammatory diseases where T cells are known to play a role in the pathogenesis of the disease and PD-1 signaling pathways may have reduced functionality.

Rosnilimab is currently not approved or marketed in any region or country.

2.2 Background

2.2.1 Nonclinical Studies

Rosnilimab has been evaluated in several nonclinical studies. The functional activity of rosnilimab was determined by *in vitro* binding assays, primary human immune cell assays, and a humanized *in vivo* model of graft-versus-host disease (GvHD). Safety pharmacology studies assessed effects of rosnilimab on complement activation, antibody-dependent cell-mediated cytotoxicity (ADCC), cytokine release, and ability to mount a T-cell-dependent antibody response (TDAR). Single-dose and 4-, 13-, and 26-week repeat-dose, Good Laboratory Practice (GLP) toxicity and toxicokinetic studies were conducted in cynomolgus monkeys. Key results are briefly summarized below:

- Functional Activity
    - Rosnilimab has high binding affinity to human and cynomolgus monkey PD-1 (dissociation constants [K_D] by kinetic exclusion assay: 75 pM and 450 pM, respectively), but no detectable binding to mouse, rat, or rabbit PD-1. Binding of rosnilimab to cluster of differentiation 28 (CD28), B- and T-lymphocyte attenuator (BTLA), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or inducible T-cell costimulator (ICOS) extracellular domains was not detectable indicating the specificity of rosnilimab for PD-1.
    - The epitope on human PD-1 bound by rosnilimab was identified to be on the opposite side of PD-1 from the PD-L1 binding region. In binding competition studies, rosnilimab did not compete with PD-L1 and is consistent with the determination of the epitope location.
    - Rosnilimab tissue staining was consistent with known PD-1 expression in human and cynomolgus monkey tissues in a GLP tissue cross-reactivity study.
    - In functional inhibitory activity assays of rosnilimab on T-cell activation using tetanus toxin (TT) antigen-specific induction and release of the cytokines interferon γ (IFNγ) and interleukin (IL)-17A in human whole blood, rosnilimab demonstrated concentration-dependent inhibition of IFNγ and IL-17A secretion indicating T-cell inhibitory activity in the human whole blood.
    - Studies of molecular signaling events induced by rosnilimab downstream of the T-cell receptor were consistent with the literature describing PD-1 signaling induced by its natural ligand PD-L1.
    - The *in vivo* efficacy of rosnilimab was evaluated in a humanized mouse model of xenogeneic acute GvHD (a T-cell-mediated disease). Animals treated with rosnilimab showed statistically significant increased overall survival compared with animals treated with control antibody indicating the immunological down-modulatory activity of rosnilimab on human T-cell responses.
- Safety Pharmacology
    - Rosnilimab showed no significant complement-dependent cytotoxicity or ADCC in assays designed to assess the cytotoxic effect of rosnilimab.
    - Rosnilimab did not significantly induce *in vitro* cytokine release in any of the 10 healthy donors evaluated when compared to phosphate buffered saline or IgG1 control in the cytokine release assays.
    - Treatment with rosnilimab did not prevent the ability of the cynomolgus monkeys to mount a TDAR.
- Pharmacokinetics
    - The observed serum half-life ($t_{1/2}$) of rosnilimab in cynomolgus monkeys was approximately 128 hours after single intravenous (IV) administration and 115 hours after single subcutaneous (SC) administration at 10 mg/kg, consistent

with the anticipated PK characteristics for a human IgG1 scaffold antibody in cynomolgus monkey.

- Toxicology
  - There were no adverse effects or target organ toxicities identified in the 4-, 13-, and 26-week repeat-dose, GLP toxicity and toxicokinetic studies using cynomolgus monkeys dosed once weekly up to 100 mg/kg/dose IV or SC. No changes were associated with administration of rosnilimab in clinical observations; body weights; ophthalmology; electrocardiography (ECG); neuromuscular, musculoskeletal, and respiratory parameters; and clinical or anatomic pathology.
  - There were no injection site reactions based on a Draize test evaluation in any of the animals administered rosnilimab via SC injection.
  - No reproductive toxicology studies have been performed.

See the Investigator's Brochure (IB) for additional information.

2.2.2 Clinical Studies

Rosnilimab has been evaluated in 2 clinical studies: a Phase 1 first in human single- and multiple-ascending-dose (SAD/MAD) study (ANB030-101; completed) and a Phase 2 proof of concept study in subjects with alopecia areata (ANB030-201; clinically complete pending final clinical study report [CSR]).

2.2.2.1 Study ANB030-101: Phase 1, First-in-Human, Single- and Multiple-Ascending-Dose Study

Study ANB030-101 was a first-in-human, double-blind, randomized, placebo-controlled, SAD/MAD study of the safety, tolerability, and PK of rosnilimab in 144 healthy male and female subjects. No deaths and 2 serious adverse events (SAE) occurred during the study. One subject receiving rosnilimab 400 mg SC in the SAD part of the study had an SAE due to a severe coronavirus infection considered unrelated to rosnilimab. One subject in the placebo group had an SAE of obstructive pancreatitis. The most common treatment-emergent adverse events (TEAEs; occurring in 3 or more subjects) were laboratory test abnormalities: C-reactive protein (CRP) increased, aspartate aminotransferase (AST) increased, and alanine aminotransferase (ALT) increased. These laboratory test abnormalities occurred sporadically relative to the time from dosing and no relationship with dose was evident. Headache was the only non-laboratory TEAE reported in more than 3 subjects; all headaches were mild. Overall, the study demonstrated that rosnilimab was well tolerated with no clinically significant safety concerns when administered as single IV and SC doses up to 600 mg and 4 weekly SC doses up to 400 mg.

Rosnilimab PK was approximately dose proportional after IV and SC administrations, with a $t_{1/2}$ of approximately 2 weeks for IV and SC doses ≥ 200 mg in both SAD and MAD cohorts, and an SC absolute bioavailability of 80%. In the MAD cohorts, time to maximum observed concentration (T_{max}) ranged from 46.9 to 48.7 hours with accumulation ratios ranging from 2.45 to 3.28 for maximum observed concentration (C_{max}) and 3.19 to 3.65 for area under the concentration-time curve over the dosing interval (AUC_{τ}) following once-weekly SC injections for 4 weeks at rosnilimab 60, 200, or 400 mg.

The overall incidence of subjects with a positive anti-drug antibodies (ADA) status to rosnilimab was generally low. None of the subjects tested positive for ADA at Baseline. Positive ADA status tended to occur in the lower single-dose cohorts (≤ 60 mg), but not higher single-dose cohorts. None of the subjects in the multiple-dose cohorts (≥ 60 mg) developed ADAs. The presence of ADAs did not appear to affect PK or safety.

Mean receptor occupancy increased in a dose-dependent manner, was consistent with PK, and full receptor occupancy (≥ 80%) was maintained for 1 month or longer at IV doses ≥ 20 mg and SC doses ≥ 200 mg.

See the IB for additional information.

2.2.2.2 Study ANB030-201: Phase 2, Proof-of-Concept Study in Subjects with Alopecia Areata

Study ANB030-201 was a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, proof-of-concept study to evaluate the safety, tolerability, and efficacy of rosnilimab in subjects with alopecia areata. The trial enrolled a total of 51 subjects randomized 2:1 to 400 mg of ANB030 monthly vs placebo for up to 24 weeks of treatment. The study is clinically complete and pending the CSR.

As of 26 January 2023, no deaths, discontinuations due to study therapy, or suspected unexpected serious adverse reactions (SUSARs) have been reported. A total of 2 SAEs (intestinal obstruction and myocardial infarction) have occurred in the Phase 2 study. For each SAE, the subject recovered, and the Investigator reported the causal relationship to investigational product as unrelated.

See the IB for additional information.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

No identified risks are known for the rosnilimab drug product.

There were no adverse effects or target organ toxicities identified in the 4-, 13-, and 26-week repeat-dose, toxicity and toxicokinetic studies (Section 2.2.1).

In Study ANB030-101, 2 of the 108 healthy subjects who received rosnilimab experienced mild injection site reactions (pain, pruritis, and erythema). No events of allergic reaction, anaphylaxis, or cytokine release syndrome were observed during the study.

No effects on safety or PK were evident among subjects with detectable antibodies against rosnilimab.

Although no evidence of allergic or immunologic reactions to rosnilimab has been observed, systemic allergic reactions, including anaphylaxis, can occur following the administration of monoclonal antibodies. Rosnilimab is contraindicated in subjects with a history of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies. There are no other known contraindications to rosnilimab.

Based on clinical studies with other monoclonal antibodies, subjects in this study may experience symptoms of an immune reaction to the treatment, also known as cytokine release syndrome. The symptoms of this vary dramatically but can include:

- Mild to moderate fever, chills, headache, nausea, and vomiting
- Moderate to severe symptoms such as edema (swelling of the skin), hypotension (low blood pressure), and pulmonary infiltrates (e.g., blood and mucus in the lung)

As expected with any recombinant antibody, rosnilimab may elicit an immune response and subjects may develop antibodies against rosnilimab. Appropriate validated screening and confirmatory assays will be used to detect ADAs at multiple time points before, during, and after treatment with rosnilimab.

2.3.2 Known Potential Benefits

Although subjects with UC may or may not receive direct benefit from participating in this study, participation in this study may help generate future benefit for larger groups of patients with UC if rosnilimab proves to be successful in treating this disease.

2.3.3 Assessment of Potential Risks and Benefits

All quality, pharmacology, toxicology, safety, and tolerability data demonstrated in nonclinical and clinical studies, and safety results observed in studies ANB030-101 and ANB030-201 are considered sufficient to expect a positive risk-benefit ratio for the treatment of UC with rosnilimab, and therefore to initiate this study.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Efficacy Objective and Efficacy Endpoints

Objective	Endpoints
Primary Efficacy Objective • To assess the clinical efficacy of rosnilimab versus placebo in subjects with moderate to severe UC.	***Primary Efficacy Endpoint*** • Mean change from Baseline in Modified Mayo (mMS) score to Week 12
	Secondary Efficacy Endpoints • Proportion of subjects achieving clinical remission (defined as a mMS ≤ 2, with a stool frequency subscore (SFS) ≤ 1, rectal bleeding subscore (RBS) = 0, and endoscopic subscore ≤ 1 without friability) at Week 12 • Proportion of subjects showing endoscopic improvement (defined as an endoscopy subscore ≤ 1 without friability) at Week 12 • Proportion of subjects achieving a clinical response (defined as a decrease from Baseline in mMS ≥ 2 points and ≥ 30% with a decrease from Baseline in RBS ≥ 1 point or an absolute RBS ≤ 1) at Week 12
	Exploratory Efficacy Endpoints • Proportion of subjects achieving endoscopic remission (defined as an endoscopy subscore = 0) at Week 12 • Proportion of subjects achieving histologic-endoscopic mucosal improvement (defined as an endoscopic subscore of 0 and a Geboes score (Geboes 2000) < 2) at Week 12 • Mean change from Baseline in the following assessments at each time point

	indicated in the Schedule of Assessments (SoA; Table 1): ○ mMS ○ Partial Modified Mayo Score (pmMS) ○ Inflammatory Bowel Disease Questionnaire (IBDQ) ○ Individual mMS subscores (RBS, SFS, and endoscopy subscore) ○ Geboes score

3.2 Safety Objective and Endpoints

Objective	Endpoints
Safety Objective • To evaluate the safety and tolerability of rosnilimab versus placebo in subjects with moderate to severe UC	***Safety Endpoints*** • Incidence, type, and severity of adverse events (AEs), SAEs, and AEs leading to treatment discontinuation and study withdrawal • Change from Baseline in vital signs and clinical laboratory parameters

3.3 Pharmacokinetics Objective and Endpoint

Objective	Endpoints
PK Objectives • To evaluate the PK of rosnilimab in subjects with moderate to severe UC	***Exploratory PK Endpoints*** • Mean observed predose (trough) rosnilimab concentration (C_{trough}) at each time point indicated in the SoA (Table 1)

3.4 Pharmacodynamics Objective and Endpoints

Objective	Endpoints
Pharmacodynamics Objective • To evaluate the PD of rosnilimab in subjects with moderate to severe UC	***Exploratory Pharmacodynamics Endpoints***

	• Mean change from Baseline in biomarkers at each time point indicated in the SoA (Table 1)

3.5 Immunogenicity Objective and Endpoints

Objective	Endpoints
Immunogenicity Objective • To evaluate the immunogenicity of rosnilimab in subjects with moderate to severe UC	***Exploratory Immunogenicity Endpoints*** • Number and percentage of subjects at each time point indicated in the SoA (Table 1) with confirmed positive ADA status and corresponding titer

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety, tolerability, PK, PD, and immunogenicity of rosnilimab in subjects with moderate to severe UC.

To be eligible for this study, a subject must be ≥ 18 years old, have a clinical diagnosis of active UC for ≥ 90 days prior to Day 1, have moderate to severe active UC (defined as a mMS during Screening of > 5 points with an endoscopic subscore [based on a central reader review] ≥ 2 with no evidence of current infection, colonic dysplasia, and/or malignancy). (The mMS is the Mayo Score [MS] excluding the physician's global assessment [PGA].) Appropriate documentation of biopsy results consistent with the diagnosis of UC, as assessed by the Investigator, must be available before Day 1. If suitable documentation is not available from a prior biopsy, it may be obtained from the Screening endoscopy.

A subject with prior exposure to PD1 or PD-L1 agonist, antagonist, or modulator, or with a history of colectomy (total or subtotal), ileoanal pouch, Kock pouch, or ileostomy will be excluded from the study. In addition, a subject who failed (i.e., had an inadequate response, loss of response, or intolerance to) any combination of 3 or more advanced UC therapy classes will be excluded from the study. For this study, advanced UC therapy classes include, but are not limited to, 1) anti-TNF antibodies (e.g., adalimumab, golimumab, infliximab), 2) other biologics (e.g., ustekinumab, vedolizumab), 3) oral JAK inhibitors (e.g., tofacitinib, upadacitinib), and 4) oral S1P receptor modulators (e.g., ozanimod).

Subjects may be taking oral corticosteroids (prednisone ≤ 20 mg/day or equivalent; see Appendix 1) before and during the study but must have been at a stable dosage of oral corticosteroids for ≥ 4 weeks prior to Day 1 and must remain on that stable steroid dosage during the first 12 weeks of study drug treatment. Concurrent steroid therapy may be tapered beginning after assessment of the primary endpoint at Week 12 (See Appendix 2).

At Screening, each subject will be provided an electronic diary (eDiary) to track daily stool frequency and rectal bleeding throughout the Screening, Blinded Treatment, and Follow-up Periods (see Section 8.1.1.1).

All subjects will undergo colonoscopies/sigmoidoscopies during Screening. The Screening endoscopy should not be performed until the majority of Screening activities have been completed and the corresponding inclusion and exclusion criteria have been confirmed. Sigmoidoscopies will be performed during Week 12 (the primary endpoint) and Week 24 (the End-of-Treatment [EOT] visit). Colon biopsies will be collected during each endoscopy. (See Section 8.1.1.2.)

The maximum study duration per subject will be up to 39 weeks consisting of a Screening Period of up to 35 days (5 weeks), a 24-week Blinded Treatment Period consisting of an initial 12-week Placebo-Controlled Treatment Period followed by a 12-week Continued Treatment Period), and a 10-week Follow-up Period.

Approximately 132 subjects will be randomized in a 1:1:1 ratio to 3 treatment groups (n = 44 in each group): rosnilimab 800 mg SC every 2 weeks (Q2W), rosnilimab 400 mg SC every 4 weeks (Q4W), or placebo SC Q2W. All subjects will receive 4 SC injections every 2 weeks to protect the blind. Each subject will receive double-blind treatment during the 12-week Placebo-Controlled Treatment Period.

At the Week-12 visit,

- Subjects originally randomized to rosnilimab will continue their assigned treatment through the 12-week Continued Treatment Period
- Subjects originally randomized to placebo who achieve Responder status (defined as a decrease from Baseline to Week 12 of ≥ 2 points and ≥ 30% in pmMS with a decrease from baseline in RBS ≥ 1 point or an absolute RBS ≤ 1) will continue their assigned placebo treatment through the 12-week Continued Treatment Period.
- Subjects originally randomized to placebo who do not achieve Responder status (i.e., nonresponders) will cross-over to active treatment (rosnilimab 800 mg SC Q2W) in a blinded manner and continue active treatment through the 12-week Continued Treatment Period

Therefore, all subjects initially randomized to rosnilimab, and those subjects initially randomized to placebo who are Responders will continue to receive their originally assigned study treatments (rosnilimab or placebo, respectively) for a total of up to 24 weeks. Subjects initially randomized to placebo who are nonresponders will receive placebo for 12 weeks and rosnilimab 800 mg SC Q2W for up to 12 weeks.

Enrollment of approximately 50% to 70% of the total study population by subjects who have prior treatment experience with advanced UC therapies is desired. Randomization will be stratified by prior experience with advanced UC therapies (experience with advanced UC therapy versus no prior advanced UC therapies) and concurrent oral steroid use (steroid use versus no steroid use).

An overview of the study design is presented in Figure 1. Safety and efficacy assessments and study procedures are outlined in the SoA (Table 1).

After a Screening Period of up to 35 days, eligible subjects will be randomized, and the first dose of study treatment will be administered on Day 1. Subjects will return for study visits during the Blinded Placebo-Controlled Treatment Period at Weeks 2, 4, 6, 8, 10 and 12 for protocol-defined assessments and administration of study treatment. All subjects will continue into the 12-week Continued Treatment Period and return for study visits at Weeks 14, 16, 18, 20, and 22 for protocol-defined assessments and administration of study treatment. After the last dose of study treatment at the Week 22 visit, subjects will return for the EOT visit at Week 24 and for Follow-up visits at Weeks 26, 30, and 34 to complete protocol-defined assessments.

Clinical efficacy and outcomes will be assessed using the mMS, pmMS, Geboes score (Geboes 2000), and IBDQ.

Safety assessments will include incidence, type, and severity of all AEs, including SAEs and AEs that lead to treatment discontinuation and study withdrawal; and changes in concomitant medications, vital signs, physical examination findings, and clinical laboratory tests.

Blood samples will be collected to assess the PK, immunogenicity (presence of ADA), and PD (i.e., biomarkers) of rosnilimab predose on Day 1 and at the time points specified in the SoA (Table 1). Circulating blood PD biomarkers may include, but are not limited to, immunophenotyping, TNF alpha (TNFα), IFNγ, IL-6, and IL-12. Fecal samples will be collected for fecal calprotectin analysis. Tissue biomarkers include gene expression panels reflective of UC disease activity and cytokine levels including the same cytokines measured in peripheral blood.

Subjects may choose to stop study treatment and/or participation in the study at any time. Subjects who permanently discontinue study treatment before or at the Week-22 visit should complete all study assessments specified in the SoA (Table 1) for the visit at which the decision is made to permanently discontinue study treatment and then return for a final Early Termination (ET) Follow-up visit approximately 12 weeks after their last dose of study treatment.

Interim analyses may be performed during the study for internal decision making. No adjustment for Type I error will be performed.

4.2 Scientific Rationale for Study Design

The proposed design is considered appropriate for assessing the efficacy, safety, tolerability, PK, PD, and immunogenicity of rosnilimab compared with placebo in subjects with moderate to severe active UC. Randomization ensures the random allocation of subjects to treatment arms and reduces potential bias. Because efficacy assessments can have a degree of subjectivity, all study subjects and assessors (Investigator or designee) are blinded during the 24-week treatment period to reduce potential bias. The highest degree of subject and assessor blinding is sought to achieve credible inference in both parts of the study. The study will also be placebo-controlled to control

for confounding factors unrelated to the study treatment, such as potential Investigator bias or placebo effect, and to ensure that the statistical procedures can be appropriately applied.

At the end of the Blinded Placebo-Controlled Treatment Period (Week 12), subjects initially randomized to placebo who do not achieve Responder status (i.e., nonresponders) will cross-over to active treatment to determine if they respond to active treatment. Any subjects initially randomized to placebo who achieve Responder status at Week 12 will continue to receive placebo to preserve the blind and limit unnecessary exposure to rosnilimab when objective benefit has already occurred spontaneously.

4.3 Justification for Dose

In Study ANB030-101, single doses of rosnilimab up to 600 mg IV and weekly doses of rosnilimab up to 400 mg SC for 4 weeks were well tolerated and demonstrated a favorable safety profile in healthy subjects (Section 2.2.2.1). Although rosnilimab 800 mg SC was not evaluated in ANB030-101, the C_{max} and area under the concentration-time curve time 0 to infinity ($AUC_{0\text{-}inf}$) following a single 600-mg IV dose of rosnilimab in Study ANB030-101 were 138 µg/mL and 17,300 hr·µg/mL, respectively. In a 26-week, repeat-dose toxicity study in cynomolgus monkeys given rosnilimab 10, 50, or 100 mg/kg SC once weekly, the no-observed-adverse-effect level (NOAEL) was 100 mg/kg. At this dose, the C_{max} and AUC from time 0 to 168 hours postdose ($AUC_{0\text{-}168}$) were 945 µg/mL and 139,000 hr·µg/mL, respectively. The predicted human C_{max} and $AUC_{0\text{-}168}$ at steady state for the 800 mg Q2W regimen, the highest dosage to be utilized in this study, are 43 µg/mL and 6873 hr·µg/mL, respectively, providing safety margins of 22-fold for C_{max} and 20-fold for $AUC_{0\text{-}168}$. The C_{max} and AUC values anticipated for the 800 mg Q2W are lower than the C_{max} and AUC values of the 600 mg IV dose studied in the Phase 1 study.

Rosnilimab 400 SC Q4W and 800 mg SC Q2W were chosen to investigate the full dose range of rosnilimab and to identify a potential minimally effective dose.

4.4 End of Study Definition

A subject is considered to have completed the study when the subject has completed the Week-34 End-of-Study (EOS) visit.

The study will be considered completed when all randomized subjects have completed the Week-34 EOS visit, discontinued from the study, or have been determined to be lost to follow-up.

4.5 Modifications to Study Conduct Due to the Coronavirus Disease 2019 Pandemic

As a consequence of the coronavirus disease of 2019 (COVID-19) pandemic, control measures in different regions may impact the ability to adhere to some of the study procedures described in this protocol. Due to challenges that include, but are not limited to, subject preferences, study site

closures, travel restrictions, and quarantines, some modifications to study conduct during the COVID-19 pandemic may be necessary to ensure study continuity. Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on site visits can be resumed. Such modifications in study conduct must be in accordance with local regulations/mandates. Any deviations to the protocol due to COVID-19 must be noted in the source documentation and be captured in the protocol deviations documentation. A detailed assessment of COVID-19 related risk and mitigation measures will be documented in the appropriate study plans.

5 STUDY POPULATION

Adult male and female subjects (age ≥ 18 years) with moderate to severe UC will be enrolled in this study. Subjects must meet all the inclusion criteria and none of the exclusion criteria to be enrolled in the study.

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

5.1 Inclusion Criteria

A subject must meet all the following inclusion criteria to be enrolled in the study:

1. Subject is an adult male or female ≥ 18 years when the subject signs the informed consent form (ICF).

2. Subject has a clinical diagnosis of UC for ≥ 90 days prior to Day 1, including appropriate documentation of biopsy results that are consistent with UC, based on the assessment of the Investigator.

3. Subject has moderate to severe, active UC, defined as a mMS ≥ 5 with an endoscopy subscore ≥ 2 (based on a central reader review) at Baseline.

4. Subject has had a surveillance colonoscopy that did not detect potential dysplasia or colon cancer performed within 1 year of Day 1.

   Note: If the subject has not had a colonoscopy within 1 year prior to entering Screening, the subject must undergo a colonoscopy (instead of a sigmoidoscopy) during Screening (see Section 8.1.1.2).

5. Subject has completed at least 3 consecutive or 4 nonconsecutive eDiary entries within 7 days before Day 1 (excluding days during bowel preparation for endoscopy).

6. Subject must meet the following tuberculosis (TB) screening criteria:

   a. Has no history of active or latent TB before Screening or has a known history of latent TB and

      i. Has completed appropriate treatment for latent TB before Day 1

      ii. Is receiving treatment for latent TB that is well tolerated, was initiated at least 14 days prior to Day 1, and will continue or complete during study participation, or

iii. Will initiate treatment for latent TB at least 14 days prior to Day 1, is able to tolerate the treatment, and will continue or complete the treatment during study participation.

Note: It is the responsibility of the Investigator to verify and document the adequacy of previous or concurrent anti-TB treatment based on current local TB treatment guidelines.

b. Has no signs or symptoms suggestive of active TB upon review of the subject's medical history and/or physical examination.

c. Has had no recent close contact with a person with active TB, based on information provided by the subject.

d. Has a negative QuantiFERON®-TB test result obtained during Screening prior to Day 1, except for subjects with a known history of latent TB who have previously completed, are currently receiving, or plan to initiate appropriate TB treatment.

Note: A subject with a newly identified positive QuantiFERON TB Screening test result must undergo an evaluation to rule out active TB, initiate appropriate treatment for latent TB (according to current local guidelines), and receive and tolerate at least 14 days of TB therapy during Screening prior to Day 1 before being allowed to enter the study.

Note: A subject whose first screening QuantiFERON-TB test result is indeterminate may have the test repeated once. A second indeterminate QuantiFERON-TB test result requires that the subject fail Screening.

7. Subject has no chest abnormalities suggestive of a malignancy or current active or latent infection, including TB, based on a report from a qualified radiologist of a chest X-ray or computerized tomography (CT) scan performed within 6 months before Day 1. If a chest X-ray or CT scan was not performed and read by a qualified radiologist within 6 months before Day 1, a chest X-ray must be performed and read by qualified radiologist during Screening and before Day 1.

8. Subject is judged by the Investigator to be in good health (except for UC) based on the subject's medical history and the results of the subject's laboratory test results, physical examination, and results of a 12-lead ECG at Screening.

9. Women of childbearing potential (WOCBP; defined below) must have a negative serum pregnancy test result at the Screening Visit (Visit 1) and a negative urine pregnancy test result on Day 1 (Visit 2) prior to administration of study treatment and must agree to use a highly effective method of birth control (as defined in Appendix 3) from the first dose of study treatment until at least 24 weeks after the last dose of study treatment.

A WOCBP is defined as a woman who is between menarche and at least 12 months postmenopausal and who is not surgically sterilized (e.g., hysterectomy, bilateral oophorectomy, or bilateral salpingectomy; tubal ligation or occlusion are not considered acceptable methods of sterilization so do not qualify women as of non-childbearing potential).

Postmenopausal is defined as being amenorrheic for at least 12 months, and, if aged < 60 years, have a serum follicle stimulating hormone (FSH) level > 20 mIU/mL. Women who are taking hormone replacement therapy do not have to have FSH assessments, but the amenorrhea before starting hormone replacement therapy must have been naturally occurring (i.e., spontaneous) and accompanied by an appropriate clinical profile (e.g., age appropriate with a history of vasomotor symptoms).

Note: If a female subject's childbearing potential changes after starting the study (e.g., a woman who is not heterosexually active becomes heterosexually active or a premenarchal woman experiences menarche), she must begin practicing a highly effective method of birth control (as defined in Appendix 3) as soon as possible and for at least 24 weeks after the last dose of study treatment.

10. Female subjects must agree to refrain from donating ova during the study and for at least 24 weeks after the last dose of study treatment.

11. Male subjects must wear a condom when engaging in any activity that allows for passage of ejaculate to another person and use condoms plus spermicide from the first dose of study treatment until at least 150 days (duration of relevant exposure plus the duration of sperm cycle) after the last dose of study treatment if sexually active with a female partner who is a WOCBP. Male subjects should also be advised of the benefit for a female sexual partner who is a WOCBP to use an additional highly effective method of contraception (as defined in Appendix 3) as condoms may occasionally fail to prevent pregnancy.

12. Male subjects must agree to refrain from donating sperm during the study and for at least 150 days (duration of relevant exposure plus the duration of sperm cycle) after the last dose of study treatment.

13. Subject is willing to participate and capable of giving voluntary written informed consent, which must be personally signed and dated by the subject and obtained prior to the initiation of any Screening or study specific procedures.

14. Subject is willing to comply with all study procedures and lifestyle considerations and must be available for the duration of the study.

5.2 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Subject has a diagnosis of Crohn's disease or indeterminate colitis.
2. Subject has a diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject has disease limited to the rectum (ulcerative proctitis) during the Screening endoscopy.
4. Subject has a history of colectomy (total or subtotal), ileoanal pouch, Kock pouch, or ileostomy or is planning bowel surgery.
5. The subject had prior exposure to a PD-1 or PD-L1 agonist, antagonist, or modulator.
6. Subject has either *Clostridioides difficile* infection within 30 days before Screening or a positive *C. difficile* toxin stool assay result at Screening, or infection with other intestinal pathogens within the 30 days before Screening.
7. Subject has prior or current GI dysplasia in any biopsy performed before or during the Screening endoscopy.
8. Subject has evidence of colonic infection during Screening.
9. Subject has a history of an inadequate response, loss of response, or intolerance to any combination of 3 or more advanced UC therapy classes.

   Note: For this study, advanced UC therapy classes are defined as, but no limited to, 1) anti-TNF antibodies (e.g., adalimumab, golimumab, infliximab), 2) other biologics (e.g., ustekinumab, vedolizumab), 3) oral JAK inhibitors (e.g., tofacitinib, upadacitinib), and 4) oral S1P receptor modulators (e.g., ozanimod).
10. Subject has a history of severe allergic or anaphylactic reaction to human, humanized, chimeric, or murine monoclonal antibodies.
11. Subject has signs, symptoms, or current diagnosis of severe, progressive, or uncontrolled renal, cardiac, vascular, pulmonary, GI (other than UC), endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances, as determined by the Investigator, at Screening or Randomization.
12. Subject had a cardiac hospitalization, myocardial infarction, or unstable cardiovascular disease (e.g., unstable angina, rapid atrial fibrillation, or clinically significant arrythmia), as determined by the Investigator, within 3 months of Randomization.

13. Subject meets New York Heart Association criteria for Class 3 or higher congestive heart failure at Screening or Randomization.

14. Subject has a history of lymphoproliferative disease (including lymphoma) or monoclonal gammopathy of undetermined significance, or signs and symptoms suggestive of possible lymphoproliferative disease (e.g., lymphadenopathy or splenomegaly) as determined by the Investigator.

15. Subject has a history of malignancy within 5 years before Randomization (except for squamous and basal cell carcinomas of the skin or carcinoma *in situ* of the cervix).

16. Subject has any factors that, in the Investigator's opinion, would predispose the subject to develop an infection, including, but not limited to:

    a. any evidence of active infection (e.g., bronchopulmonary, urinary, or gastrointestinal; excluding localized oral or genital herpes simplex that, in the opinion of the Investigator, is well controlled) that required systemic antibacterial, antifungal, or antiviral therapy within 4 weeks before Randomization.

    b. any open, draining, or infected skin wounds or ulcers within 3 months before Randomization.

    c. a history of chronic or recurrent infectious disease, including but not limited to, chronic renal infections, chronic chest infections (e.g., bronchiectasis), recurrent urinary tract infections (e.g., recurrent pyelonephritis or chronic nonremitting cystitis), and deep fungal infections (e.g., mucocutaneous candidiasis) within 6 months before Randomization.

    d. a history of an opportunistic infection (e.g., *Pneumocystis jirovecii*, aspergillosis, or mycobacteria other than TB) or parasitic infections (e.g., helminths, protozoa, *Trypanosoma cruzi*) within 12 weeks before Randomization.

    e. a history of recurrent herpes zoster or 1 or more episodes of disseminated herpes zoster.

    f. a history of 1 or more episodes of disseminated herpes simplex (including eczema herpeticum).

17. Subject has a known or suspected congenital or acquired immunodeficiency state, or condition that would compromise their immune status (e.g., previous recipient of an organ transplant which requires continued immunosuppression, history of splenectomy).

18. Subject has had surgery within 4 weeks of Randomization or plans to have surgery during the study that would interfere with their ability to participate in the study, in the opinion of the Investigator.

19. Subject has a history of clinically significant drug or alcohol abuse in the 12 months before Randomization, or other factors limiting the ability to cooperate or comply with the study protocol, as determined by the Investigator.

20. Subject is a pregnant or lactating woman, or a woman who intends to become pregnant during the study.

21. Subject is not able to tolerate SC drug administration.

22. Subject has a history of any significant drug allergy or reaction to polysorbate 80 (a component of the study treatment formulation) or any other inactive ingredients (excipients) in the study treatment formulation.

23. Subject tests positive for any of the following at Screening:

    a. Hepatitis C antibody with positive hepatitis C RNA,

    b. Hepatitis B surface antigen (HBsAg), or

    c. Human immunodeficiency virus (HIV) 1 or HIV 2 antibodies.

24. Subjects with initial positive hepatitis B core antibody ($HBcAb^+$), negative hepatitis B surface antigen ($HBsAg^-$), and negative hepatitis B surface antibody ($HBsAb^-$) test results at Screening will require additional reflexive testing and cannot be randomized if hepatitis B virus DNA is detectable. (See Appendix 4)

25. Subject meets any of the following laboratory criteria at Screening:

    a. Hemoglobin < 10 g/dL

    b. White blood cell count < 2.5×10^9/L

    c. Platelets < 100×10^9/L

    d. Serum creatinine > 132.6 µmol/L (> 1.5 mg/dL)

    e. ALT or AST > 2 × upper limit of normal (ULN)

    f. Total bilirubin > 1.5 × ULN. Subjects with Gilberts' disease who have serum bilirubin < 3 × ULN may be included.

26. Subject has been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study treatment or is currently enrolled in another clinical study.

27. Subject has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstances that might, in the opinion of the Investigator, confound the results of the study, interfere with the subject's ability to comply with the study procedure, or make participation in the study not in the subject's best interest.

28. The subject receiving any of the therapies listed in Table 2 within the washout period specified in the table:

Table 2 List of Prohibited Medications and Procedures

Prohibited Medications/Procedure	Washout Period Before Day 1
Oral corticosteroids (equivalent to prednisone > 20 mg per day; see Appendix 1)	For oral corticosteroids equivalent to prednisone ≤ 20 mg per day, must be on stable dose ≥ 4 weeks prior to Day 1
Live or live attenuated vaccines	12 weeks before the first dose of study drug
Rectal aminosalicylates or corticosteroids, other enemas/suppositories (other than required for endoscopy)	Within 14 days prior to Screening endoscopy and during the remainder of the Screening Period prior to Baseline
Ciclosporin, tacrolimus, mycophenolate mofetil, methotrexate, or thalidomide	30 days prior to Baseline
Azathioprine or 6-methyl prednisolone	10 days prior to Baseline
IV corticosteroids	14 days prior to Baseline
Oral aminosalicylates	Must be on stable dose of oral aminosalicylates for at least 14 days prior to Baseline Must not discontinue use of aminosalicylates within 14 days of Baseline
Fecal microbial transplantation	30 days prior to Baseline
UC-related antibiotics	Must be on stable dose for at least 14 days prior to Baseline or discontinue within 14 days of Baseline
Biologic therapy	12 weeks or 5 half-lives (whichever is longer) prior to Randomization
Janus kinase (JAK) inhibitor (e.g., tofacitinib, baricitinib, filgotinib, upadacitinib)	7 days prior to Baseline
Non-steroidal anti-inflammatory drugs (NSAIDs) except topical or low dose aspirin for cardiovascular prophylaxis	7 days prior to Baseline

Abbreviations: IV: Intravenous; UC: Ulcerative colitis.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study and sign the ICF but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure subjects to meet the Consolidated Standards of Reporting Trials (COSORT) publishing requirements (Turner 2012) and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure reasons, eligibility criteria not met, and any SAE.

Individuals who are screen failures (i.e., do not meet the eligibility criteria for participation in the study) may be rescreened one time if there is a valid reason to believe they will subsequently qualify for the study and after discussion with the medical monitor. Rescreened subjects should be assigned a new screening number and not be assigned the same screening number used for the initial screening. All procedures scheduled for the Screening Visit indicated in the SoA (Table 1) will need to be repeated, including re-signing of a new ICF and TB testing. However, chest X-rays/CT scans do not need to be repeated if they have been performed within 6 months before Day 1.

5.4 Strategies for Recruitment and Retention

The recruitment and retention strategies for the study will be covered in the Study Recruitment and Retention Plan.

6 STUDY TREATMENT

6.1 Study Treatment Administration

6.1.1 Study Treatment Description

Rosnilimab is a humanized IgG1, kappa monoclonal antibody that binds to PD-1, triggers PD-1 signaling, and down regulates T-cell-mediated immune responses. Rosnilimab is formulated for SC injection (See Section 6.2.2).

The placebo is formulated to be identical in composition to the rosnilimab drug product, except that it lacks the active ingredient, rosnilimab.

6.1.2 Dosing and Administration

Study treatment will be administered Q2W starting on Day 1 through the Week 22 visit by staff trained in best practices for SC administration of drug. Each subject will receive 4 SC 2-mL injections for a total injection volume of 8 mL at each administration of study treatment as indicated in Table 3.

Table 3 Study Treatment Administration

Dosage	Injection 1	Injection 2	Injection 3	Injection 4	Total Injection Volume
Rosnilimab 800 mg SC Q2W	2 mL 100 mg/mL Rosnilimab [a]	2 mL 100 mg/mL Rosnilimab [a]	2 mL 100 mg/mL Rosnilimab [a]	2 mL 100 mg/mL Rosnilimab [a]	8 mL
Rosnilimab 400 mg SC Q4W [b]	2 mL 100 mg/mL Rosnilimab [a]	2 mL 100 mg/mL Rosnilimab [a]	2 mL placebo [a]	2 mL placebo [a]	8 mL
Placebo SC Q2W	2 mL placebo	2 mL placebo	2 mL placebo	2 mL placebo	8 mL

[a] Study treatment will be provided in vials containing approximately 1 mL/vial of 100 mg/mL rosnilimab or placebo. Four, 2-mL injections Q2W will be prepared from 8 individual vials by trained unblinded personnel according to the Study Pharmacy Manual. To maintain the blind, all subjects will receive 4 SC 2-mL injections Q2W of either active drug or placebo depending on treatment assignment.

[b] For subjects in the Rosnilimab 400 mg Q4W SC groups, placebo will alternate with active treatment Q2W starting 2 weeks after the first dose of rosnilimab on Day 1.

Abbreviations: Q2W: every 2 weeks; Q4W: every 4 weeks; SC: subcutaneous

Injections will be administered into the SC tissue of the upper arm, anterior thigh, or abdomen, separated by at least 3 cm. The injection site must be recorded in the source documents at each treatment visit and recorded in the electronic case report form (eCRF).

The preferred anatomical site of SC administration is the abdomen; however, the injection may be made in the upper arm or anterior thigh, if needed. The same anatomical site (abdomen, arm, or thigh) should be used throughout the entire study for a given subject (e.g., do not administer 1 dose into the upper arm and at a subsequent visit administer the next dose into the abdomen). Subsequent doses should be rotated within an anatomical site. For example, if the upper left abdominal quadrant is used as the site for the 4 injections of the first dose, then the next administration at a subsequent visit should be rotated to the upper right quadrant. Similarly, if a deltoid is the site for the first dose, the deltoids should be alternated for subsequent doses. The site of administration is NOT to be massaged by either the clinic staff or by the subject for at least 60 minutes after drug administration.

Subcutaneous injections should not be given into moles, scars, tattoos, or areas where the skin is tender, bruised, red, hard, or not intact.

The prescribed dosage, timing, and mode of administration may not be changed. The date and time of administration, dose administered (entire dose/incomplete dose), any leakage or backflow of fluid from the administration site onto the surface of the skin, and any departures from the intended dose will be documented in the subject's source documentation and eCRF.

Because systemic allergic reactions, including anaphylaxis, can occur following the administration of monoclonal antibodies, personnel appropriately trained to perform resuscitative measures and medications such as aqueous epinephrine for intramuscular (IM) or SC administration should be available at the study site prior to administration of study drug. Following receipt of study drug, all subjects should be observed for symptoms of an allergic reaction, which may include hypotension, shortness of breath, rash, urticaria, flushing, chest pain, fever, back pain, edema of the face or extremities, vasovagal reactions, chills/rigors, nausea/emesis, headache, diaphoresis, lightheadedness, somnolence, or myalgia (Sampson 2006).

Study treatment administration must be carried out according to these instructions. Further details on study treatment administration are provided in a Study Pharmacy Manual.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Rosnilimab and placebo will be provided as described in Section 6.2.2 by AnaptysBio.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment disposition, accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and that any discrepancies are reported and resolved before use. Vials are

intended for single use only; therefore, any remaining solution and used vials must be returned to the depot, unless destroyed per Local Site Standard Operating Procedure (SOP), after accountability/reconciliation have been completed. On-site destruction of study treatment/vials will be permitted if the study center has a drug destruction SOP on file.

Only subjects enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment.

Further guidance and information for the final disposition of unused study treatment are provided in the Study Pharmacy Manual.

Drug accountability forms must be available for inspection at any time.

6.2.2 Formulation, appearance, Packaging, and Labeling

Rosnilimab drug product is a sterile, colorless to brown-yellow, and clear to opalescent solution for SC injection consisting of rosnilimab monoclonal antibody concentrated to 100 mg/mL in a buffered solution of 10 mM *L*-histidine, 100 mM *L*-arginine, 90 mM *L*-proline, 0.03% (w/v) polysorbate 80 at pH 6.2. The drug product is filled into a single-use, 2R, Type I, clear glass vial closed with a coated elastomeric stopper and sealed with aluminum overseals and polypropylene flip-off style caps. Each single-use glass vial contains a nominal volume of 1 mL of rosnilimab 100 mg/mL solution.

The placebo is a solution for SC injection formulated to be identical in composition to rosnilimab drug product except that it lacks the active ingredient. It is a sterile solution of 10 mM *L*-histidine, 100 mM *L*-arginine, 90 mM *L*-proline, 0.03% (w/v) polysorbate 80 at pH 6.2 that is visually similar to the rosnilimab drug product. Placebo is filled into a single-use, 2R, Type I, clear glass vial closed with a coated elastomeric stopper and sealed with aluminum overseals and polypropylene flip-off style caps. Each single-use glass vial contains a nominal volume of 1 mL of solution.

All investigational product vials will be packaged and labeled as required per country requirements.

6.2.3 Product Storage and Stability

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

The rosnilimab and placebo vials must be refrigerated at 2°C to 8°C (36°F to 46°F) until the day of use and should not be used beyond the expiration date provided by the manufacturer. The vial

contents should not be frozen or shaken, and the vials should remain in their cartons during storage and until use to provide protection from light.

Rosnilimab and placebo vials may be stored at room temperature (8°C to 25°C [46°F to 77°F]) for up to 4 hours. Once rosnilimab or placebo product is withdrawn from the vial and into a suitable syringe, the dose must be administered within 4 hours. Deviations from the storage requirements must be documented and reported to the Sponsor.

6.2.4 Preparation

Study treatment will be prepared by a trained, unblinded pharmacist or designee (e.g., a state/country approved healthcare provider) to maintain blinding of the Investigators and study subjects. Dose preparation records will be completed and securely maintained by the dose preparer. Both rosnilimab and the placebo are similar in appearance, thereby ensuring that the study center staff administering the study treatments will remain blinded to study treatment.

Details of study treatment preparation will be provided in the Study Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

This is a randomized study.

After verification that all inclusion and no exclusion criteria have been met, each eligible subject will be randomized in a 1:1:1 ratio to receive rosnilimab 800 mg SC Q2W, rosnilimab 400 mg SC Q4W, or placebo SC Q2W from Day 1 through the Week-12 visit and assigned a unique randomization/subject identification number using Interactive Response Technology (IRT) and a computer-generated randomization schedule. The subject will then be considered enrolled in the study.

Randomization will be stratified by prior experience with advanced UC therapies (i.e., experience with advanced UC therapies versus no experience with prior advanced UC therapies) and concurrent oral steroid use (steroid use versus no steroid use).

Computer generated randomization schedules will be programmed by a qualified statistician or designee (i.e., the randomization statistician) not otherwise involved in the study and provided to the IRT vendor for programming of the IRT system. To minimize bias and ensure that the study remains blinded, the randomization statistician or IRT vendor will not release the randomization schedule to any personnel directly involved in the conduct of the study until after database lock at the end of the study as outlined in the Study Blinding Plan.

6.3.2 Blinding

This is a double-blind study. The blinding procedures will be maintained throughout the study with limited and controlled access to the randomization code and study treatment preparation records. The Sponsor, Investigator, study center staff, and subjects will be blinded to treatment assignment and only the unblinded pharmacist or designee (e.g., a state/country approved physician or registered nurse not otherwise involved in the study) and randomization statistician will be aware of the treatment assignment.

Unblinding of treatment assignment during the study should occur only for the purpose of providing urgent subject care and knowledge of the subject's treatment assignment will alter subsequent care (emergency unblinding) or if it is necessary to know what treatment subjects received to ensure subject safety. The process for breaking the blind will be handled through IRT by a predetermined process detailed in the Study Manual to ensure that participating subjects and study team are not unblinded unnecessarily and study results are not compromised. If emergency unblinding is necessary, the Investigator must ensure that the unblinding of the treatment assignment is performed in a discrete manner and the treatment is disclosed only to those persons involved with the direct medical care of the subject. After emergency unblinding has occurred, the Investigator must provide the reason for unblinding to the Medical Monitor.

AnaptysBio and the contract research organization (CRO) must be notified when a subject's treatment assignment is unblinded during the study. The IRT will create the blinded and/or unblinded notification when the blind is broken, which can be sent via email as per the user role of IRT. The unblinding will be captured in the IRT audit trail. Pertinent information regarding the circumstances of unblinding of a subject's treatment assignment must be documented in the subject's source documents.

Subjects who are unblinded should discontinue study treatment at the time of unblinding. The subject will then return for a final ET follow up visit to complete all the assessments indicated in the SoA (Table 1) approximately 12 weeks after their last dose of study treatment.

Additional measures to ensure treatment assignments remain blinded during the study are provided in the Study Blinding Plan.

6.4 Study Treatment Compliance

Because study treatment will be administered by trained staff at study visits, study treatment compliance will be under the direct control of the Investigator or designee who is administering and documenting the administration of study treatment.

6.5 Prior and Concomitant Therapy

All prior medications or treatments used to treat UC at any time before the Screening visit (Visit 1), any other medications taken within 4 weeks before the Screening visit, any vaccines taken within 12 weeks of Day 1, and any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of the Screening visit, during Screening, on Day 1, and/or during the study must be recorded on the subject's eCRF along with the:

- Reason for use (i.e., indication),
- Start and end dates of administration, and
- Dosage information including dose, route, and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Therapies

Treatments excluded from the List of Prohibited Medications and Procedures (Table 2) are permitted during the study.

The following therapies are allowed during the study:

- Oral corticosteroids equivalent to prednisone ≤ 20 mg/day (Appendix 1) that have been at a stable dose ≥ 4 weeks prior to the first dose of study treatment.
- Acetaminophen is allowed but must have been at a stable dose ≥ 4 weeks prior to the first dose of study treatment.
- Currently authorized vaccines that are not live or live-attenuated, including COVID-19 vaccines (e.g., RNA based vaccines, protein-based vaccines, and nonreplicating viral vector-based vaccines). Note: The Medical Monitor should be consulted if there are any questions about whether the vaccine to be administered is allowed and if subject participation in the study should be continued.

Subjects taking acetaminophen, oral corticosteroids (equivalent to prednisone ≤ 20 mg/day), or inhaled corticosteroids should continue their stable doses throughout the Blinded Placebo-Controlled Treatment Period.

6.5.2 Prohibited Medications or Procedures

Therapies that are not allowed during the study include, but are not limited to, the medications and therapies listed in Table 2. These therapies should be discontinued before the first administration of study treatment on Day 1 according to the washout periods in Table 2.

The Sponsor must be notified in advance of (if possible) or as soon as possible after any administration of a prohibited therapy.

The use of prohibited medication/therapy is a protocol deviation. Subjects who start prohibited medications or therapies that have been demonstrated to be effective for treatment of UC during the study will be withdrawn from study treatment. Subjects who start any other prohibited medications or therapies during the study may be withdrawn from study treatment if an impact on efficacy assessment or safety of the subjects is expected. If in any doubt, the Investigator is advised to discuss medications with the Medical Monitor. In addition, the Investigator must notify the Medical Monitor to decide as to whether the subject will be withdrawn from the study.

6.6 Dose Modification

No dose modification is allowed during the study. Study treatment can be interrupted temporarily (see Section 7.1.1) or permanently if deemed necessary at the Investigator's discretion (see Section 7.1).

6.7 Treatment After the End of the Study

All subjects will return to the study site for the Week-34 EOS visit for final safety and EOS assessments. After this visit, subjects should be treated according to the clinical judgment of the subject's physician. Care after EOS will not be provided by AnaptysBio. Any SAE or pregnancy occurring through the EOS visit should be reported to the pharmacovigilance unit (Section 8.2.1.6) and followed up until an outcome is determined.

7 STUDY TREATMENT DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Subjects may choose to stop study treatment and/or participation in the study at any time.

Discontinuation from study treatment does not mean discontinuation from the study.

For subjects who permanently discontinue study treatment before or at the Week-22 visit, all study assessments specified in the SoA (Table 1) will be completed for the visit at which the decision to permanently discontinue study treatment is made. Subjects who permanently discontinue study treatment will then return for an ET visit approximately 12 weeks after their last dose of study treatment.

The following events may be considered sufficient reasons for discontinuing a subject from study treatment:

- Pregnancy (all pregnancies should be followed until the outcome is known; refer to Appendix 3 and Section 8.2.1.7)
- Significant deviation or lack of compliance with the protocol
- Confirmed severe liver abnormalities including
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for more than 2 weeks
  - ALT or AST > 3 × ULN and (total bilirubin > 2 × ULN or international normalized ratio [INR] > 1.5)
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

(In the event of severe liver abnormalities, [1] discontinue study treatment, [2] repeat liver chemistry tests (including ALT, AST, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, and INR) as soon as possible (preferably within 24 hours), [3] notify the Medical Monitor and Sponsor of the event, and [4] monitor the subject twice weekly until the liver chemistry test abnormalities resolve.)

- Any significant AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject in the opinion of the Investigator
- The subject has a malignancy, excluding squamous and basal cell carcinomas of the skin and carcinoma *in situ* of the cervix
- Use of any prohibited medication or treatment (refer to Section 6.5.2)

An ad hoc Safety Monitoring Team meeting will be convened for any of the following:

- ≥ 2 subjects with confirmed severe liver abnormalities (as defined above in Section 7.1)
- ≥ 2 subjects with severe infection ("severe" defined as life-threatening or incapacitating as described in Section 8.2.1.3.1)
- ≥ 2 subjects with malignancy or lymphoproliferative disorder
- ≥ 2 subjects with anaphylaxis

The Safety Monitoring Team will review the relevant unblinded data and make a formal recommendation to continue the study, pause the study while additional information is reviewed, or stop the study. At a minimum, the Safety Monitoring Team will comprise internal AnaptysBio experts in Clinical Development, Safety, and Biostatistics who are not involved in the day-to-day oversight of the study and at least 1 external clinical expert advisor.

The date of and reason for discontinuation of study treatment will be recorded in the subject's source documentation and eCRF.

7.1.1 Temporary Interruption or Missed Dose

Study treatment may be interrupted temporarily for an individual subject in the case of an AE per the Investigator's discretion. The Medical Monitor should be informed. Restarting of study treatment can be done after discussion with the Medical Monitor. The Medical Monitor should be informed if a dose is missed or is outside of the dosing window. The date and reason for a temporary interruption of study treatment will be recorded in the subject's source documentation and eCRF.

7.1.2 Re-Challenge

The study treatment can be reintroduced at the next scheduled administration visit at the Investigator's discretion and after discussion with the Medical Monitor. In case of positive re-challenge, the study treatment should be discontinued permanently.

7.2 Subject Discontinuation/Withdrawal from the Study

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

If a decision is made to withdraw from the study early and immediately, with the intention that the subject will not return for additional future visits, the procedures listed for an ET visit in the SoA (Table 1) should be performed at that time if possible.

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Withdrawal of consent
- Lost to follow-up

The date of and reason for subject discontinuation or withdrawal from the study will be recorded in the subject's source documentation and eCRF.

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

7.3 Lost to Follow-Up

A subject will be considered lost to follow-up if the subject fails to return for scheduled visits and is unable to be contacted by the study center staff.

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

- The study center personnel must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study. If the rescheduled visit falls within the next visit's window, then the visit should be considered a missed visit, and the subject should come in for the next scheduled visit as planned. Missed visits must be captured in the subject's source documentation and eCRF and recorded as a protocol deviation.
- Before a subject is deemed lost to follow up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source documentation.

Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up. The date of and reason for study discontinuation will be recorded in the subject's source documentation and eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures and their timing are summarized in the SoA (Table 1).

All screening evaluations must be completed and reviewed prior to randomization on Day 1 to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable (see Section 5.3).

The same assessor should perform all assessments for an individual subject for the duration of the study unless exceptional circumstances prevent it.

Assessments scheduled on Day 1 must be performed prior to the study treatment administration unless otherwise noted. When more than 1 assessment is to be completed at the same time point, the site should follow the recommended order for performing the study assessments listed in Section 1.3. Adherence to the study design requirements, including those specified in the SoA, is essential to maintain subject safety and the integrity of the study data, and required for study conduct.

Prospective approval of protocol deviations to assessments or procedures, also known as protocol waivers or exemptions, are not permitted.

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Repeat or unscheduled assessments and samples may be performed or collected as needed for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments and Outcomes

Planned time points for all efficacy assessments and subject-reported outcomes are provided in the SoA (Table 1).

The efficacy of rosnilimab and subject-reported outcomes for the treatment of UC will be evaluated using the following:

- Modified and Partial Modified Mayo Scores (Schroeder 1987; D'Haens 2007; Sandborn 2022)
  - eDiary for stool frequency and rectal bleeding
  - Endoscopy
    - Geboes Histologic Score (Geboes 2000)
    - Subject-reported outcomes:
  - IBDQ

8.1.1 Modified and Partial Modified Mayo Scores

The MS is an endoscopic and clinical scale used to assess the UC disease activity (Schroder 1987). It consists of four subscores: RBS, SFS, PGA, and an endoscopy subscore. Each subscore is graded from 0 to 3 points. The total MS is the sum of the individual subscores and ranges from 0 to 12 points with higher scores indicating more severe disease.

Variants of the MS are shown in Table 4 and include the Partial Mayo Score, mMS, and pmMS (Naegeli 2021; Lewis 2008; Sandborn 2022). Of these variants, only the mMS and pmMS will be calculated and assessed in this study.

Table 4 Mayo Scoring for Ulcerative Colitis Severity

	RBS	SFS	PGA	Endoscopy Subscore	Total Score [a]
Mayo Score (range 0 [normal] to 12 [most severe]) (Schroeder 1987; D'Haens 2007)	0 to 3	0 to 3	0 to 3	0 to 3	0 to 12
Partial Mayo Score (range 0 to 9) (Lewis 2008)	0 to 3	0 to 3	0 to 3	NA	0 to 9
Modified Mayo Score (range 0 to 9) (Sandborn 2022)	0 to 3	0 to 3	NA	0 to 3	0 to 9
Partial Modified Mayo Score (range 0 to 6)	0 to 3	0 to 3	NA	NA	0 to 6

[a] Higher scores indicate more severe disease

Abbreviations: NA: Not applicable; PGA: Physician Global Assessment; RBS: Rectal bleeding subscore; SFS: Stool frequency subscore

The mMS and pmMS will be calculated using the SFS and RBS from subjects' daily eDiaries, and a centrally read endoscopy score, as applicable, at the visits indicated in the SoA (Table 1). Guidance for determining mMS subscores is provided in Appendix 5.

As the Physician's Global Assessment is neither a patient-reported outcome nor an objective assessment of disease activity, and the concept that it purports to measure is not distinct from the other components of the mMS score, use of the PGA as a component of the Mayo score approach used to assess UC severity in clinical trials is no longer recommended by the Food and Drug Administration or European regulatory authorities (FDA UC Guidance 2022, EMA UC Guidance 2018).

8.1.1.1 Daily Electronic Diary for Stool Frequency and Rectal Bleeding

Each subject will be provided an eDiary at the Screening visit to track daily stool frequency and rectal bleeding. At the Screening visit, trained staff will train subjects on the use of the eDiary and provide instructions for determining the daily SFS and RBS (see Appendix 6). At each subsequent visit indicated in the SoA (Table 1), trained staff will review the subject's eDiary for completeness,

and retrain the subject as necessary on the use of the eDiary, determining daily SFS and RBS, and the importance of completing the eDiary daily.

8.1.1.2 Endoscopy

Endoscopies will be performed at the time points indicated in the SoA (Table 1). Colon biopsies for the analysis of tissue biomarkers (Section 8.3.5) and for Geboes Histological Score (Section 8.1.2) will be collected during each endoscopy. Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate Study Laboratory Manual.

The Screening endoscopy should not be performed until the majority of Screening activities have been completed and the corresponding inclusion and exclusion criteria have been confirmed.

During Screening, sigmoidoscopies will be performed unless a subject does not have a surveillance colonoscopy to rule out malignancy and lesions suspicious for colonic dysplasia within 1 year of Day 1. Subjects who do not have a surveillance colonoscopy within 1 year of Day 1 must undergo a colonoscopy during Screening. Endoscopy during Screening should be scheduled within 1 week before Day 1 unless extenuating circumstances preclude it.

Only sigmoidoscopies will be performed following randomization. Each post-randomization endoscopy should be scheduled within 1 week before or at the visit indicated in the SoA (Table 1).

8.1.2 Geboes Histological Score

The Geboes grading system for UC evaluates the histologic severity of UC utilizing 6 domains: structural (architectural change), chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction, and erosions or ulcerations. Scores can range from 0 to 5.4, with higher scores indicating more severe histological inflammation (Geboes 2000).

Tissue biopsies collected during each endoscopy will be sent to a qualified pathologist for evaluation using the Geboes grading system.

8.1.3 Inflammatory Bowel Disease Questionnaire

The IBDQ is a 32-item subject-completed questionnaire that measures 4 aspects of subjects' lives: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Responses are graded on a 7-point Likert-like scale from 1 (worst situation) to 7 (best situation). The total score ranges from 32 to 224 with higher scores representing better quality of life (Pallis 2004; Guyatt 1989). An example of the IBDQ is provided in Appendix 7.

Subjects will complete the questionnaire before any other procedures are performed at the visits indicated in the SoA (Table 1). Trained site staff will review the subject's responses to the questionnaire immediately after completion by the subject to ensure that all questions are answered and with a single response. The questionnaire will be administered electronically or using a paper backup. The subject's completed questionnaire will be included in the subject's source documentation. If a paper backup is used, the subject's responses will be entered in the subject's eCRF by trained site staff.

8.2 Safety Assessments

Safety will be assessed through the incidence, type, and severity of TEAEs, SAEs, treatment-related TEAEs, TEAEs leading to study treatment discontinuation, and TEAEs leading to study discontinuation, and changes from Baseline in vital signs and clinical laboratory parameters.

Safety assessments will be performed as indicated in the SoA (Table 1). Unscheduled or additional safety assessments may be performed at any time during the study to ensure subject safety.

8.2.1 Adverse Events and Serious Adverse Events

8.2.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a subject temporally associated with the use of a study treatment, whether considered related to the study treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment that does not necessarily have a causal relationship with this treatment.

A TEAE is defined as a new AE that occurs during or after the first dose of study treatment or an existing condition or AE present at Baseline that worsens in either intensity or frequency after the first dose of study treatment.

8.2.1.1.1 Events Meeting the Adverse Event Definition

Events meeting the AE definition include:

- Any abnormal laboratory test results (hematology, biochemistry, or urinalysis) or other safety assessments (e.g., ECG, vital signs measurements), including those that worsen from Day 1, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease)

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

8.2.1.1.2 Events Not Meeting the Adverse Event Definition

Events not meeting the AE definition include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

Note: The condition that leads to the procedure should be reported as an AE

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease or condition present or detected at the start of the study that do not worsen

8.2.1.2 Definition of Serious Adverse Event

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or AnaptysBio, it results in any of the following outcomes:

- **Death**
- **Life-threatening AE** – The term 'life threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Inpatient hospitalization or prolongation of existing hospitalization** – In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an SAE.
- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions** – The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly/birth defect**
- **Other important medical events** – Events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include invasive or malignant cancers, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.1.3 Classification of an Adverse Event

8.2.1.3.1 Severity of Event

The intensity of an AE is an estimate of the relative severity of the event. The Investigator will assess intensity for each AE and SAE reported during the study based on his or her clinical

experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- **Mild** – Event requires minimal or no treatment, is easily tolerated by the subject, and causes minimal discomfort, and does not interfere with the subject's daily activities.
- **Moderate** – Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and sufficient discomfort to the subject.
- **Severe** – Event interrupts a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious". An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes described in Section 8.2.1.2, NOT when it is rated as severe.

8.2.1.3.2 Relationship to Study Treatment

All AEs must have their relationship to study treatment assessed by the Investigator who examines and evaluates the subject based on temporal relationship and his or her clinical judgment. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The Investigator will also consult the IB during assessment. In a clinical study, the study treatment must always be suspect.

The degree of certainty about causality will be graded using the following categories:

- **Unrelated** – Clinical event incontrovertibly not related to the study treatment
- **Unlikely related** – Clinical event with an incompatible time relationship to study treatment administration which makes a causal relationship improbable, and in which an underlying condition or other drugs or chemicals provides plausible explanations
- **Possibly related** – Clinical event with a reasonable time relationship to study treatment administration, and that is unlikely to be attributed to concurrent condition or other drugs or chemicals. Assessment should be based on availability of evidence of a causal relationship, rather than it "cannot be definitively ruled out".
- **Related** – Clinical event with plausible time relationship to study treatment administration and that cannot be explained by a concurrent condition or other drugs or chemicals

For each AE/SAE, the Investigator must document in the medical notes that he or she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the pharmacovigilance unit. However, it is very important that the Investigator always assesses causality for every event before the initial transmission of the SAE data to the pharmacovigilance unit within 24 hours of awareness of the event.

The Investigator may change his or her opinion of causality in light of follow-up information and send a SAE follow-up report and update the subject's eCRF with the updated causality assessment. The reason for updating the causality assessment should be recorded in the subject's source documents.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

8.2.1.3.3 Expectedness

The pharmacovigilance unit will be responsible for determining whether an AE is expected or unexpected as interpreted using the reference safety information in the IB. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study treatment.

8.2.1.4 Time Period and Frequency for Event Assessment and Follow-Up

Subjects will be instructed to report any AEs to the Investigator and/or site staff. Beginning with the Screening Visit, information on AEs and SAEs will be elicited at each visit by asking the subject open-ended questions such as: "Since you were last asked, have you felt unwell or different from usual in any way?". Subjects may report AEs spontaneously at any time.

All AEs, which may include observed, elicited, or volunteered problems, complaints, signs, or symptoms, or abnormal clinical laboratory results, are to be recorded in the subject's source documentation and eCRF. The Investigator is responsible for reporting and evaluating each AE.

All AEs, including SAEs, will be collected throughout the study period, beginning from the time the subject signs the ICF until the subject completes the study (Section 4.4), discontinues the study (Section 7.2), or is lost to follow-up (Section 7.3).

Adverse events, including SAEs, that occur after a subject completes the study or discontinues from the study will not be reported unless the Investigator determines that there is a reasonable possibility that the AE/SAE is related to study treatment or a study-related procedure.

All AEs and SAEs will be followed until the event and/or its sequelae resolves, becomes stable, or monitoring is no longer considered needed as determined by the Investigator. The Investigator is responsible for appropriate medical care of subjects during the study. After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. The Investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. The subject should be followed until the event is resolved or stable. If an AE is ongoing at the end of study, the follow-up duration is left to the discretion of the Investigator. Follow-up frequency will be performed at the discretion of the Investigator.

8.2.1.5 Adverse Event Reporting

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information in the subject's eCRF.

The following information will be captured for each AE:

- Description of the AE:
  - A specific diagnosis (e.g., disease or syndrome) rather than individual associated signs and/or symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific diagnosis by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition or event that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as the AE, not the procedure.
  - Any medical condition already present at Screening should not be reported as an AE unless the medical condition, signs, or symptoms present at Baseline worsen in severity or seriousness at any time during the study. In this case, it should be reported as an AE.
  - Clinically significant abnormal laboratory or other examination findings (e.g., abnormal ECG or physical exam finding) that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory or other abnormal finding is clinically significant. Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.
  - Abnormal laboratory or other abnormal finding (e.g., abnormal ECG) that is determined to be an error should not be reported as an AE.

- Date and time of onset of the AE
- Date and time of resolution of the AE
- Severity of the AE (as defined in Section 8.2.1.3.1) as determined by the Investigator

  - Changes in the severity of an AE/SAE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

- Relationship to study treatment (as defined in Section 8.2.1.3.2) as determined by the Investigator

  - Investigators will determine the relatedness of an AE to study treatment based on the temporal relationship to the study treatment administration, as well as whether the event is unexplained given the subject's clinical course, previous medical conditions, and concomitant medications.
  - If a subject has an AE after signing the ICF but before the administration of the first dose of study treatment, the AE will be reported as unrelated to study treatment.

- Seriousness criteria (as defined in Section 8.2.1.2) as determined by the Investigator
- Action taken with study treatment (e.g., none, study treatment discontinued, study treatment interrupted)

  - If study treatment is interrupted or discontinued because of an AE, study personnel will document the circumstances and data leading to interruption or discontinuation of treatment.

- Subject discontinued or not discontinued from the study

  - If a subject is discontinued from the study because of an AE, study personnel will document the circumstances and data leading to discontinuation from the study.

- Treatments administered

  - Any treatments administered because of an AE will be recorded in the subject's source documentation and on the concomitant medication page or surgical/medical procedure page of the subject's eCRF as applicable.

- Outcome (e.g., resolved, resolved with sequelae, not resolved, fatal)

  - Indicate the outcome as not resolved when an AE changes in severity or seriousness but did not resolve.

It is not acceptable for the Investigator to send photocopies of the subject's medical records to the pharmacovigilance unit in lieu of completion of the AE/SAE page of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the pharmacovigilance unit. In these instances, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the pharmacovigilance unit.

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the pharmacovigilance unit to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded in the subject's source documentation and eCRF.

8.2.1.6 Serious Adverse Event Reporting

All SAEs will be reported to the pharmacovigilance unit within 24 hours of becoming aware of the event (see Section 8.2.1.6.1). The Investigator will submit any updated SAE data to the pharmacovigilance unit within 24 hours of receipt of the information as outlined in the Safety Reporting Instructions that will be provided to study sites and in the study Safety Management Plan.

Prompt notification of an SAE to the pharmacovigilance unit by the Investigator is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

AnaptysBio or its designee has a legal responsibility to notify regulatory authorities (including authorities in the European Economic Area via EudraVigilance) and study Investigators about unexpected SAEs and potential changes to the safety profile of a study treatment under clinical investigation and comply with country-specific regulatory requirements related to safety reporting.

When a study Investigator receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the pharmacovigilance unit, the Investigator will promptly review the report then file it with the IB and notify the IRB/EC, if appropriate, according to local requirements.

If a subject dies while participating in the study, the Investigator will provide the pharmacovigilance unit with a copy of any postmortem findings.

8.2.1.6.1 Reporting via an Electronic Data Collection

The primary mechanism for reporting an SAE to the pharmacovigilance unit will be for the study site to complete the SAE page of the subject's eCRF within 24 hours of becoming aware of the event. If the electronic data capture (EDC) system is not available, then the study site will use the paper SAE Report Form (see Section 8.2.1.6.2).

After the study is completed and the database is locked, the EDC system will be taken offline to prevent the entry of new data or changes to existing data. If a study site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the EDC system

is locked, then the study site can report this information on a paper SAE Report Form and email the form to the pharmacovigilance unit.

Contact information for SAE reporting can be found on the SAE Report Form and in the Safety Reporting Instructions provided to the study sites.

8.2.1.6.2 Reporting via Paper SAE Report Form

If the EDC system is not available, the study site will complete the paper SAE Report Form and email the form to the pharmacovigilance unit within 24 hours of becoming aware of the event. Once the EDC is restored, the SAE must be reported through the EDC system within 24 hours of it becoming available.

In rare circumstances, such as when the EDC system and email are not available, notifying the pharmacovigilance unit of an SAE by telephone within 24 hours of becoming aware of the event is acceptable. If email is restored before the EDC system, the site will email the completed paper SAE Report Form to the pharmacovigilance unit within 24 hours of email becoming available. Once the EDC is restored, the SAE must be reported through the EDC system within 24 hours of it becoming available.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE page of the subject's CRF within the designated reporting time frames.

Contact information for SAE reporting can be found on the SAE Report Form and in the Safety Reporting Instructions provided to the study sites.

8.2.1.7 Reporting of Pregnancy

If a female subject becomes pregnant during the study or within 24 weeks after the last dose of study treatment or a female partner of a male subject becomes pregnant during the study or within 150 days after the last dose of study treatment, the subject should inform the study site as soon as possible.

If a pregnancy is reported, the Investigator should inform the pharmacovigilance unit within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.

If a pregnancy occurs, it will be followed for up to 8 weeks after the delivery date to determine the outcome if consent has been obtained to do so.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported within 24 hours of the site becoming aware of the event as described in Section 8.2.1.6.

8.2.1.8 Treatment of Overdose

For this study, any dose of study treatment (rosnilimab or placebo) administered in a total injection volume > 8 mL (see Section 6.1.2) will be considered an overdose.

In the event of a suspected overdose, the following procedures should be executed:

- Administration is to be discontinued.
- The subject is to be monitored clinically for any AEs. Supportive measures are to be undertaken as clinically indicated.
- Contact the Medical Monitor immediately.
- Obtain a serum sample for PK analysis.
- Document the quantity of the excess dose as well as the duration of the overdose in the subject's source documentation and eCRF.
- If clinically indicated, ECG and clinical laboratory evaluations (i.e., blood glucose, hepatic enzymes, creatinine, blood urea nitrogen, creatine kinase, and complete blood count) are to be performed and followed until all values return to Baseline levels and AEs resolve, if applicable.

Based on the results of the Phase 1 study (Section 2.2.2), single doses up to rosnilimab 600 mg IV and weekly doses of rosnilimab 400 mg SC for 4 weeks have been well tolerated with no dose limiting toxicities. The C_{max} and AUC values anticipated for the 800 mg Q2W are lower than the C_{max} and AUC values of the 600 mg IV dose studied in the Phase 1 study (see Section 4.3). No experiments have been performed to determine if the effects of an overdose can be reversed. There are no known antidotes, and it is unknown whether rosnilimab can be dialyzed.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject (see Section 7.1.1).

8.2.2 Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will be performed as indicated in the SoA (Table 1). Blood samples for clinical laboratory assessments will be collected before the administration of study treatment at the visits indicated in the SoA when study treatment is administered. Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate Study Laboratory Manual. The date and time of each sample will be recorded in the subject's source documentation and eCRF.

A central laboratory will be used to perform all clinical safety laboratory tests except the urine pregnancy dipstick, which will be assessed by study site staff. Clinical laboratory tests to be performed are listed in Appendix 8.

Local laboratory tests are allowed when central laboratory test results may not be available in time for an Investigator to make immediate decisions regarding subject safety. If local laboratory tests are required, 2 samples will be obtained at the same time so that 1 sample can be sent to the local laboratory and the other sample can be sent to the central laboratory.

The Investigator must review all laboratory reports (from local and central laboratories) and document the review and any clinically significant changes in the subject's source documentation and eCRF. All laboratory reports must be filed with the subject's source documents. Abnormal laboratory findings that are typically associated with the subject's underlying disease under study should generally not be considered clinically significant unless the Investigator judges the finding to be more severe than expected for the subject's condition. Any clinically significant change that meets the criteria of an AE (see Section 8.2.1.1) should be reported as detailed in Section 8.2.1.5).

All clinically significant laboratory findings (including findings at the subject's last [EOS/ET] visit) should be followed until the values return to normal or Baseline, are no longer considered clinically significant, or are judged to be medically stabilized by the Investigator. If the laboratory test does not return to normal or Baseline within a reasonable period as determined by the Investigator, the etiology should be investigated and AnaptysBio notified.

8.2.3 Vital Signs

Body temperature (°C), pulse rate (beats/minute), blood pressure (mm Hg), and respiratory rate (breaths/minute) will be assessed at the time points specified in SoA (Table 1).

Blood pressure and pulse rate will be measured in a seated position after at least 5 minutes of rest in a quiet setting without distractions (e.g., television, cell phones) using a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.4 Height, Weight, and Body Mass Index

Height (cm) and weight (kg) will be collected as specified in the SoA (Table 1) to calculate the body mass index (BMI).

8.2.5 Physical Examination

Complete physical examinations will be performed at the time points indicated in the SoA (Table 1).

A complete physical examination will include the following: general appearance; skin and oral mucosa; eyes, ears, nose, and throat; head, neck, and thyroid; cardiovascular; respiratory; abdomen; lymph nodes; neurologic; and musculoskeletal.

8.2.6 12-Lead Electrocardiogram

A single 12-lead ECG will be obtained at Screening (Table 1) using an ECG machine that measures RR, PR, QRS, and QT intervals and automatically calculates the heart rate and QT interval corrected for heart rate using Fridericia's formula (QTcF).

ECGs will be reviewed and assessed for clinical significance by the Investigator or qualified designee who is experienced in the evaluation of ECGs.

ECGs may be performed at any time during the study if, in the opinion of the Investigator, it is clinically warranted.

ECG results, interpretation, and clinical significance will be documented in the subject's source documentation and eCRF, and a copy of the Screening ECG will be kept with the subject's source documentation to serve as a Baseline reference for comparison if a subsequent cardiovascular related safety even occurs.

8.3 Other Assessments

8.3.1 Demographics

Demographic data will be collected at Screening. Trained site staff will collect and record each subject's demographic data (e.g., age at Screening, sex, childbearing potential, ethnicity, race) in the subject's source documentation and eCRF.

8.3.2 Medical History and Prior Medications

Each subject's medical history and prior medication data will be collected at the Screening Visit. Trained site staff will record each subject's medical history (i.e., previous conditions, diagnoses, disease, or surgeries). The following medical history information will be collected: description of the condition/diagnosis, year (and date if available) of onset, year (and date if available) of resolution, and if the condition is ongoing at the time of the Screening Visit.

Trained site staff will record each subject's prior and ongoing medications (including COVID-19 vaccine, vitamin preparations, and herbal or health supplements; see Section 6.5). Each medication taken for a previous condition, diagnosis, disease, or surgery, should have a corresponding entry in the subject's medical history.

In addition, a detailed history of the subject's UC and conditions otherwise relevant to the study of UC including all prior medications used to treat UC (Section 6.5), will be collected.

8.3.3 Chest X-ray or Computerized Tomography Scan

If chest radiographs (posterior anterior and lateral views) or a chest CT scan were not obtained within 6 months before Day 1 and read by a qualified radiologist (see Inclusion Criterion 7), posterior anterior and lateral chest radiographs or a chest CT scan will be performed during Screening and read by a qualified radiologist before Day 1.

8.3.4 Pharmacokinetics

Blood samples for the measurement of serum rosnilimab concentration and determination of rosnilimab PK parameters will be collected as indicated in the SoA (Table 1). A Baseline PK blood sample will be collected on Day 1 before the administration of the first dose of study treatment. At visits when study treatment is administered, PK blood samples will be collected before the administration of study treatment. At visits when study treatment is not administered, PK blood samples may be collected at any time during the visit. Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate Study Laboratory Manual. The date and time of each sample will be recorded in the subject's source documentation and eCRF.

Serum rosnilimab concentrations will be determined using a validated assay.

While PK samples must be collected from subjects assigned to the placebo arm to maintain the blinding of treatment assignments, PK assay results for these subjects are not needed for the safe conduct or proper interpretation of this study. These samples will not be analyzed unless analysis is required to investigate if a dosing error has occurred. Although personnel at the bioanalytical laboratory performing PK assays will be unblinded to treatment assignments, the clinical study team members, Investigators, site staff (apart from the unblinded pharmacist), and subjects will remain blinded to initial treatment for the duration of the study.

8.3.5 Pharmacodynamic Biomarkers and Immunophenotyping

Blood transcriptomic profiling and PD biomarkers may include, but are not limited to, TNFα, IFNγ, IL-6, and IL-12.

Blood samples for blood transcriptomic profiling, PD biomarkers, and immunophenotyping will be collected as indicated in the SoA (Table 1). Baseline transcriptomic profiling, biomarker, and immunophenotyping blood samples will be collected on Day 1 before the administration of the first dose of study treatment. At visits when study treatment is administered, transcriptomic profiling, biomarker, and immunophenotyping blood samples will be collected before the administration of study treatment. At visits when study treatment is not administered, transcriptomic profiling, biomarker, and immunophenotyping blood samples may be collected at any time during the visit. Instructions for the collection and handling of biological samples will

be provided by the Sponsor in a separate Study Laboratory Manual. The date and time of each sample will be recorded in the subject's source documentation and eCRF.

Collection of colon tissue by endoscopic biopsy will be performed as indicated in the SoA (Table 1). Tissue biomarkers include gene expression panels reflective of UC disease activity and cytokine levels including the same cytokines measured in peripheral blood.

Fecal samples will be collected for fecal calprotectin analysis as indicated in the SoA (Table 1).

Transcriptomic profiling, analyses for blood PD and tissue biomarkers, calprotectin analysis, and immunophenotyping will be performed using validated assays.

8.3.6 Immunogenicity

Blood samples for the measurement of ADA to rosnilimab will be collected as indicated in the SoA (Table 1). A Baseline ADA blood sample will be collected on Day 1 before the administration of the first dose of study treatment. At visits when study treatment is administered, ADA blood samples will be collected before the administration of study treatment. At visits when study treatment is not administered, ADA blood samples may be collected at any time during the visit. Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate Study Laboratory Manual. The date and time of each sample will be recorded in the subject's source documentation and eCRF.

The detection and characterization of antibodies to rosnilimab will be performed using validated assays.

9 STATISTICAL CONSIDERATIONS

This section briefly describes the planned statistical methods for this study. A Statistical Analysis Plan (SAP) describing specific statistical methods in detail will be developed and approved by the Sponsor prior to database lock. If there are differences between the protocol and the SAP, the SAP will take precedence over the protocol.

9.1 Statistical Hypotheses

The primary analysis for this study is to compare the mean change in mMS from Baseline to Week 12 for rosnilimab versus placebo at a 10% (2-sided) significance level:

- Null Hypothesis (H_0): $\mu_{rosnilimab} - \mu_{placebo} = 0$
- Alternative hypothesis (H_A): $\mu_{rosnilimab} - \mu_{placebo} \neq 0$

Any testing being performed for secondary or exploratory endpoints will be considered exploratory in nature based on a 2-sided $\alpha = 0.10$.

9.2 Sample Size Determination

Approximately 132 subjects will be randomized into 3 treatment groups (44 subjects/treatment group). Assuming a dropout rate of 9% by Week 12, approximately 120 evaluable subjects (40 subjects/treatment group) will complete the primary efficacy endpoint at the end of Week 12. Tests of both high and low doses of rosnilimab versus placebo will have 80.8% power to detect a between-group treatment difference of 0.59 in the mean change in mMS from Baseline to Week 12, using a 2-sided, equal variance, t-test at a significance level of $\alpha = 0.10$, with the assumption of a common standard deviation of 1.04 based on the QUASAR trial (Dignass 2022).

For the mMS-based clinical remission secondary endpoint, if we assume that the placebo rate for the trial proposed in this protocol will be similar to the rates reported in similar Phase 3 clinical trials, then tests of both high and low doses of rosnilimab versus placebo will have 81.9% power to detect a difference of 21.5 percentage points in mMS remission rate (29.6% versus 8.1%) at Week 12. This power calculation used unpooled variance estimates for a 2-sided test at a significance level of $\alpha = 0.1$.

9.3 Populations for Analyses

The analysis sets are defined in Table 5.

Table 5 Analysis Sets

Analysis Set	Description
ITT Analysis Set	The ITT Analysis Set will include all randomized subjects. In this analysis set, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they receive. ITT Analysis Set will be used for primary, secondary, and exploratory efficacy analyses.
Safety Analysis Set	The Safety Analysis Set will include all randomized subjects who receive at least 1 dose of rosnilimab or placebo. The Safety Analysis Set will be used for all safety analyses. Subjects will be analyzed as treated.
Per Protocol (PP) Analysis Set	The Per Protocol Analysis Set will include all subjects in the ITT Analysis Set who do not have important protocol deviations that would affect the evaluation of the primary efficacy endpoint.
PK Analysis Set	The PK Analysis Set will include all subjects in the Safety Analysis Set who have at least 1 quantifiable postdose PK sample available and who do not have events or protocol deviations that could potentially affect rosnilimab concentrations. The PK Analysis Set will be used for all PK analyses.
PD Analysis Set	The PD Analysis Set will include all subjects in the Safety Analysis Set who have a PD measurement at Baseline, at least 1 postdose PD sample available, and who do not have events or protocol deviations that could potentially affect PD parameters. The PD Analysis Set will be used for all PD analyses.

Abbreviations: ITT: intent-to-treat; PD: pharmacodynamic(s); PK: pharmacokinetic(s); PP: per protocol

9.4 Statistical Analyses

9.4.1 General Approach

Statistical analysis will be performed using SAS; the version of SAS used will be specified in the SAP.

Continuous variables will be summarized by visit and treatment arm. In general, continuous variables will be summarized by treatment to indicate the population sample size (N), number of subjects with available data (n), arithmetic mean, standard deviation, median, minimum, and maximum values. The geometric mean, confidence interval (CI), and coefficient of variation (CV) may also be provided as appropriate (e.g., for variables with lognormal distributions).

Mixed-effects models for repeated measures (MMRM) method for longitudinal, continuous data will be used for testing with treatment group as main effect, visit and interaction of treatment and visit as factors, and with baseline value of response and stratification factors as covariates.

Categorical variables will be summarized by visit and treatment arm. Frequency and the percentage of subjects in each category will be tabulated. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data.

The versions of Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug Dictionaries to be used for coding will be specified in the Data Management Plan.

In general, Baseline values will be defined as the last non-missing measurement before the first administration of study treatment unless indicated otherwise.

Only data provided by the central laboratory will be used for safety analyses; values from local laboratories will not be used in the statistical analyses and listed only.

Given the exploratory nature of this study, no Type 1 error adjustments for multiplicity will be used.

Data from all assessments will be presented in by-subject listings.

9.4.2 Subject Disposition

Subject disposition (including the number of subjects screened, randomized, treated, and completed; the number of dropouts with reasons for discontinuation; and important protocol deviations) will be summarized descriptively by treatment and overall, for all screened subjects. Analysis population data and important protocol deviations will be tabulated by treatment group and overall, on the Intent-to-Treat (ITT) Analysis Set.

A listing will present the dates of Screening, treatment assigned or screen failure with reason, completion, or early discontinuation of treatment with reason, and early discontinuation from the study with reason, if applicable, for each subject. Prior to final study database lock, AnaptysBio will review and categorize protocol deviations as important or nonimportant and determine if any subjects or visits should be excluded from the Per Protocol (PP), PK, or PD Analysis Sets.

During the COVID-19 pandemic, protocol deviations related to COVID-19 will be documented and information on how they will be handled in the analyses will be detailed in the SAP.

9.4.3 Demographics and Baseline Characteristics

Subject demographics (e.g., age, sex, race, and ethnicity) will be summarized for each analysis set separately. Baseline characteristics (e.g., duration of disease, disease severity, concurrent use of corticosteroids, prior advanced UC therapies) will be summarized for the ITT Analysis Set using

descriptive statistics. Tables summarizing demographics and other baseline characteristics will also include a column for all subjects combined. All data will be provided in by-subject listings.

Medical history will be coded using the MedDRA. Medical history will be summarized by system organ class (SOC) and preferred term (PT) and listed using the Safety Analysis Set.

9.4.4 Prior and Concomitant Therapy

All medications and therapies will be coded using the WHO Drug Dictionary and Anatomical Therapeutic Chemical (ATC) System. Each medication will be classified as a prior medication or therapy if it is stopped prior to the first dose of study treatment, or as a concomitant medication or therapy if it is ongoing at the time of the first dose or is started after the first dose of study treatment. Prior and concomitant medications will be listed by subject and summarized using descriptive statistics.

9.4.5 Analysis of Efficacy Endpoints

All efficacy endpoints will be analyzed on the ITT Analysis Set. Primary and secondary endpoints will also be analyzed on the PP Analysis Set.

9.4.5.1 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change in mMS from Baseline to Week 12.

The primary estimand comprises 5 components and is defined as follows:

a. The target population consists of subjects with UC and are eligible to be included in the clinical trial based on the inclusion/exclusion criteria (Section 5).

b. The treatment conditions of interest are rosnilimab 800 mg SC Q2W, rosnilimab 400 mg SC Q4W, and placebo.

c. The primary variable is change in mMS from Baseline to Week 12.

d. The population level summary measures will be the population mean differences in the primary variable between each dose of rosnilimab and placebo at Week 12.

e. Intercurrent events include discontinuation of treatment because of an AE, treatment with a prohibited medication, or other early termination prior to the primary endpoint. Data collected after an intercurrent event will be considered missing in the analysis.

The primary efficacy endpoint, change in mMS from Baseline to Week 12, will be analyzed using a MMRM with restricted maximum likelihood estimation. The change from baseline in mMS will

be the dependent variable with treatment arm, baseline mMS, categorical time point, and treatment × time point interaction as fixed effects along with the stratification factors (prior experience with advanced UC therapies [experience with advanced UC therapy versus no prior advanced UC therapies] and steroid use [steroid use versus no steroid use]). The Kenward-Roger method will be used to calculate the denominator degrees of freedom and adjust standard errors for the test of fixed effects. The MMRM uses all available data and assumes that missing data because of dropouts are missing at random.

Sensitivity analyses using multiple imputation under missing-at-random and not missing-at-random assumptions may be performed as indicated in the SAP. Possible effect of any other covariates as well as investigation of variables through sub-group analysis may also be investigated.

9.4.5.2 Analysis of Secondary Efficacy Endpoints

Because all secondary efficacy endpoints (i.e., proportion of subjects achieving clinical remission at Week 12, proportion of subjects showing endoscopic improvement at Week 12, and the proportion of subjects achieving a clinical response at Week 12) are categorical, the analyses of the secondary efficacy endpoints will be conducted using the Cochran-Mantel-Haenszel χ^2-test, adjusted for stratification factors (i.e., prior experience with advanced UC therapies [experience with advanced UC therapy versus no prior advanced UC therapies] and steroid use [steroid use versus no steroid use]). Estimates of the difference between treatments (rosnilimab – placebo) will be presented along with the associated 90% CIs.

9.4.5.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will be analyzed with comparable methods for continuous or categorical data as were employed for the corresponding primary or secondary analyses. Some exploratory endpoints may only be analyzed descriptively, however, and these analyses will be detailed in the SAP. All exploratory analyses will be performed on the ITT Analysis Set only.

The IBDQ will be analyzed by subscale and overall and follow the applicable scoring manual, if any, for analysis conventions. Further details will be provided in the SAP.

9.4.6 Safety Analyses

The following are the safety and tolerability endpoints:

- Incidence, type, and severity of all TEAEs, SAEs, treatment-related TEAEs, TEAEs leading to study treatment discontinuation and TEAEs leading to study discontinuation
- Changes from Baseline in vital signs (body temperature, heart rate, respiratory rate, and blood pressure)

- Changes from Baseline in clinical laboratory assessments (hematology, biochemistry, and urinalysis)

All safety analyses will be performed on the Safety Analysis Set.

9.4.6.1 Adverse Events and Serious Adverse Events

TEAEs are defined in Section 8.2.1.1.

Numbers and percentages of TEAEs, SAEs, TEAEs leading to death, TEAEs leading to study treatment discontinuation, and TEAEs leading to study discontinuation will be presented by SOC, PT, seriousness, and/or severity for each treatment arm. Multiple occurrences of an AE will only be counted once per primary SOC and PT. Percentages will be determined relative to the subjects in the Safety Analysis Set for the given treatment arm. If the intensity or seriousness of an AE changes, the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences.

All AEs will be coded using MedDRA. Only TEAEs will be summarized. Summaries will also be presented by the relatedness to study treatment and the severity of the TEAE. All AE data will be listed for each subject.

9.4.6.2 Clinical Safety Laboratory Tests and Vital Signs

Summaries and listings of data for vital signs, weight, body mass index, and safety laboratory tests result (hematology, biochemistry, and urinalysis) will be presented. Appropriate descriptive statistics will be summarized for the observed value at each scheduled assessment and for the corresponding change from Baseline.

For hematology and biochemistry tests, listings of subject data will also flag any abnormal or out of range values. Clinically significant changes in the laboratory test parameters will be summarized and listed. Hematology and biochemistry data will be reported in International System of Units.

9.4.7 Pharmacokinetic Analyses

Limited rosnilimab PK parameter analysis will be evaluated by assessment of serum concentration time data. All PK analyses will be performed on the PK Analysis Set.

9.4.7.1 Derivation of Pharmacokinetic Parameters

Noncompartmental analysis is not planned for the PK analyses of this study, thus, PK parameters will not be estimated.

9.4.7.2 Pharmacokinetic Concentration Data Analysis

A subject listing of all serum concentration-time data following SC injections will be presented by subject and scheduled sample collection time.

Mean trough serum concentration-time data of rosnilimab will be summarized for samples collected at the visits specified in the SoA (Table 1) by day and nominal time point using the number of observations, arithmetic mean, standard deviation, geometric mean, CV, minimum, median, and maximum. Time to steady state may also be explored by using inferential statistics, if deemed appropriate.

Graphs for mean concentration-time data following SC administration will be presented. Individual subject concentration-time plots may be presented. Other presentations of data may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in a separate analysis plan.

9.4.7.3 Population Pharmacokinetics Analysis

Pharmacokinetic data from the study may also be used for population PK and exposure response analyses. The data may be combined with PK data from other rosnilimab studies, if needed, to conduct the population PK analysis. If done, a separate analysis plan will be prepared, and results will be reported separately from the CSR.

9.4.8 Biomarker Analysis

Biomarker data (if available) will be summarized using descriptive statistics by visit and treatment arm as appropriate on the PD Analysis Set. By-subject listings will be presented for each assessment by visit. If biomarker data is not available at the time of the CSR, the results will be reported separately from the CSR.

9.4.9 Immunogenicity Analyses

Observed values for ADA levels/status will be listed by subject and summarized with descriptive statistics based on the Safety Analysis Set. If data permits, correlation will be analyzed between ADA status and/or titers and serum concentration, safety, or efficacy endpoints.

Frequency and percentage of ADA response by type of assay will be presented and listed and correlated to safety and PK endpoints. In addition, ADA incidences (overall, pre-existing immune reactivity, treatment-emergent, and treatment boosted) will be summarized.

9.4.10 Immunophenotyping Analysis

Raw values and change from baseline of immunophenotyping parameters (if available) will be summarized using descriptive statistics by visit and treatment arm as appropriate on the PD Analysis Set, as specified in the SAP. By-subject listings will be presented for each assessment by visit. If immunophenotyping data are not available at the time of the CSR, the results will be reported separately from the CSR.

9.4.11 Planned Interim Analysis

Interim analyses may be performed for assessment of all primary and secondary efficacy endpoints, and evaluation of all safety data available. The rationale for these analyses is to assist in making decisions for potential future development of this treatment. No adjustments to the current protocol are planned as a result of the interim analyses; therefore, the overall α of the primary analysis is expected to be maintained at 0.05, 2-sided. Details of any interim analyses will be specified in the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to AnaptysBio or representative. The study will not start at any study site at which the Investigator has not signed the protocol.

10.1.1 Informed Consent Process

10.1.1.1 Consent and Other Informational Documents Provided to Subjects

An ICF describing in detail the study treatments, study procedures, and risks will be given to subjects, and written documentation of informed consent is required prior to starting any study related procedures. The following materials will be submitted to the Institutional Review board (IRB)/Ethics Committee (EC) with this protocol: subject self-reported questionnaires, ICF, IB, and other relevant documents (e.g., advertisements).

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Each informed consent document must adhere to the ethical principles stated in the Declaration of Helsinki and include the elements required by Food and Drug Administration (FDA) regulations in Title 21 Part 50 of the Code of Federal Regulations (21 CFR Part 50), Clinical Trials Regulation (European Union [EU] 536/2014), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guideline, and applicable federal and local regulatory requirements. The ICF will be approved by the IRB/EC.

The Investigator or designated representative will explain the research study to each subject and answer any questions that may arise. A verbal explanation of the following will be provided in terms suited to the subject's comprehension: the purposes, procedures, and potential risks of the study; the subject's rights as a research subject; that participation in the study is voluntary; and that the subject may withdraw from the study at any time without prejudice. The subject's rights and welfare will be protected by emphasizing that the quality of the subject's medical care will not be adversely affected if the subject declines to participate in the study. Each subject will have the opportunity to carefully read the ICF, think about participating in the study, discuss their participation in the study with their family or surrogates, and ask questions prior to agreeing to participate in the study and signing the ICF. The subject must sign and date the ICF before any study specific procedures are performed. The authorized person obtaining the informed consent

must also sign the ICF. The original signed and dated ICF will be filed with the site's study documentation. A copy of the signed ICF will be given to the subject for their records.

The subject must sign the ICF before any protocol specific procedures are performed, and the site must document the informed consent process in the subject's source documentation and eCRF. The subject's medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date when written consent was obtained.

Subjects must be re-consented with the most current version of the IRB/EC approved ICF whenever the ICF is changed (e.g., because of a protocol amendment) during the subject's participation in the study. Subjects who are rescreened are required to be re-consented and sign a new ICF.

10.1.2 Study Suspension, Discontinuation, and Closure

The Sponsor reserves the right to close a study site, and temporarily suspend or prematurely terminate the study at any time.

Circumstances that may warrant suspension or termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Scientific or corporate reasons

If temporarily suspended, the study may resume once any concerns about safety, protocol compliance, or data quality are addressed, and satisfy AnaptysBio, the IRB/EC, and/or regulatory authorities.

If the study is suspended or prematurely terminated, the Sponsor will promptly provide written notification, documenting the reason for study suspension or termination to the Investigators and regulatory authorities, as applicable. The Investigators will promptly inform study subjects and the IRB/EC and will provide the reason(s) for the suspension or termination.

10.1.3 Confidentiality and Privacy

Subject confidentiality and privacy will be strictly held in trust by the participating Investigators, their staff, and AnaptysBio and its authorized representatives. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information

generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of AnaptysBio.

All research activities will be conducted in a setting as private as possible. The Investigator must ensure that the subjects' anonymity will be maintained, and that subjects' identities are protected from unauthorized parties. Subjects should be identified by an identification code only on electronic and paper case report forms (CRFs) and other documents submitted to AnaptysBio and NOT by their names or initials or include other personally identifying information (e.g., date of birth, address, or tax identification number). The Investigator should keep a subject log relating codes with the names of subjects, which will not be shared with the Sponsor or filed in the site's study files or in the Trial Master File. The Investigator should maintain in strict confidence documents not for submission to AnaptysBio (e.g., subjects' signed ICFs).

The study monitor, other authorized representatives of AnaptysBio, and representatives of the IRB/EC, regulatory agencies, or pharmaceutical company supplying study treatment may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB/EC, institutional policies, or AnaptysBio requirements.

Study subject research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management company responsible for data management, analysis, and reporting. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical study sites and by data management research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by AnaptysBio.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from AnaptysBio. Authorized regulatory officials and AnaptysBio personnel (or their representatives) will be allowed full access to inspect and copy the records. All study investigational products, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by AnaptysBio.

In the United States, each ICF will also include authorization allowing the institution, Investigator, and AnaptysBio to use and disclose personal health information in compliance with the Health Information Portability and Accountability Act (HIPAA).

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 case of a data security breach, the Sponsor will follow the requirements of General Data Protection Regulation (GDPR) with respect to notification and reporting of any suspected or actual data breach and will undertake efforts to identify the source of the breach, the nature of data potentially exposed, and the extent of such data exposure, with remedial actions to be implemented based on the type of unauthorized access to study participant data that may occur. All organizational, contractual, and technical security measures to guarantee the protection of patient's privacy will be reassessed in order to mitigate the possible adverse effects.

10.1.4 Future Use of Stored Specimens and Data

With the subject's approval and approval by IRB/EC, de-identified biological samples will be stored at a certified, licensed central laboratory. Once samples have been analyzed, the samples will be destroyed. If no analyses have been completed within 5 years following the completion of the study, the samples will be destroyed.

Any remaining serum/plasma from samples collected for PK/PD/immunogenicity endpoints may be retained for assay method development, troubleshooting, or validation. These samples may also be used for research purposes but will not be used for any type of genetic analyses.

During the conduct of the study, a subject may choose to withdraw consent to have biological specimens stored for future research.

10.1.5 Medical Monitoring

Medical monitoring will be conducted to ensure the early recognition, identification, and reporting of issues impacting subjects' health and well-being throughout the trial. Details of medical monitoring with contact information of the Medical Monitors will be documented in a Medical Monitoring Plan.

10.1.6 Safety Oversight

No data and safety monitoring board is required for this study.

10.1.7 Clinical Monitoring

All aspects of the study will be monitored by AnaptysBio or authorized representatives of AnaptysBio according to GCP and SOPs for compliance with applicable government regulations, (e.g., Informed Consent Regulations [US 21CFR, Part 50], EU 536/2014, and Institutional Review Board regulations [US 21CFR, Part 56.103]). Access to all records, both during the study and

after study completion, should be made available to AnaptysBio at any time for review and auditing to ensure compliance with GCP and SOPs and to ensure the integrity of the data.

Before study initiation, a representative from AnaptysBio will review the protocol and study eCRFs with the Investigator(s) and their staff at a study site initiation visit or Investigators Meeting.

The Investigator must conduct the study in compliance with the Declaration of Helsinki and in accordance with applicable GCP regulations and guidelines including applicable informed consent regulations (e.g., US 21CFR, Part 50, EU 536/2014). Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data are not recorded per protocol, the reasons must be clearly documented in the subject's source documentation and eCRF. The Investigator must promptly complete the eCRFs after the subject's visit. A copy of the eCRFs will be retained by the Investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol and any protocol amendments and the IB.

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. During the study, the study monitor will visit the study site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that consent is being sought and obtained in compliance with applicable regulations, and that the study treatments are being stored, dispensed, and accounted for according to specifications. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study specific Monitoring Plan. The monitor is responsible for reviewing the eCRFs and clarifying and resolving any data queries.

The Investigator and key study personnel must be available to assist the monitor during these visits. The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will be left at the study site.

The Investigator must notify AnaptysBio immediately if the responsible IRB/EC has been disqualified or if proceedings leading to disqualification have begun.

The Investigator must provide AnaptysBio and the responsible IRB/EC with a study summary shortly after study completion or as designated by AnaptysBio.

10.1.8 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, and documentation completion.

Quality control (QC) procedures will be implemented beginning with the data entry system. Data QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted, data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., GLP, Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by AnaptysBio, and inspection by IRB/EC and regulatory authorities.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

All protocol specified data will be recorded in site source documents. Study data will be entered within the clinical database eCRFs from the original source documents. Upon each subject's completion of the study, the Investigator is required to sign and affirm the data entered in the subject's eCRF along with a statement attesting that all pages of the subject's CRF have been reviewed. All Investigator data attestation signatures will be made through the 21 CFR, Part 11 compliant EDC system. Signature stamps and "per signatures" are not acceptable.

AnaptysBio's policy is that study data be verifiable with the source data; this necessitates that the site provide access to all original recordings, laboratory reports, and other records for each subject. The Investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data.

Subjects must also allow access to their medical records. Subjects will be informed of the importance of increased record access during the informed consent process and authorize the use of their protected health information by signing the ICF prior to Screening in accordance with the applicable GCP guidelines and privacy requirements. Subjects who do not give permission to use and disclose protected health information will not be eligible to participate in the study.

The data recorded during the study will be documented in the eCRF and/or the study specific forms. Checks will be performed to ensure quality, consistency, and completeness of the data. Instances of missing or uninterpretable data will be resolved with the Investigator or study coordinator. Data queries, documented within the clinical database will be accessible to the research facility through the EDC system. Study site personnel will be responsible for providing resolutions to data queries and for correcting the eCRFs, as appropriate.

The Investigator must keep written or electronic source documents for every subject participating in the clinical study for the appropriate document retention period. The subject file that identifies the study that the subject is participating in must include the subject's available demographic and medical information including:

- Name
- Contact information
- Year of birth
- Sex
- Medical history
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- Investigational product administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment (e.g., laboratory value listings) must be included in the subject's source documentation. All these documents must have at least the subject's study number, and the date of the evaluation.

Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (as appropriate), and countersigned by the Investigator or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. The Investigator must state his/her reason for the correction of any data. In the case of missing data/remarks, the entry spaces provided in the eCRF should be cancelled out so as to avoid unnecessary follow-up inquiries.

The Investigator will ensure that the study documents forwarded to AnaptysBio, and any other documents, contain no mention of subject names or other personally identifying information.

It is the responsibility of the Investigator to ensure that the study site file is maintained in accordance with the ICH E6(R2) Guidelines for GCP, Section 8, Essential Documents for the Conduct of a Clinical Trial.

Before or at study termination, all data must be forwarded to AnaptysBio. The data will then be recorded, evaluated, and stored in anonymous or coded form in accordance with data protection regulations. Electronic CRFs will be kept by AnaptysBio or an authorized designee in a secured area. Clinical data will be recorded in a computer format for subsequent statistical analyses. Data

files will be stored on electronic media with a final master data file kept by AnaptysBio after descriptive and statistical analyses and reports have been generated and are complete.

10.1.9.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment. These documents should be retained for a longer period, however, if required by local regulations or as specified in the study agreement, whichever retention period is longer.

If the Investigator withdraws from the study (e.g., relocation, retirement), all study-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to AnaptysBio in writing. No records will be destroyed without the written consent of AnaptysBio, if applicable. It is the responsibility of AnaptysBio to inform the Investigator when these documents no longer need to be retained.

10.1.10Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. Protocol deviations related to COVID-19 pandemic will be identified and documented accordingly. Please refer to Section 4.5 for further details. These practices are consistent with the ICH E6 (R2), Guideline for GCP.

It is the responsibility of the Investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents, and applicable deviations must be sent to the IRB/EC per the IRB/EC's policies. The Investigator is responsible for knowing and adhering to IRB/EC requirements. Details about the handling of protocol deviations will be included in the Protocol Deviation Management Plan, Data Management Plan, Medical Monitoring Plan, blind data review documentation, and SAP.

This study will be conducted as described in this protocol, except for an emergency in which the protection, safety, and well-being of a subject requires immediate intervention based on the judgment of the Investigator or an appropriately trained professional designated by the Investigator. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact the Medical Monitor and AnaptysBio at the earliest possible time by telephone to allow an early joint decision regarding the subject's continuation on study treatment and/or in the study. This decision will be documented by the Investigator and the Medical Monitor.

The monitor must ensure that prompt action is taken to secure compliance. If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the AnaptysBio or its designee should perform a root cause analysis and implement appropriate corrective and preventive actions.

10.1.11 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations: It is understood by the Investigator that the information generated in this study will be used by AnaptysBio in connection with the development of the product. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the AnaptysBio with complete test results, all study data, and access to all study records.

Any results of medical investigations with AnaptysBio's products and/or publication/lecture/manuscripts based thereon, shall be exchanged, and discussed by the Investigator and AnaptysBio representative(s), 30 days before submission for publication or presentation. Due regard shall be given to AnaptysBio's legitimate interests for example, manuscript authorship, obtaining optimal patent protection, coordinating, and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information. AnaptysBio shall be furnished with a copy of any proposed publication. Comments shall be rendered without undue delay.

In cases of publications or presentations of material arising from multicenter clinical investigations, AnaptysBio is to serve as coordinator and referee. Individual Investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent of the other participating Investigators and the prior review of AnaptysBio.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. AnaptysBio will not quote from publications by Investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

A description of this study, including the main results when available, will be available on https://www.anaptysbio.com/ and http://www.clinicaltrials.gov and other websites according to the regulations of the countries in which the study is conducted. Study results will be uploaded to the Clinical Trials Information System within 1 year after the end of the trial in accordance with the Clinical Trials Regulation (EU 536/2014) Annex IV.

10.1.12Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, financial interest, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study. AnaptysBio has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Additional Considerations

10.2.1 Ethics and Responsibility

This study must be conducted in compliance with the protocol, the Declaration of Helsinki, ICH E6(R2) Guidelines for GCP, IRB/EC requirements, and all applicable national and local regulatory requirements. Investigators must submit all essential regulatory documentation, as required by local and national regulations (including approval of the protocol and ICF by a registered IRB/EC) to AnaptysBio before investigational product will be shipped to the respective study sites.

10.2.2 Amendment Policy

Only AnaptysBio (or designee) may modify the protocol. Amendments must be approved by all applicable national and local committees including, but not limited to, the government regulatory authorities and/or regional IRB/EC before implementation. The only exception is when an Investigator believes that following the standard amendment approval process at their site would result in a delay to implementation that could result in a subject being harmed. Under these circumstances, approval of the chairperson of the IRB/EC, or an authorized designee, may be sought to allow the approval of the amendment to be expedited. The Investigator should inform AnaptysBio and the full IRB/EC as soon as possible, but no later than 5 working days after an expedited approval of a protocol amendment occurs. The protocol specified safety reporting requirements must be adhered to, independent of any other variables.

For deviations from the protocol due to safety concerns, see Section 10.1.10.

10.2.3 Insurance

AnaptysBio will provide insurance in accordance with local guidelines and requirements for the subjects in this study. The terms of the insurance will be kept in the study files.

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12 APPENDICES

Appendix 1 Corticosteroid Maximum Stable Daily Permitted Oral Dose

Corticosteroid Maximum Stable Daily Permitted Oral Dose	
Steroid	**Maximum Oral Dose (mg/day)**
Prednisone	20
Budesonide	9
Methylprednisolone	16
Prednisolone	20
Dexamethasone	3
Hydrocortisone	80
Cortisone	100

Appendix 2 Corticosteroid Taper

Starting at the Week-12 visit, subjects whose clinical status allow may initiate corticosteroid dose tapering according to the following proposed schedule or based on the Investigator's discretion:

- Oral prednisone (or equivalent)
  - >10 mg/day: taper 5 mg/day/week until receiving 10 mg/day, then continue tapering by 2.5 mg/day/week until 0 mg/day
  - ≤10 mg/day: taper 2.5 mg/day/week until 0 mg/day
- Oral budesonide/oral budesonide-multimatrix (≤9 mg/day)
  - Reduce dosage to 9 mg two days out three for 2 weeks followed by 9 mg one day out of three for 2 weeks, then discontinue or
  - Taper dosage from 9 mg/day to 9 mg every other day for 2 weeks then discontinue
- Oral beclomethasone (≤5 mg/day)
  - taper to 5 mg every other day for 2 weeks then discontinue

If a subject experiences worsening of UC during corticosteroid tapering, the corticosteroid daily dose may be increased at the Investigator's discretion up to 20 mg of prednisone equivalent.

Subjects that utilize a steroid dose equivalent that exceeds the dose used at baseline will be considered nonresponders for efficacy assessments from that point through the end of the study.

Appendix 3 Contraceptive Guidance and Collection of Pregnancy Information

Female subjects who are women of childbearing potential (WOCBP; defined below) are required to use a highly effective method of birth control. Highly effective methods of birth control have a failure rate < 1% per year when used consistently and correctly. Acceptable methods of birth control have a failure rate > 1% per year. Highly effective methods of birth control are listed in Table 6.

The following methods of birth control are not acceptable: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).

A WOCBP is defined as a woman who is between menarche and at least 12 months postmenopausal and who is not surgically sterilized (e.g., hysterectomy, bilateral oophorectomy, or bilateral salpingectomy; tubal ligation is not acceptable).

Postmenopausal is defined as amenorrheic for at least 12 months, and, if aged < 60 years, have a serum follicle stimulating hormone (FSH) level > 20 mIU/mL. Women who are taking hormone replacement therapy do not have to have FSH assessments, but the amenorrhea before starting hormone replacement therapy must have been naturally occurring (i.e., spontaneous) and accompanied by an appropriate clinical profile (e.g., age appropriate with a history of vasomotor symptoms).

If a female subject's childbearing potential changes after start of the study (e.g., a woman who is not heterosexually active becomes active or a premenarchal woman experiences menarche), she must begin practicing a highly effective method of birth control as soon as possible and until at least 24 weeks after the last dose of study treatment.

The Investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study treatment.

Table 6 Method of Birth Control

Highly Effective Methods of Birth Control (Failure Rate < 1% per year)
• Combined (estrogen and progestin containing) hormonal contraception associated with inhibition of ovulation [a]
○ Oral
○ Intravaginal
○ Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation [a]
○ Oral
○ Injectable

○ Implantable
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [a]
• Bilateral tubal occlusion or tubal ligation
• Vasectomized partner [b]
• Sexual abstinence [c]
[a] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraception method. [b] Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the trial subject and that the vasectomized partner has received medical assessment of the surgical success. [c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Abbreviations: IUD: intrauterine device; IUS: intrauterine hormone releasing system Source: CTFG 2020

Pregnancy Testing

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at Screening as needed and urine pregnancy test on Day 1 (prior to study treatment administration). Additional pregnancy testing should be performed as indicated in the SoA (Table 1).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Positive urine pregnancy test results should be confirmed with a serum test.

Collection of Pregnancy Information

Male Subjects with Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study from the first dose of study treatment until at least 150 days after the last dose of study treatment. This applies only to male subjects who receive study treatment.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate pregnancy form and submit it to the pharmacovigilance unit within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to AnaptysBio. Generally, the follow-up will be no longer than 8 weeks following the estimated delivery date. Any termination of the pregnancy will

be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Any SAEs associated with the pregnancy in the male subject's partner should also be reported to the pharmacovigilance unit within 24 hours of the event using the backup Paper Report Form.

Female Subjects Who Become Pregnant

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study from the first dose of study treatment until at least 24 weeks after the last dose of study treatment. Information will be recorded on the appropriate form and submitted to the pharmacovigilance unit within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on the subject and the neonate, and the information will be forwarded to AnaptysBio. Generally, follow-up will not be required for longer than 8 weeks after the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported as described in Section 8.2.1.7. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will be withdrawn from study treatment.

Appendix 4 Hepatitis B Virus Screening and DNA Testing Result Interpretation

Hepatitis B Test Result Interpretation			
Hepatitis B Surface Antigen (HBsAg)	**Hepatitis B Surface Antibody (HBsAb)**	**Hepatitis B Core Antibody (HBcAb)**	**Action**
−	−	−	**Include**
−	+	−	
−	+	+	
+	− *or* +	− *or* +	**Exclude**
−	−	+	**Requires additional testing for presence of Hepatitis B virus DNA** [a]

[a] If hepatitis B virus DNA is not detected, the subject may be included in the study. If hepatitis B virus DNA is detected or if hepatitis B virus DNA testing cannot be performed, or if there is evidence of chronic liver disease, the subject must be excluded from the clinical study.

Appendix 5 Modified Mayo Score Subscore Definitions

mMS Subscores by Category	
Stool Frequency*	
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 more than normal
Rectal Bleeding**	
0	No blood seen
1	Stool with streaks of blood
2	Stool with more than streaks of blood
3	Blood alone passed
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, ulcerations)

* Each patient provides own baseline against which to compare the degree of abnormality in stool frequency.
** Represents the worst bleeding score for that day.

Source: Ulcerative Colitis: Developing Drugs for Treatment. FDA Guidance for Industry, 2022

Appendix 6 Instructions for Recording Stool Frequency and Rectal Bleeding Scores

Category of Instructions	Specific Instructions to Patients
Definition of *stool frequency*	• Patients should be instructed to report the number of trips to the toilet when the patient had a bowel movement (including passing feces, blood alone, blood and mucus, or mucus only).
Reference remission stool frequency (in a 24-hour period)	• The patient should be asked to identify at the screening visit how many stools he or she had in a 24-hour period when in remission from ulcerative colitis (UC). • If the patient does not report achieving remission, then the patient should be asked to identify the number of stools he or she had in a 24-hour period before initial onset of signs and symptoms of UC. If the patient has not experienced remission, this value will be used to calculate the stool frequency endpoint. – Sponsors should record if the reference remission stool frequency is based on reported stool frequency when the patient was in remission or reported stool frequency before initial onset of signs and symptoms of UC. – Both the remission and the pre-UC stool frequency should be collected at baseline when feasible. This allows exploration of the natural history of prediagnosis stool frequency versus remission stool frequency.
Most severe category of rectal bleeding (in a given 24-hour period)	• Patients should be instructed to indicate the most severe category that describes the amount of blood they had in their stools for a given 24-hour period. • Categories of rectal bleeding should be defined as follows (in order of increasing severity): – Not applicable; no bowel movement** – No blood seen – Stool has streaks of blood – Stool has more than just streaks of blood – Blood alone passed
Completion of event log or diary	• Patients should be trained on the completion of the event log or diary. • The instructions for completion of the stool frequency and rectal bleeding assessments should be incorporated into the event log or diary for ready reference by the patient.
Recording of rectal bleeding and stool frequency assessments	• Patients should be directed to capture their rectal bleeding and stool frequency assessments in event logs or daily diaries for a minimum of 7 days before each visit.

Source: Ulcerative Colitis: Developing Drugs for Treatment. FDA Guidance for Industry, 2022

Appendix 7 Inflammatory Bowel Disease Questionnaire (IBDQ)

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your ulcerative colitis, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem. Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom (bathroom, toilet)? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME

5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom (bathroom, toilet) close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much a problem have you had maintaining or getting to, the weight you would like to be at. Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME

5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom (toilet) even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling

of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
b A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from:

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

Appendix 8 Clinical Laboratory Tests

Clinical Laboratory Assessments		
Laboratory Assessments	**Parameters**	
Hematology	Hematocrit Hemoglobin Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Packed cell volume (PCV) Platelet count Red blood cell (RBC) count	White blood cell (WBC) count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Biochemistry	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Blood urea nitrogen (BUN; urea) Bicarbonate Calcium Chloride Creatine kinase (CK) Creatinine Direct bilirubin	Glucose C-reactive protein Inorganic phosphate Lactate dehydrogenase Potassium Sodium Total bilirubin Total cholesterol (fractions) Total protein Triglycerides Uric acid
Pregnancy Testing	In women of childbearing potential only: • Serum human chorionic gonadotropin (hCG) pregnancy test (at Screening only) • Urine pregnancy (all visits except Screening)	
Follicle-stimulating Hormone (FSH)	In postmenopausal woman with at least 12 months of amenorrhea without an alternative medical cause (at Screening only)	
Urinalysis	Bilirubin Blood Glucose Ketones Leukocytes Nitrites	pH Protein Specific gravity Urobilinogen Microscopy (at discretion of Investigator based on urinalysis results)

Clinical Laboratory Assessments	
Laboratory Assessments	**Parameters**
Viral Serology	Hepatitis B surface antigen (HBsAg) Hepatitis B surface antibody (HBsAb) Hepatitis B core antibody (HBcAb) Reflex hepatitis B DNA testing in subjects who are $HBcAb^{+}$, $HBsAg^{-}$, and $HBsAb^{-}$ Hepatitis C antibody and reflex hepatitis C RNA testing in subjects who are positive for hepatitis C antibodies Human immunodeficiency virus (HIV) 1 and HIV 2 antibodies
Tuberculosis (TB) Screening	QuantiFERON-TB Gold In-Tube® (third generation test), QuantiFERON-TB Gold Plus® (QFT-Plus; fourth generation test), or a subsequent generation of QuantiFERON-TB tests may be used for TB Screening. Early generation QuantiFERON-TB tests are not to be used. If the test is indeterminate, it can be retested only once. Chest x-ray or computerized tomography (CT) scan
Biomarkers	Circulating blood biomarkers (including, but are not limited to, TNFα, IFNγ, IL-6, and IL-12) Immunophenotyping Calprotectin
Other	*Clostridioides difficile* toxin stool assay

NOTES:

- Please see the Schedule of Activities (Table 1) for laboratory tests time points.
- All blood samples must be drawn prior to administration of the study treatment on Day 1, unless otherwise specified. The date and exact time of sample collection must be recorded.
- At sites where the tuberculin skin test is mandated by local health authorities, the tuberculin skin test should also be performed. Only the QuantiFERON-TB result will be considered for subject eligibility.

Abbreviations: IL: interleukin; IFN: interferon; PD-1: program cell death protein 1; TNF: tumor necrosis factor

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