Clinical Study Protocol	
Study Intervention	Brazikumab
Study Code	D5272C00001 (Legacy #3151-201-008)
Version	Amendment 6 v7.0
Date	10Mar2022

Redacted for Public Disclosure

A 54-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 2 Study to Assess the Efficacy and Safety of Brazikumab in Participants with Moderately to Severely Active Ulcerative Colitis (Expedition Lead-in)

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: Study D5272C00001 (Legacy #3151-201-008)

Amendment Number: 6
Study Intervention: Brazikumab, placebo
Study Phase: Phase 2

Short Title: Phase 2 Dose-finding UC Study

Acronym: Expedition Lead-in

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

AstraZeneca Protocol D5272C00001 (Legacy #3151-201-008)

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	March 2022
Amendment 5	March 2021
Amendment 4	August 2020
Amendment 3	March 2019
Amendment 2	October 2018
Amendment 1	June 2018
Original Protocol	April 2018

Amendment 6 [10-March-2022]

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.**Overall Rationale for the Amendment:**

In the original protocol, the study intervention for CCI was not provided by AstraZeneca. The preparation was handled by an unblinded pharmacist (or appropriately qualified individual). In order to commence central blinded supply and preparation for CCI CCI, the presented changes include the introduction of placebo vials. The inclusion of placebo vials will support study integrity by enabling blinded qualified site personnel to prepare the study intervention for both brazikumab and placebo.

The remaining changes relate to providing further clarity on protocol text or removing unnecessary procedures relating to collection of participant assessments.

The granular summary of changes in the tabular format is included below.

Section # and Name	Description of Change	Brief Rationale
Throughout	Corrected typographical errors.	Corrected to improve accuracy.
Throughout	Removed the study number of the OLE brazikumab study.	Removed to avoid needing additional updates to the D5272C00001 study protocol if future changes occur on the open-label study number.
Section 1.1 Synopsis	Added table footnote clarifying that primary and secondary efficacy endpoints will be evaluated in the BM+ and BM- populations.	Revisions were made for clarity.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 1	Added window for Screening Period. Replaced -35 with Visit 1 for the first visit heading.	Clarification that Screening maybe up to 35 days.
Section 1.3 Schedule of Activities, Table 1	Revised ePRO to PRO for pMS notes.	Revision made to inform sites that PRO scores calculated at Screening Visit 1 are determined by patient recall and not through electronic device.
Section 1.3 Schedule of Activities, Table 1	Changed from Day -35 to Visit 1 in Physician's Global Assessment notes.	Revisions were made to align with change from Day -35 to Visit 1 for the first visit heading.
Section 1.3 Schedule of Activities, Table 1 and Section 8.1.7 PRO Assessments	Added notes describing time periods of ePRO data and Visit 2 in relation to the Screening endoscopy.	Revisions were made for clarity.
Section 1.3 Schedule of Activities, Table 1	Added a footnote explaining that the term endoscopy refers to both colonoscopy and flexible sigmoidoscopy and specifying the timepoints each should be performed.	Revisions were made to clarify endoscopy terminology in the protocol.
Section 1.3 Schedule of Activities, Table 2	CCI [redacted]	Revision was made to correct errors. No dosing is associated with these visits, negating a need for postdose injection-site reaction assessment.
Section 1.3 Schedule of Activities, Table 2	Removed timepoints for QFT-TB testing during the Treatment Period.	Investigators will take a risk-based approach to repeat QFT-TB testing through the study based upon participant presentation.
Section 1.3 Schedule of Activities, Table 2	Removed timepoints for HBV, HCV, and HIV screening during the Treatment Period.	Investigators will take a risk-based approach to repeat HBV, HCV, and HIV screening through the study based upon participant presentation.
Section 1.3 Schedule of Activities, Table 2	Merged PK sampling information from 3 rows to 2 rows, and included more notes.	Simplification of PK sampling instructions for sites.
Section 1.3 Schedule of Activities, Table 2	Removed timepoints for testing of stool for *Clostridium difficile* during the Treatment Period.	Investigators will take a risk-based approach to repeat *C. difficile* testing throughout the study based upon participant presentation.
Section 1.3 Schedule of Activities, Table 2	Added study intervention note that first dose should not be more than 14 days after the Screening colonoscopy.	Revision was made for detailed guidance and aligns with Section 5.1.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 3	Added window to the follow-up visits.	Revision was made to give sites and participants flexibility in visit scheduling, increasing the opportunity to complete safety follow-up assessments.
Section 1.3 Schedule of Activities, Table 3	Added timepoint for serum for ADA during the Safety Follow-up Period.	End-of-study sample was added for ADA analysis when the majority of brazikumab has cleared from circulation.
Section 3 Objectives and Endpoints, Table 5	Added an additional (exploratory) objective needed to cover any/all BM analyses to be completed, even if not planned for inclusion in the clinical study report.	Biomarker sampling is mandatory per the SoA and ICF, and planned sample analysis is well defined (Section 8.6). This addition is to ensure intended use is appropriately reflected in the study objectives.
Section 3 Objectives and Endpoints, Table 5	Added a footnote explaining that additional exploratory efficacy endpoints may be described, with corresponding statistical analyses in the SAP.	Addition made so that the study team may identify more exploratory variables to analyze.
Section 3 Objectives and Endpoints, Table 5	Added a footnote explaining that exploratory endpoints will be evaluated in the BM- populations as well.	Revisions were made for clarity.
Section 5.1 Inclusion Criteria, #11	Revised the QFT-TB test criteria for study inclusion.	Participants with repeated indeterminate QFT-TB testing to be excluded from the study, as TB status cannot be determined, reducing risk to potential participants.
Section 6.1 Study Interventions Administered Section 6.1.3 Study Supplies Section 6.2 Preparation/Handling/ Storage/Accountability	Introduced placebo vials to be provided centrally for placebo CCI CCI.	The inclusion of CCI will support study integrity by enabling blinded qualified site personnel to prepare the study intervention for both brazikumab and placebo.
Section 6.1 Study Interventions Administered, Table 7	Added a footnote explaining instructions for preparation of CCI CCI	Revisions were made for more detailed guidance.
Section 6.1 Study Interventions Administered	Added descriptions of brazikumab and placebo for CCI and “all formulations” subheading.	Added for consistency with other protocol documents so there is no discrepancy in language.

Section # and Name	Description of Change	Brief Rationale
Section 6.1.1 Dosing Regimen, Section 6.1.1.2 SC Administration, Section 6.2 Preparation/Handling/ Storage/Accountability, Section 6.3 Measures to Minimize Bias: Randomization and Blinding, Section 6.4 Study Intervention Compliance	Revised the language describing the involvement of the individual(s) who will be administering the IP.	Revisions were made to outline the modified requirement for blinded staff given the introduction of the placebo CCI to the study.
Section 6.1.1.2 SC Administration, Section 6.2 Preparation/Handling/ Storage/Accountability	Additional injection sites for CCI CCI were added.	CCI were added to reduce the risk of AEs when the same site is repeatedly used, and to collect safety and tolerability information for different injection sites.
Section 6.1.3 Study Supplies	Revised from CCI	Fixed typo.
Section 6.2 Preparation/Handling/ Storage/Accountability	Updated the volumes of CCI CCI that will be removed from the CCI and replaced with brazikumab and placebo, in preparation for the CCI	With the introduction of the placebo CCI and blinded pharmacist, it is necessary to use 1 brazikumab CCI and 1 placebo CCI during preparation of CCI dose to ensure blinding between dose levels, as 2 brazikumab CCI are required for CCI
Section 6.2 Preparation/Handling/ Storage/Accountability	Revised the language for the time and temperature of the CCI CCI. Included a standard clause regarding storing CCI	Further investigation has determined that an equilibration time of at least 40 minutes at room temperature is required for CCI
Section 6.3 Measures to Minimize bias: Randomization and Blinding	A sentence was added explaining that regular transfers of the live randomization schema will be performed from the IxRS vendor to the bioanalytical lab until randomization is complete for correct identification of brazikumab participants for PK analyses.	AstraZeneca's standard process does not analyze placebo samples. Therefore, the Bioanalytical Lab will need the random live list to identify placebo samples. Details are added to improve clarity and transparency of process that affect the blind.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.3 Corticosteroid Study Guidelines	Removed text to clarify CS tapering guidance.	To maintain participant safety by clarifying that clinical status should be considered before considering CS taper.
Section 6.5.4 Prohibited Interventions During the Study	Added details to clarify the duration to avoid prohibited therapies.	To maintain participant safety by clarifying that prohibited medications are prohibited throughout the study including the Safety Follow-up Period.
Section 8.1.1 Modified Mayo Score	Revised the language to state that the participant's average evening eDiary data should be recorded over the most recent 3 days of allowable data within 7 days of colonoscopy, and an additional 7 days of evening diary data area required for the Screening colonoscopy.	Ensure consistency of mMS calculation during the study.
Section 8.1.2 Partial Mayo Score	Added language that the calculation of Stool Frequency and Rectal Bleeding scores will be based on the participant's recall of the previous 7 days.	Clarify that investigators use participant recall to calculate pMS at Screening.
Section 8.1.3 Endoscopy	Revised the language to state that video recordings will be performed with biopsies taken upon endoscopic withdrawal.	Ensures that endoscopic Mayo score will not be negatively impacted by the biopsy procedure.
Section 8.1.3 Endoscopy	Revised the language to remove marking and labelling of bowel segments.	Language updated to ensure consistency between protocol and endoscopy training and procedures to provide clarity for investigators and ensure best practice.
8.1.7 PRO Assessments	Added language that a minimum of 2 consecutive weeks of ePRO data is required prior to the Screening colonoscopy to meet eligibility requirements.	Added to provide clarity that a minimum Run-in Period is required to allow participants to gain familiarity with the ePRO device, daily completion to facilitate robust baseline Mayo score generation, and consistent data throughout the study.
Section 8.1.11 Participant Qualitative Interview Sub-study	Added extra English-speaking countries to sub-study.	Added to ensure recruitment target to sub-study will be met.
Section 8.2.4 Clinical Safety Laboratory Assessments	Clarified that laboratory values requiring a change in participant management or considered clinically significant will be recorded in the eCRF.	Revision was made to align with the data collection methods within AstraZeneca.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.4 Clinical Safety Laboratory Assessments, Table 12	Removed aPTT/prothrombin time/INR assessments from the hematology panel for the clinical laboratory assessments.	Coagulopathy is adequately assessed by the Hy's Law kit.
Section 8.3.8 Reporting of SAEs	Revised the language of safety reporting via EDC.	Revision was made to align with current AstraZeneca standard safety reporting.
8.3.9.1 Maternal Exposure	Revised the language of pregnancy reporting.	Revision was made to align with current AstraZeneca pregnancy reporting.
Section 9.3 Populations for Analyses	Added language describing the Full Analysis Set and Maintenance Period population.	Added to provide clarity of the implications of the removal of treatment arms on the analysis populations.
Section 9.4.1 General Considerations	Revised language on the analyses that will be performed with the study data collected prior to Protocol Amendment 5.	Details were added to improve clarity.
Section 9.4.2.2 Efficacy Analyses	Revised language on the analyses that will be performed and the statistics that will be presented.	Revision was made to align modifications of the outputs from the primary analysis Cochran-Mantel-Haenszel test with AstraZeneca standards and guidance.
Appendix F Procedures for Tuberculosis Testing from Screening	Revised the procedures for TB testing from Screening.	Aligned with updated TB inclusion criteria; maintain risk-based monitoring of participants especially in high-risk countries/regions.

ADA = anti-drug antibody(ies); AE = adverse event; aPTT = activated partial thromboplastin time; BM- = biomarker serum IL-22 concentrations below a pre-established cutoff; BM+ = biomarker serum IL-22 concentrations at or above a pre-established cutoff; CS = corticosteroid; *C. difficile* = *Clostridium difficile*; eCRF = electronic case report form; eDiary = electronic diary; EDC = electronic data capture; ePRO = electronic patient-reported outcomes; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; INR = International Normalized Ratio; IP = investigational product; CCI [redacted]; IxRS = interactive voice/web response system; mMS = modified Mayo score; OLE = open-label extension; PK = pharmacokinetic(s); pMS = partial Mayo score; PRO = patient-reported outcomes; QFT-TB = QuantiFERON-TB; SAP = Statistical Analysis Plan; CCI [redacted] SoA = schedule of activities; TB = tuberculosis.

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 3
TABLE OF CONTENTS 9
1 PROTOCOL SUMMARY 15
1.1 Synopsis 15
1.2 Schema 21
1.3 Schedule of Activities 23
2 INTRODUCTION 34
2.1 Study Rationale 34
2.2 Background 35
2.3 Benefit/Risk Assessment 38
3 OBJECTIVES AND ENDPOINTS 41
4 STUDY DESIGN 48
4.1 Overall Design 48
4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis 49
4.2 Scientific Rationale for Study Design 49
4.3 Justification for Dose 50
4.4 End of Study Definition 52
5 STUDY POPULATION 53
5.1 Inclusion Criteria 53
5.2 Exclusion Criteria 56
5.3 Lifestyle Considerations 60
5.3.1 Meals and Dietary Restrictions 61
5.3.2 Caffeine, Alcohol, and Tobacco 61
5.4 Screen Failures 61
6 STUDY INTERVENTION 62
6.1 Study Interventions Administered 62
6.1.1 Dosing Regimen 63
6.1.1.1 CCI [redacted] 64
6.1.1.2 CCI [redacted] 64
6.1.2 Study Intervention Administration Rescheduling 66
6.1.3 Study Supplies 66
6.2 Preparation/Handling/Storage/Accountability 67
6.3 Measures to Minimize Bias: Randomization and Blinding 69
6.4 Study Intervention Compliance 70
6.5 Concomitant Therapy 70

6.5.1 Prior Medications Requiring Stable Dose Regimen 70
6.5.2 Permitted Concomitant Treatments 71
6.5.3 Corticosteroid Study Guidelines 72
6.5.4 Prohibited Interventions During the Study 73
6.5.5 Rescue Treatment 74
6.6 Dose Modification 76
6.7 Intervention After the End of the Study 76
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 77
7.1 Discontinuation of Study Intervention 77
7.2 Participant Withdrawal from the Study 79
7.3 Lost to Follow-up 80
8 STUDY ASSESSMENTS AND PROCEDURES 81
8.1 Efficacy Assessments 81
8.1.1 Modified Mayo Score (mMS) 81
8.1.2 Partial Mayo Score (pMS) 83
8.1.3 Endoscopy 83
8.1.4 Colon Mucosal Biopsies 84
8.1.5 Geboes Histological Index 84
8.1.6 Robarts Histopathology Index 84
8.1.7 PRO Assessments 85
8.1.8 Bowel Movement eDiary 85
8.1.9 Evening Diary 86
8.1.10 Site Visit Assessments 86
8.1.11 Participant Qualitative Interview Sub-study 87
8.2 Safety Assessments 88
8.2.1 Physical Examinations 88
8.2.2 Vital Signs 88
8.2.3 Electrocardiograms 89
8.2.4 Clinical Safety Laboratory Assessments 89
8.3 AEs and SAEs 91
8.3.1 Time Period and Frequency for Collecting AE and SAE Information 91
8.3.2 Follow-up of AEs and SAEs 91
8.3.3 Causality Collection 92
8.3.4 AEs Based on Signs and Symptoms 92
8.3.5 AEs Based on Examinations and Tests 93
8.3.6 Hy's Law 93
8.3.7 Disease Under Study 93
8.3.8 Reporting of SAEs 94
8.3.9 Pregnancy 94
8.3.9.1 Maternal Exposure 94
8.3.9.2 Paternal Exposure 95
8.3.10 Adverse Events of Special Interest 95
8.3.10.1 CCI [redacted] 95

8.3.10.2 Malignancies 96
8.3.10.3 Hypersensitivity Reactions (Including Anaphylaxis) 96
8.3.10.4 Infections 96
8.3.11 Medication Error 97
8.4 Overdose 98
8.5 Human Biological Samples 98
8.5.1 Pharmacokinetics 99
8.5.1.1 Determination of Drug Concentration 99
8.5.2 Immunogenicity Assessments 99
8.5.3 Pharmacodynamics 100
8.6 Human Biological Sample Biomarkers 100
8.6.1 Collection of Mandatory Samples for Biomarker Analysis 100
8.7 Optional Genomics Initiative Sample 101
8.8 Healthcare Resource Utilization 101
9 STATISTICAL CONSIDERATIONS 102
9.1 Statistical Hypotheses 102
9.2 Sample Size Determination 102
9.3 Populations for Analyses 103
9.4 Statistical Analyses 103
9.4.1 General Considerations 104
9.4.2 Efficacy 105
9.4.2.1 Efficacy Endpoints 105
9.4.2.2 Efficacy Analyses 107
9.4.3 Safety 107
9.4.3.1 Adverse Events 107
9.4.3.2 Clinical Laboratory Assessments 108
9.4.3.3 Vital Signs 108
9.4.3.4 Electrocardiograms 109
9.4.4 Other Analyses 109
9.4.4.1 Pharmacokinetic Analyses 109
9.4.4.2 Biomarker Analyses 109
9.5 Interim Analyses 110
9.6 Data Safety Monitoring Board 110
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 111
11 REFERENCES 197

LIST OF FIGURES

Figure 1 Study Design 22

LIST OF TABLES

Table 1 Schedule of Activities – Screening Period 23
Table 2 Schedule of Activities – Treatment Period 26
Table 3 Schedule of Activities – Safety Follow-up Period 32
Table 4 Schedule of Activities – PRO Assessments (in clinic and at home) 33
Table 5 Objectives and Endpoints 42
Table 6 Summary of Brazikumab Cynomolgus Monkey to Human Margins of Exposure 51
Table 7 Study Interventions 62
Table 8 Medications Requiring Stable Dose Regimen 70
Table 9 Permitted Concomitant Treatments 71
Table 10 Corticosteroid Tapering Guidelines 73
Table 11 Mayo Scoring System for Assessment of Ulcerative Colitis Activity 82
Table 12 Protocol-required Safety Laboratory Assessments 90
Table 13 Primary Estimand 102
Table 14 Populations for Analysis 103
Table 15 Efficacy Endpoints 106

LIST OF APPENDICES

Appendix A Regulatory, Ethical, and Study Oversight Considerations 112
Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 117
Appendix C Handling of Human Biological Samples 123
Appendix D Optional Genomics Initiative Sample 125
Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law 128
Appendix F Procedures for Tuberculosis Testing from Screening 134
Appendix G Patient-reported Outcomes Questionnaires, Descriptions, and Instructions 135
Appendix H Standard Discontinuation Criteria 157
Appendix I Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis 159
Appendix J Abbreviations 162
Appendix K Protocol Amendment History 167

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A 54-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 2 Study to Assess the Efficacy and Safety of Brazikumab in Participants with Moderately to Severely Active Ulcerative Colitis (Expedition Lead-in)

Short Title: Phase 2 Dose-finding UC Study

Rationale:

Ulcerative colitis is a chronic, relapsing-remitting, inflammatory disease of the gastrointestinal tract. Some patients may have persistent clinically active disease. The current treatment options for patients with moderate to severe UC, refractory to standard therapies that include 5-aminosalicylates, glucocorticosteroids, 6-mercaptopurine, azathioprine, methotrexate, anti-TNFα monoclonal antibodies, and vedolizumab, are limited. Brazikumab is being developed as a treatment for IBD to reduce intestinal inflammation and improve signs and symptoms.

The present study (D5272C00001/Legacy #3151-201-008) aims to evaluate brazikumab in patients with moderately to severely active UC and will include assessments of clinical responses as demonstrated by improvement of symptoms and of colonic mucosal appearance as observed on endoscopy.

Objectives and Endpoints

The objectives, endpoints, and estimands are presented below.

Objective	Endpoint	Population	Intercurrent Event Strategy	Population-level Summary (Analysis)
Primary				
To compare the efficacy of brazikumab with that of placebo to achieve clinical remission	Clinical remission defined as: • mMS at Week 10: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Responder counts (number of responders) and percentages (proportion of responders)
Secondary				
To compare the efficacy of brazikumab with that of placebo to achieve sustained clinical remission	Sustained clinical remission defined as: • mMS at both Week 10 and Week 54: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary

Objective	Endpoint	Population	Intercurrent Event Strategy	Population-level Summary (Analysis)
To compare the efficacy of brazikumab with that of placebo to achieve CS-free clinical remission	CS-free clinical remission defined as: • mMS at Week 54 for participants who are CS-free for at least the last 12 weeks before the assessment at Week 54: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 54: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve clinical response	Clinical response is defined as: • Reduction in mMS ≥ 2 points from baseline AND ≥ 30% from baseline AND a decrease in the rectal bleeding score ≥ 1 point from baseline or a score of 0 or 1 at Week 10	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic improvement	Endoscopic improvement is defined as: • Endoscopy subscore ≤ 1 at Week 10	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary
To evaluate the PK and immunogenicity of brazikumab	Population PK model of serum concentrations of brazikumab and analysis for serum anti-brazikumab antibodies	Participants with moderately to severely active UC		

Objective	Endpoint	Population	Intercurrent Event Strategy	Population-level Summary (Analysis)
To characterize the exposure-response relationships of brazikumab	Exposure-response model linking primary endpoints to metrics of model-predicted individual brazikumab exposures	Participants with moderately to severely active UC		
Safety				
To evaluate the safety and tolerability of brazikumab	AEs, clinical laboratory values, vital signs, physical exams, ECGs	Participants with moderately to severely active UC		

All primary and secondary efficacy endpoints will be evaluated in the BM+ and BM- populations as well.
AE = adverse event; CS = corticosteroid; ECG = electrocardiogram; mMS = modified Mayo score; NRI = non-responder imputation; PK = pharmacokinetic(s); UC = ulcerative colitis.

For exploratory objectives, endpoints, and estimands, see Section 3 of the protocol.

Overall Design

Global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2, 54-week study.

The purpose of this study is to assess efficacy and safety of brazikumab in participants with moderately to severely active UC. After meeting all eligibility criteria, participants will be randomized in a 1:1:1 ratio to receive study intervention CCI CCI during the Induction Period (up to Week 10). Participants will be stratified according to prior treatment experience, biological-naïve or prior biological use (failed or were intolerant to prior biological treatment). Following Induction, participants receiving brazikumab will be re-randomized 1:1 (stratified according to the same stratification factors listed for the Induction Period and by induction dose) at Week 10 to receive either CCI participants randomized into the Induction Period placebo treatment arm will receive placebo CCI in the Maintenance Period.

The study will be unblinded and the primary analysis for the study will be conducted after the last participant has completed the Week 10 visit. AstraZeneca personnel who are directly involved with the conduct of the study, study site personnel, as well as participants will remain blinded to the treatment assignment for individual participants until the completion of the study. Details on what roles will remain blinded and how trial integrity will be maintained will be documented separately.

Participants who complete the study or discontinue participation due to lack of efficacy after Week 10 may be eligible to enroll into an open-label extension study.

Disclosure Statement: This is a global (up to approximately CCI sites), multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2, 54-week study with 3 arms that is participant and investigator blinded.

Number of Participants:

Approximately CCI participants will be randomized to the study.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned/assigned in the study, are considered "screen failures," unless otherwise specified by the protocol.

Intervention Groups and Duration:

Intervention groups:

- Brazikumab low dose: CCI [redacted]
- Brazikumab high-dose: CCI [redacted]
- Placebo: CCI [redacted]

Investigation groups for participants randomized per the previous protocol (D5272C00001 [Legacy #3151-201-008] Amendment 4) will remain in intervention group assigned at the time of randomization.

Study Duration: Following a Screening Period of up to 5 weeks, the study duration is up to 68 weeks, consisting of a 54-week Treatment Period (last dose of study intervention is at Week 50) and an 18-week post-last brazikumab/brazikumab placebo dose (Week 50) Safety Follow-up Period. For participants who qualify and enroll into an OLE study of brazikumab, the Safety Follow-up Period will not be applicable.

Data Monitoring Committee: Yes (independent DSMB)

Statistical Methods

The primary null hypothesis is that the clinical remission rates at Week 10 derived from mMS (primary efficacy endpoint) for each of the CCI brazikumab CCI and IV brazikumab CCI [redacted] groups is not different from that for the CCI placebo treatment group. The alternative hypothesis for each of the brazikumab treatment groups is that the clinical remission rates associated with the brazikumab treatment group is different from that for the placebo treatment group.Brazikumab and placebo responder rates are assumed to be 22.4% and 5.4%, respectively, considering previous study results and available external data, along with the expected ratio of biologic naïve to biologic intolerant of refractory participants. Based on these assumptions, a continuity-corrected Cochran-Mantel-Haenszel test of odds ratio = 1 for 2 × 2 tables will have 81% power to detect an odds ratio of 5.3 using a 2-sided 5% test level, when the sample size in each group is 75 and given pre-specified stratum and response proportions.

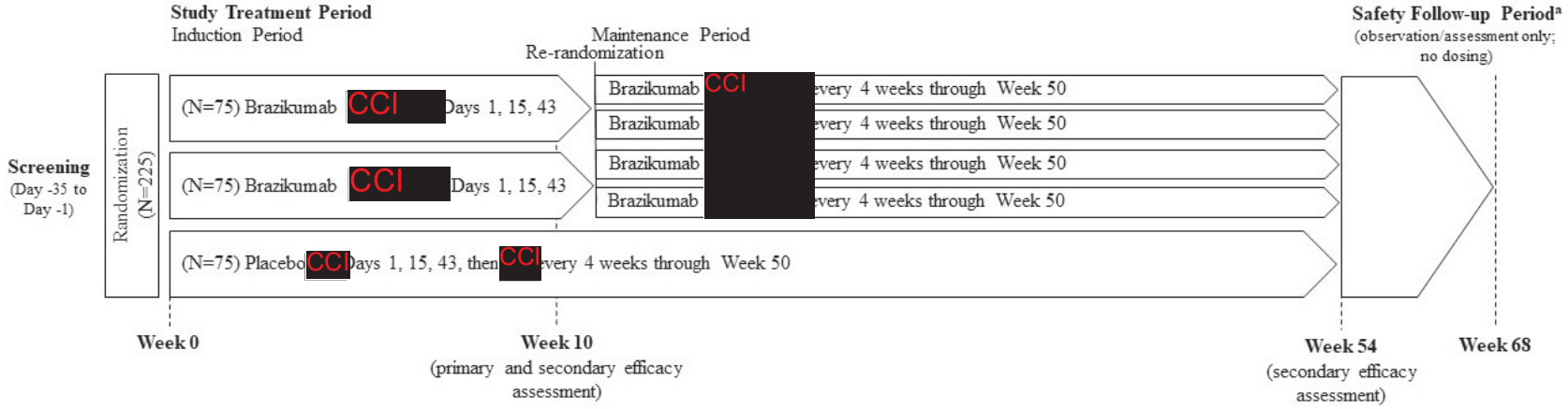
The efficacy analyses will be based on the Full Analysis Set. All statistical tests will be 2-sided hypothesis tests. All CIs will be 2-sided 95% CIs, unless stated otherwise.For all responder endpoints, participants who do not meet responder criteria, either due to missing assessments or early discontinuation, are considered non-responders for analysis purposes.

This method will be applied to both primary and secondary efficacy endpoints. Considering that this is not a confirmatory study, no multiplicity adjustments are planned.

1.2 Schema

A study schematic is provided in Figure 1.

Figure 1 Study Design



[a] The Safety Follow-up Period is calculated to be 18 weeks post-last double-blind brazikumab/brazikumab placebo dose (Week 50).
CCI .

1.3 Schedule of Activities

Study procedures are to be completed prior to study intervention administration if possible. Any PROs should be completed prior to other assessments.

Separate SoAs are presented for the Screening Period (Table 1), the Treatment Period (Table 2), the Safety Follow-up Period (Table 3), and for the PROs (Table 4).

Table 1 Schedule of Activities – Screening Period

Visit number	**1**			
Visit name, window	**Screening, up to 35 days (+3 days)**			
Visit	**Visit 1**	**Colonoscopy -14 to -7**	**Notes**	**Details in CSP section or appendix**
Activities				
Informed consent	X			5.1 and 8.1.11
Inclusion and exclusion criteria	X	X	Verify all available eligibility criteria prior to endoscopy, including Mayo rectal bleeding score of ≥ 1 and stool frequency ≥ 1	5.1 and 5.2
Demographics	X			
Medical history (including surgical history and UC history)	X		Includes substance use	
Physical examination	X			
12-lead ECG	X			
Vital signs, weight, and height	X			5.1, 5.2, and 8.2.1
Laboratory assessments			Laboratory assessments may be re-tested once per investigator's discretion.	
Serum chemistry, hematology, CRP	X			8.2.4
Serum pregnancy test (WOCBP only)	X		For women not of childbearing potential, FSH if applicable	Inclusion criteria #8 and #9 and 8.2.4
HBV, HCV, and HIV screening	X			8.2.4
Urinalysis	X			8.2.4
QFT-TB test	X		Participants with an indeterminate QFT-TB test result are to have the test repeated during Screening.	Inclusion criterion #11 and Appendix F

Visit number	**1**			
Visit name, window	**Screening, up to 35 days (+3 days)**			
Visit	**Visit 1**	**Colonoscopy -14 to -7**	**Notes**	**Details in CSP section or appendix**
Chest x-ray (if required)	X			Inclusion criterion #11 and Appendix F
Serum sample for IL-22	X			8.5
Stool for *C. difficile* test	X		Must be collected prior to start of bowel prep for colonoscopy.	8.2.4
Stool for fecal calprotectin and fecal lactoferrin	X		Must be collected prior to start of bowel prep for colonoscopy.	8.6.1
Efficacy assessments				
Provide PRO device and instructions	X			Table 4 and 8.1.7
Check ePRO compliance		X	Confirm compliance on ePRO prior to bowel prep for colonoscopy	Table 4, 8.1.7, and 8.1.9
Mayo score – partial (p) or modified (m)	P	M	Partial Mayo score to be calculated based upon participant recall of previous 7 days PRO data (stool frequency and rectal bleeding) and PGA. Modified Mayo score calculated from ePRO (stool frequency and rectal bleeding) over the most recent 3 days of allowable data, within 7 days of the colonoscopy.	8.1.1 and 8.1.2
Physician's Global Assessment	X	X	If PGA is not possible at the same time as the endoscopy visit (if endoscopy suite is at another site), the PGA score from Visit 1 may be used.	8.1.1
Endoscopy, colon mucosal biopsies [a]		X	A minimum of 2 consecutive weeks of ePRO data is required prior to colonoscopy. All other Screening assessments results should be available and reviewed before endoscopy and biopsies. Visit 2 (Week 0) should not be more than 14 days after the colonoscopy.	8.1.3 and 8.1.4
Safety assessments				
AEs/SAEs	X	X		8.3
Concomitant medication	X			6.5

[a] The term 'endoscopy' refers to both colonoscopy and flexible sigmoidoscopy. A colonoscopy must be performed at Screening but a flexible sigmoidoscopy can be performed, as clinically indicated, at other timepoints in the study.

AE = adverse event; *C. difficile* = *Clostridium difficile*; CRP = C-reactive protein; CSP = clinical study protocol; ECG = electrocardiogram; ePRO = electronic patient-reported outcomes; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IL = interleukin; PGA = Physician's Global Assessment; PRO= patient-reported outcomes; QFT-TB = QuantiFERON-TB; SAE = serious adverse event; TB = tuberculosis; UC = ulcerative colitis; WOCBP = women of childbearing potential.

Table 2 Schedule of Activities – Treatment Period

Procedure	Induction period					Maintenance period											UNS [a]	ET or ED		
Visit number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**				
Visit name	**W0**	**W2**	**W4**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W30**	**W34**	**W38**	**W42**	**W46**	**W50**	**W54**				
Visit day and window (days) [b]	**1**	**15 ±3**	**29 ±3**	**43 ±3**	**71 ±3**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±7**	**211 ±7**	**239 ±7**	**267 ±7**	**295 ±7**	**323 ±7**	**351 ±7**	**379 ±7**			**Notes**	**Details in CSP Section or Appendix**
Review eligibility criteria	X																			5.1 and 5.2
Efficacy assessments																				
Review ePRO compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	eDiary assessment at-home and at site	Table 4, 8.1.7, and 8.1.9
Select visit date on the handheld device for the scheduled visit assessments; confirm that all PRO assessments have been completed	X			X	X		X			X			X			X		X		Table 4 and 8.1.10
Remind participants selected for qualitative sub-study interview															X					

Procedure	Induction period					Maintenance period											UNS [a]	ET or ED	Notes	Details in CSP Section or Appendix
Visit number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**				
Visit name	**W0**	**W2**	**W4**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W30**	**W34**	**W38**	**W42**	**W46**	**W50**	**W54**				
Visit day and window (days) [b]	**1**	**15 ±3**	**29 ±3**	**43 ±3**	**71 ±3**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±7**	**211 ±7**	**239 ±7**	**267 ±7**	**295 ±7**	**323 ±7**	**351 ±7**	**379 ±7**				
Mayo score, including endoscopy and colon mucosal biopsies					X											X	X	X		8.1.1, 8.1.2, and 8.1.4
Physician's Global Assessment	X			X	X		X			X			X			X	X	X		8.1.1
Safety assessments																				
Physical examination including EIM	X	X		X	X		X			X			X			X	X	X		8.2.1
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2.2
12-lead ECG	X				X					X						X		X		8.2.3
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.3
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.5
Assessment of CCI	CCI [redacted]																			

Procedure	Induction period					Maintenance period											UNS [a]	ET or ED		
Visit number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**				
Visit name	**W0**	**W2**	**W4**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W30**	**W34**	**W38**	**W42**	**W46**	**W50**	**W54**				
Visit day and window (days) [b]	**1**	**15 ±3**	**29 ±3**	**43 ±3**	**71 ±3**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±7**	**211 ±7**	**239 ±7**	**267 ±7**	**295 ±7**	**323 ±7**	**351 ±7**	**379 ±7**			**Notes**	**Details in CSP Section or Appendix**
Laboratory assessments																				
Serum chemistry, hematology, and urinalysis	X		X		X					X						X	X	X		8.2.4
CRP	X			X	X					X						X	X	X		8.2.4
Urine pregnancy test performed locally (WOCBP only)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2.4
PK and BMs sampling																				
Predose PK blood sample	X	X		X	X	X				X									Note the exact time and date of sampling	8.5.1

Procedure	Induction period					Maintenance period											UNS [a]	ET or ED	Notes	Details in CSP Section or Appendix
Visit number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**				
Visit name	**W0**	**W2**	**W4**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W30**	**W34**	**W38**	**W42**	**W46**	**W50**	**W54**				
Visit day and window (days) [b]	**1**	**15 ±3**	**29 ±3**	**43 ±3**	**71 ±3**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±7**	**211 ±7**	**239 ±7**	**267 ±7**	**295 ±7**	**323 ±7**	**351 ±7**	**379 ±7**				
PK blood samples (postdose or flexible)	X		X	X												X	X	X	Days 1 and 43: a sample at 1 hour and a sample at 2-4 hours postdose. On days without dosing, sampling time is flexible (but has to be recorded).	8.5.1
Serum for ADA	X			X	X					X						X	X	X		8.5.2
Serum for IL-22	X	X		X	X	X				X						X		X	Sample to be collected before dosing	8.6.1
CCI [redacted]																				8.6.1
Blood for investigative BMs	X	X		X	X	X				X						X		X		8.6.1

Procedure	Induction period					Maintenance period											UNS [a]	ET or ED		
Visit number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**				
Visit name	**W0**	**W2**	**W4**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W30**	**W34**	**W38**	**W42**	**W46**	**W50**	**W54**				
Visit day and window (days) [b]	**1**	**15 ±3**	**29 ±3**	**43 ±3**	**71 ±3**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±7**	**211 ±7**	**239 ±7**	**267 ±7**	**295 ±7**	**323 ±7**	**351 ±7**	**379 ±7**			**Notes**	**Details in CSP Section or Appendix**
PAXgene for whole blood RNA transcript profiling	X				X											X		X	Do not collect if whole blood transfusion within 120 days	8.6.1
Genomics Initiative optional, exploratory genetic sample	X																		Do not collect if whole blood transfusion within 120 days	8.7 and Appendix D
Stool for fecal calprotectin, fecal lactoferrin, and exploratory BMs	X				X					X						X	X	X	Must be collected prior to start of bowel prep for visits when colonoscopy is performed.	8.6.1
Study intervention administration																				
Randomization	X																			6.3

Procedure	Induction period					Maintenance period											UNS [a]	ET or ED		
Visit number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**				
Visit name	**W0**	**W2**	**W4**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W30**	**W34**	**W38**	**W42**	**W46**	**W50**	**W54**				
Visit day and window (days) [b]	**1**	**15 ±3**	**29 ±3**	**43 ±3**	**71 ±3**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±7**	**211 ±7**	**239 ±7**	**267 ±7**	**295 ±7**	**323 ±7**	**351 ±7**	**379 ±7**			**Notes**	**Details in CSP Section or Appendix**
Study intervention	IV	IV		IV	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC				First dose should not be more than 14 days after the Screening colonoscopy.	6.1

[a] Unscheduled visit: Not all assessments indicated for the unscheduled visit need to be performed. The assessments are to be performed at the discretion of the investigator, as clinically indicated. Assessments that are performed as part of an unscheduled visit may be used for evaluation of guidelines for rescue treatment (eg, endoscopy).

[b] The visit schedule will always be calculated from randomization visit date.

ADA = anti-drug antibody(ies); AE = adverse event; BM = biomarker; CRP = C-reactive protein; CSP = clinical study protocol; ECG = electrocardiogram; ED = early discontinuation of study intervention; eDiary = electronic diary; EIM = extra-intestinal manifestation; ePRO = electronic patient-reported outcomes; ET = early termination; IL = interleukin; CCI [redacted] PK = pharmacokinetic(s); PRO = patient-reported outcomes; RNA = ribonucleic acid; SAE = serious adverse event; CCI [redacted] UNS = unscheduled; W = Week; WOCBP = women of childbearing potential.

Table 3 Schedule of Activities – Safety Follow-up Period

Study period	18-Week safety follow-up		Notes	Details in CSP Section or Appendix
Visit name	**Follow-up 1**	**Follow-up 2**		
Visit day and window	**8 weeks post-last dose (±7 days)**	**18 weeks post-last dose (±7 days)**		
Safety assessments				
AEs/SAEs	X	X		8.3
Concomitant medications	X	X		6.5
Assessment of injection-site reactions	X	X		8.3.10.1
Physical examination	X	X		8.2.1
12-lead ECG	X	X		8.2.3
Vital signs and weight	X	X		8.2.2
Laboratory assessments				
Serum chemistry, hematology, and urinalysis	X	X		8.2.4
CRP	X	X		8.2.4
Urine pregnancy test performed locally (WOCBP only)	X	X		8.2.4
PK and BMs sampling				
PK blood sample	X	X		8.5.1
Serum for ADA	X	X		8.5.2
Serum for IL-22	X	X		8.6.1
CCI	X	X		8.6.1
Blood for investigative BMs	X	X		8.6.1
Stool for fecal calprotectin, fecal lactoferrin, and exploratory biomarkers	X			8.6.1

ADA = anti-drug antibody; AE = adverse event; BM = biomarker; CRP = C-reactive protein; CSP = clinical study protocol; ECG = electrocardiogram; IL = interleukin; CCI ; PK = pharmacokinetic(s); SAE = serious adverse event; WOCBP = women of childbearing potential.

All on-site PRO assessments will be completed at the site before any other study procedures are conducted.

Table 4 Schedule of Activities – PRO Assessments (in clinic and at home)

Instruments	Schedule [a]
Event-driven: Bowel Movement eDiary	Every day from the first Screening visit through Week 54; real-time entry after every bowel movement
Daily PRO: Evening eDiary: • mMS items (> normal number of bowel movements and rectal bleeding) • NRS items (abdominal pain, fatigue, tiredness, weakness, lack of energy, joint pain, and flatulence) • Entry of additional bowel movements not reported in real time	Every evening [b]. First assessment at home from the first Screening visit through Week 54
Site-collected PROs: IBDQ, FACIT-F, PGIS-UC	At Weeks 0, 6, 10, 18, 30, 42, and 54; also complete at ET/ED
Site-collected PRO: PGIC-UC	At Weeks 6, 10, 18, 30, 42, and 54; also complete at ET/ED
Site-collected PROs: EQ-5D-5L, SF-36v2	At site at Screening and Weeks 0, 10, 30, and 54
Other assessments: Qualitative participant interview	One-on-one phone interview after the participant completes the Week 54 visit. Select sites only: Participants will be introduced to the sub-study during the informed consent process. Sites will remind consented participants of upcoming interview in Qualitative Participant Interview Sub-study

[a] The visit schedule will always be calculated from randomization visit date.
[b] Evening is defined as 18:00 to 23:59.
ED = early discontinuation of study intervention; eDiary = electronic diary; EQ-5D-5L = European Quality of Life – 5 Dimensions; ET = early termination; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; IBDQ = Inflammatory Bowel Disease Questionnaire; mMS = modified Mayo score; NRS = Numeric Rating Scale; PGIC-UC = Patient Global Impression of Change – Ulcerative Colitis; PGIS-UC = Patient Global Impression of Severity – Ulcerative Colitis; PRO = patient-reported outcome; SF-36v2 = 36-item Health Survey Version 2.

2 INTRODUCTION

Ulcerative colitis is an idiopathic, chronic inflammatory disorder of the colonic mucosa, which starts in the rectum and generally extends proximally in a continuous manner through part of, or the entire, colon. Bloody diarrhea is the characteristic symptom of the disease, with prominent symptoms of rectal urgency and tenesmus. The clinical course is unpredictable, marked by alternating periods of exacerbation and remission, which may occur spontaneously or in response to treatment or intercurrent illnesses. The precise cause of IBD is unknown; however, genetically susceptible individuals seem to have a dysregulated mucosal immune response to commensal gut flora, which results in bowel inflammation. North America and northern Europe have the highest incidence and prevalence rates of UC, with incidence varying from 9 to 20 cases per 100,000 person-years, and prevalence rates from 156 to 291 cases per 100,000 people, with similar prevalence among males and females. Ulcerative colitis has a bimodal pattern of incidence, with the main onset peak between ages 15 and 30 years, and a second smaller peak between ages 50 and 70 years. It is currently estimated that there are approximately 800,000 people afflicted with UC in the US and 1.4 million in Europe.

Brazikumab is being developed as a treatment for UC and CD to reduce intestinal inflammation and improve signs and symptoms in participants with moderately to severely active IBD. Brazikumab is a human immunoglobulin that selectively binds to human IL-23 with high affinity and prevents IL-23 from interacting with the IL-23 receptor. The roles of IL-23 are believed to be important for the recruitment and activation of a range of inflammatory cells involved in IBD. In preclinical models and studies in patients, anti-IL-12/23 p40 antibodies (eg, ustekinumab [approved for treatment of CD and psoriasis] and briakinumab) and anti-IL-23p19 antibodies have been shown to induce clinical responses in CD (Mannon et al, 2004; Sandborn et al, 2012; Feagan et al, 2016; Feagan et al, 2017) and UC (Sandborn et al, 2020). Phase 2 data in patients with CD (Sands et al, 2017) have demonstrated clinical efficacy of brazikumab comparable with antibodies targeting both IL-12 and IL-23, indicating that therapeutic effects of the anti-IL-12/23p40 antibodies may be due to neutralization of IL-23 alone, suggesting that IL-23 activity may play an important, if not dominant, role in the inflammatory conditions under study. Thus, IL-23 blockade represents a novel mechanism to inhibit the inflammation and reduce clinical symptoms associated with UC. Specifically targeting IL-23 with brazikumab may offer a better benefit:risk profile compared with the IL-12/23 antibodies.

2.1 Study Rationale

Ulcerative colitis is a chronic, relapsing-remitting, inflammatory disease of the gastrointestinal tract. Some patients may have persistent clinically active disease. Treatment options for moderate to severe UC include 5-aminosalicylates, glucocorticosteroids, 6-mercaptopurine, azathioprine, methotrexate, anti-TNFα monoclonal antibodies, and vedolizumab. Many patients, however, have an inadequate response or loss of response over time to these

medications, and there remains an unmet need for effective therapies with novel mechanisms of action. Brazikumab is being developed as a treatment for IBD to reduce intestinal inflammation and improve signs and symptoms.

The present study (D5272C00001/Legacy #3151-201-008) aims to evaluate brazikumab in patients with moderately to severely active UC and will include assessments of clinical responses as demonstrated by improvement of symptoms and of colonic mucosal appearance as observed on endoscopy.

2.2 Background

Interleukin-23, a member of the IL-12 family of cytokines, is a heterodimeric cytokine consisting of 2 subunits: p40 and p19. The p40 subunit is shared by IL-12 and IL-23 as a common subunit, and is targeted by inhibitors of IL-12/23 (eg, ustekinumab and briakinumab). The main known effects of IL-23 are to drive the differentiation of T helper 17 cells, as well as macrophages, natural killer cells, dendritic cells, and innate lymphoid cells leading to up-regulation of IL-17, IL-22, TNFα, granulocyte-macrophage colony-stimulating factor, and IFNγ, and down-regulation of IL-10 (Bettelli et al, 2007).

Studies in patients have demonstrated that IL-23 is upregulated in cells and target tissues of CD and UC while IL-12 is not (Schmidt et al, 2005). Similar observations have been reported in psoriatic skin lesions (Lee et al, 2004), dendritic cells from patients with multiple sclerosis (Vaknin-Dembinsky et al, 2006), and active lesions from patients with multiple sclerosis (Li et al, 2007). Genome-wide association studies in CD and psoriasis patients showed significant association between polymorphisms in the unique IL-23 receptor component and disease (Cargill et al, 2007; Duerr et al, 2006). Furthermore, allelic variants of IL-23 receptor have shown significant correlation with the frequency of UC (Cargill et al, 2007), rheumatoid arthritis (Farago et al, 2008), ankylosing spondylitis (Burton et al, 2007), and multiple sclerosis (Illes et al, 2008).

In the clinic, anti-IL-12/23p40 antibodies (eg, ustekinumab and briakinumab) and anti-IL-23p19 antibodies have been shown to induce clinical responses in CD (Feagan et al, 2017; Sandborn et al, 2012; Mannon et al, 2004), UC (Sandborn et al, 2020), and psoriasis (Phase 2 and Phase 3 studies; Gordon et al, 2012; Kimball et al, 2012; Langley et al, 2012; Gottlieb et al, 2011; Reich et al, 2011; Strober et al, 2011; Leonardi et al, 2008; Papp et al, 2008). Phase 1 and Phase 2 clinical studies with anti–IL-23 p19 antibodies brazikumab (Amgen Study 20080767) and CNTO 1959 (Sofen et al, 2011) in participants with psoriasis have demonstrated clinical efficacy comparable with antibodies targeting both IL-12 and IL-23, indicating that therapeutic effects of the anti–IL-12/23p40 antibodies may be due to neutralization of IL-23 alone.

Brazikumab, previously known as MEDI2070 and AMG 139, is briefly described below. Refer to the current brazikumab IB (Brazikumab, 2021) for details.

Brazikumab is a human, Chinese hamster ovary cell–derived, immunoglobulin G2 monoclonal antibody consisting of 2 heavy chains of the immunoglobulin G2 subclass and 2 light chains of the lambda subclass, which are covalently linked through disulfide bonds.

The nonclinical safety of brazikumab was evaluated in several studies with cynomolgus monkeys as the pharmacologically relevant species. In a safety pharmacology study, no brazikumab-related effects were noted on evaluated cardiovascular, respiratory, or neurobehavioral parameters after CCI In studies of 2 weeks, 3 months, and 6 months duration in cynomolgus monkeys, brazikumab was generally well tolerated when CCI Brazikumab administration at doses up to and including CCI had no effect on in-life observations, peripheral blood immunophenotyping, or clinical and anatomic pathology, and no sex-related differences in exposure. In the 6-month toxicology study, administration of brazikumab to cynomolgus monkeys by CCI once weekly for 26 weeks had no toxicologically significant effects on study parameters. Approximately CCI of the brazikumab-treated animals developed binding ADA during the dosing period and CCI CCI of animals at CCI developed binding ADA in the recovery period. No neutralizing antibodies were detected in animals that tested positive for binding ADA, and binding ADA did not decrease brazikumab exposure. The NOAEL following CCI of brazikumab was 300 mg/kg, the maximum dose tested, corresponding to a C_{max} of CCI and an AUC of CCI on Study Day 176.

Four clinical studies with brazikumab have been completed: Phase 1a Study 20080767, Phase 1b Study 20090519, Phase 2a Study CD-IA-MEDI2070-1147, and Phase 1 Study 3150-101-008.

The first study with brazikumab was Study 20080767 (conducted by Amgen), a 2-part, single-dose study in healthy participants (Part A) and participants with moderate to severe psoriasis (Part B). A total of 73 participants was administered brazikumab as a CCI CCI or CCI or placebo. Overall, brazikumab demonstrated an acceptable safety profile that supported further clinical development. In participants with psoriasis, CCI and an CCI of CCI brazikumab also showed evidence of clinical efficacy as demonstrated by improvements in the Psoriasis Area Severity Index score.

The Phase 1b study, Study 20090519, was a randomized, double-blind, placebo-controlled, ascending multiple-dose study to evaluate safety, tolerability, PK, and PD of brazikumab in healthy participants (Part A) and these same parameters, plus efficacy, in participants with mild to severe CD (Part B). A total of 40 participants were randomized and received at least

one dose of IP (brazikumab or placebo) in Part A and an additional 8 participants with CD were randomized into Part B of the study and received IP (brazikumab or placebo). No TESAEs or deaths were reported, and no participant withdrew from the study because of a TEAE.

Study CD-IA-MEDI2070-1147 was a 2-part, Phase 2a study comprising a 12-week, double-blind, placebo-controlled period followed by a 100-week, open-label period to evaluate the short-term efficacy and the short- and long-term safety of brazikumab in participants with moderate to severe, active CD who failed or were intolerant to anti-TNFα therapy. During the double-blind period of the study, participants received a fixed IV dose of brazikumab (700 mg) or placebo at Weeks 0 and 4. At the completion of the double-blind, placebo-controlled period (Week 12), all participants had the option to enter a 100-week, open-label period where they received open-label brazikumab CCI (Week 12 through Week 112). Of 119 participants who received IP during the double-blind period of the study, 112 participants had completed study participation through Week 8 (primary efficacy time point) and 104 participants had completed the double-blind period to Week 12 and entered the open-label period of the study. All 104 participants received at least CCI CCI brazikumab in the open-label period; 93 participants (89.4%) completed their Week 24 visit; and 57 participants (54.8%) completed the 100-week open-label period.

The primary efficacy endpoint of Study CD-IA-MEDI2070-1147, CDAI response at Week 8 (defined by either a CDAI score of < 150 or a reduction from baseline of at least 100 points), was met. The proportion of participants that achieved a CDAI response at Week 8 was statistically significantly higher in the brazikumab group than in the placebo group (49.2% versus 26.7%, respectively, p = 0.010). The secondary efficacy endpoints generally supported the findings of the primary efficacy analysis. The proportion of participants that achieved a CDAI 100-point improvement at Week 8 was statistically significantly higher in the brazikumab group than in the placebo group (45.8% versus 25.0%, respectively, p = 0.017). A marginal treatment group difference compared with placebo was also observed for CDAI remission at Week 8 (27.1% versus 15.0%) that was not statistically significant.

The median IL-22 serum concentration at baseline for the entire study population was 15.6 pg/mL. In the analyses of CDAI clinical response and CDAI remission stratified by the median baseline IL-22 serum concentration for the population (CCI CCI it was observed that among participants with baseline IL-22 serum concentrations CCI the brazikumab-treated participants had an increased likelihood of CDAI clinical response and clinical remission at Week 8. In the subgroup of participants meeting this threshold, the placebo-adjusted CDAI clinical response rate was CCI for brazikumab versus placebo) and the placebo-adjusted CDAI clinical remission rate was CCI (CCI for brazikumab versus placebo). In contrast, among participants with baseline IL-22 serum concentrations of CCI brazikumab-treated

participants had CDAI clinical response and remission rates similar to participants receiving placebo; the placebo-adjusted rates were 3.0% and -3.9%, respectively (p = 0.8026 and p = 0.6681, respectively), for brazikumab compared with placebo.

The safety data from Study CD-IA-MEDI2070-1147 for CCI (CCI of brazikumab CCI and CCI (brazikumab CCI showed an acceptable safety profile that is consistent with previous studies and supports clinical development. Adverse events reported in this study were generally mild or moderate in intensity. There were no deaths reported.

Study 3150-101-008 was a randomized, double-blind, placebo-controlled, ascending-dose study to evaluate the PK and dose proportionality of brazikumab in healthy white and Japanese male and female participants aged 18 to 50 years. The objectives of the study were: (1) to evaluate the PK and dose proportionality of brazikumab in healthy Japanese and white participants; (2) to evaluate safety and tolerability of brazikumab in healthy Japanese and white participants; (3) to explore the differences in the PK and safety of brazikumab in healthy Japanese versus white participants; and (4) to evaluate the impact of CCI on the PK, safety, and tolerability of brazikumab in white participants. CCI administered doses CCI of CCI and CCI and multiple CCI doses of CCI CCI followed by an CCI dose of CCI brazikumab or placebo were administered to 3 groups of 16 male and female study participants (8 Japanese and 8 white). A CCI dose of brazikumab in a CCI was also administered to 8 white male and female participants. All dose strengths were well tolerated. In Study D5272C00001 (Legacy #3151-201-008), the brazikumab and brazikumab placebo induction doses will be administered in a CCI

2.3 Benefit/Risk Assessment

Medical therapy of IBD remains complex with the need to individualize treatment based on various clinical factors including concomitant medical conditions and medications, prior treatment response to therapy, and consideration of potential short- and long-term toxicity associated with treatment based on individual risks. The overall goal of treatment in IBD is diminishing inflammation and improving signs and symptoms of IBD. Treatment options for moderate to severe UC include 5-aminosalicylates, glucocorticosteroids, 6-mercaptopurine, azathioprine, methotrexate, anti-TNFα monoclonal antibodies, and vedolizumab. Many patients, however, have an inadequate response or loss of response over time to these medications, and there remains an unmet need for effective therapies with novel mechanisms of action. Brazikumab is being developed to meet this unmet need.

Interleukin-23 blockade represents a novel mechanism to inhibit the inflammation and clinical symptoms associated with autoimmune diseases such as CD, UC, and psoriasis. Therapeutic agents have previously targeted the IL-12/23p40 subunit, including the monoclonal antibodies ustekinumab and briakinumab. Because the IL-12/23p40 subunit is common to IL-12 and IL-

23, these agents inhibit the actions of both cytokines. In contrast, brazikumab is a monoclonal antibody that specifically targets the IL-23p19 subunit, preventing IL-23 from interacting with the IL-23 receptor subunit of the IL-23 receptor complex so as to inhibit the actions of IL-23 but not those of IL-12.

In a Phase 2a study of brazikumab (comprising a 12-week, double-blind, placebo-controlled, Treatment Period followed by a 100-week, open-label period, in participants with moderate to severe, active CD who had failed or were intolerant to anti-TNFα therapy), the primary endpoint of the study, CDAI response at Week 8 (defined by either a CDAI score of < 150 or a CDAI score reduction from baseline of at least 100 points), was met. In the modified intent-to-treat population, the proportion of participants that achieved a CDAI response at Week 8 was statistically significantly higher in the brazikumab group than in the placebo group. Brazikumab, at doses of CCI 4 weeks apart or CCI every 4 weeks, was well tolerated and showed an acceptable short- and long-term safety profile. During the entire study period, 21 of 111 (18.9%) participants experienced a Grade 3 TEAE, and there were no Grade 4 (life-threatening) or Grade 5 (fatal) TEAEs. Crohn's disease was the most frequently reported SAE. No malignancies were reported and no MACE occurred. Clinically significant infections were mostly urinary tract infection, vulvovaginal mycotic infection, sinusitis, bronchitis, and upper respiratory tract infection. No clinically significant trends were observed in the clinical laboratory evaluations, vital sign measurements, ECGs, or physical findings.

The important potential risks remain hypothetical, based on the mechanism of action and class effect. The following have been defined as important potential risks based on the mechanism of action and class effect, to be closely monitored in the clinical development program:

- Serious and medically significant infections
- Malignancies
- Vaccine complications
- CCI
- Severe hypersensitivity (including anaphylaxis)
- Immune complex disease

Brazikumab is a selective inhibitor of IL-23, which has been specifically implicated in mucosal immunology, but spares the IL-12 pathway. Several preclinical studies have shown a higher rate of malignancy with IL-12 blockade compared with IL-23 blockade and increased IL-23 expression associated with IBD with colorectal carcinoma. Therefore, selective inhibition of IL-23 is thought to be effective in suppressing mucosal inflammation in IBD without increasing the risk of malignancy.

Other factors for consideration when assessing benefit/risk of study participation may include:

- Study requirement of 3 endoscopy procedures with procedural risks that may include perforation, bleeding after collection of biopsy samples, and complications related to sedation when administered. Individual risks and benefits of the endoscopy procedure should be further discussed with participants and consent for the procedure should be obtained per local guidelines.
- Risk of disease worsening for which mitigation strategies include a provision for the use of rescue therapy and a requirement to assess the need for rescue therapy at any visit per the investigator's discretion in addition to specific study visits.

In conclusion, AstraZeneca considers that the benefit/risk balance is favorable and supports further clinical development of brazikumab as a treatment for UC. For additional information regarding the efficacy and safety of brazikumab, please refer to Section 2.2 and the current IB for previous clinical study experience with brazikumab.

3 OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate the efficacy and safety of brazikumab versus placebo to induce clinical remission based on endoscopic improvement, rectal bleeding, and stool frequency scores in participants with moderate to severe UC who have failed or are intolerant to conventional therapy (5-aminosalicylates, CSs, or immunomodulators; 6-mercaptopurine, azathioprine, methotrexate). The study population will also include participants who are biological intervention naïve, have demonstrated a successful response to prior biological intervention, or who have failed or were intolerant to biological intervention.

Table 5 Objectives and Endpoints

Objective	Endpoint	Population	Intercurrent event strategy	Population-level summary (analysis)
Primary				
To compare the efficacy of brazikumab with that of placebo to achieve clinical remission	Clinical remission defined as: • mMS at Week 10: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Percentage of participants achieving the endpoint
Secondary				
To compare the efficacy of brazikumab with that of placebo to achieve sustained clinical remission	Sustained clinical remission defined as: • mMS at both Week 10 and Week 54: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary

Objective	Endpoint	Population	Intercurrent event strategy	Population-level summary (analysis)
To compare the efficacy of brazikumab with that of placebo to achieve CS-free clinical remission	CS-free clinical remission defined as: • mMS at Week 54 for participants who are CS-free for at least the last 12 weeks before the assessment at Week 54: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 54: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve clinical response	Clinical response is defined as • Reduction in mMS ≥ 2 points from baseline AND ≥ 30% from baseline AND a decrease in the rectal bleeding score ≥ 1 point from baseline or a score of 0 or 1 at Week 10	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic improvement	Endoscopic improvement is defined as • Endoscopy subscore ≤ 1 at Week 10	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary

Objective	Endpoint	Population	Intercurrent event strategy	Population-level summary (analysis)
To evaluate the PK and immunogenicity of brazikumab	Population PK model of serum concentrations of brazikumab and analysis for serum anti-brazikumab antibodies	Participants with moderately to severely active UC		
To characterize the exposure-response relationships of brazikumab	Exposure-response model linking primary endpoints to metrics of model-predicted individual brazikumab exposures	Participants with moderately to severely active UC		
Safety				
To evaluate the safety and tolerability of brazikumab	AEs, clinical laboratory values, vital signs, physical exams, ECGs	Participants with moderately to severely active UC		
Exploratory				
To establish the serum IL-22 concentration baseline clinical cutoff for its value in predicting the efficacy of brazikumab	Exploration of the relationship of baseline serum IL-22 concentration with efficacy of brazikumab at Week 10 and establishment of the serum IL-22 concentration clinical cutoff through clinical remission at Week 10	Participants with moderately to severely active UC	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Differential approach method

Objective	Endpoint	Population	Intercurrent event strategy	Population-level summary (analysis)
To compare the efficacy of brazikumab with that of placebo to achieve clinical remission, in participants who are BM+ [a]	Clinical remission defined as: • mMS at Week 10: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC who are BM+ [a]	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve sustained clinical remission, in participants who are BM+ [a]	Sustained clinical remission defined as: • mMS at both Week 10 and Week 54: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC who are BM+ [a]	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescues treatment • uses prohibited treatment	Same as primary

Objective	Endpoint	Population	Intercurrent event strategy	Population-level summary (analysis)
To compare the efficacy of brazikumab with that of placebo to achieve CS-free clinical remission, in participants who are BM+ [a]	CS-free clinical remission defined as: • mMS at Week 54 for participants who are CS-free for at least the last 12 weeks before the assessment at Week 54: – Endoscopy subscore = 0 or 1, AND – Rectal bleeding subscore = 0, AND – Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline	Participants with moderately to severely active UC who are BM+ [a]	NRI will be used for the following intercurrent events before Week 54: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve clinical response, in participants who are BM+ [a]	Clinical response is defined as: • Reduction in mMS ≥ 2 points from baseline AND ≥ 30% from baseline AND a decrease in the rectal bleeding score ≥ 1 point from baseline or a score of 0 or 1 at Week 10	Participants with moderately to severely active UC who are BM+ [a]	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic improvement, in participants who are BM+ [a]	Endoscopic improvement is defined as: • Endoscopy subscore ≤ 1	Participants with moderately to severely active UC who are BM+ [a]	NRI will be used for the following intercurrent events before Week 10: • discontinues treatment prematurely for any reason • takes rescue treatment • uses prohibited treatment	Same as primary

Objective	Endpoint	Population	Intercurrent event strategy	Population-level summary (analysis)
To explore transcriptional, histological, protein, and microbiome BMs in study participants and their relationship with study intervention, disease features, clinical outcomes, and patient characteristics	• Serum, plasma, fecal, or gut tissue proteins; whole blood or gut tissue transcriptional changes; histological and microbiome assessments	Participants with moderately to severely active UC who are BM+ [a]	Exploratory analysis plans, including intercurrent event strategy and summary statistics, to be detailed in the SAP or separate exploratory analysis plan	

[a] The exploratory efficacy endpoints will be evaluated in the BM- populations as well.

Note: Additional exploratory efficacy endpoints may be described, with corresponding statistical analyses in the SAP.

AE = adverse event; BM = biomarker; BM- = biomarker serum IL-22 concentrations below a pre-established cutoff; BM+ = biomarker serum IL-22 concentrations at or above a pre-established cutoff; CS = corticosteroid; ECG = electrocardiogram; IL = interleukin; mMS = modified Mayo score; NRI = non-responder imputation; PK = pharmacokinetic(s); SAP = Statistical Analysis Plan; UC = ulcerative colitis.

4 STUDY DESIGN

4.1 Overall Design

- Global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 54-week study
- After meeting all eligibility criteria, participants will be randomized 1:1:1 into 1 of 3 treatment arms. Participants randomized into the brazikumab treatment arms will be re-randomized via IRT after the third CCI at Week 10 to receive 1 of 2 CCI brazikumab doses, either CCI or CCI for the Maintenance Period.
- Intervention groups:
  - Brazikumab low dose: CCI brazikumab CCI on Week 0 (Day 1), Week 2, and Week 6 followed by CCI brazikumab CCI or CCI every 4 weeks beginning at Week 10
  - Brazikumab high-dose: CCI brazikumab CCI at Week 0 (Day 1), Week 2, and Week 6 followed by CCI brazikumab CCI or CCI every 4 weeks beginning at Week 10
  - Placebo: CCI placebo at Week 0 (Day 1), Week 2, and Week 6 followed by CCI placebo every 4 weeks beginning at Week 10

Participants will be stratified according to prior treatment experience, biological-naïve (or biological treatment non-refractory) OR prior biological use (failed or were intolerant to prior biological treatment) at randomization prior to Induction Period dosing and at re-randomization prior to Maintenance Period dosing. Participants who were assigned to receive CCI brazikumab during the Induction Period will be re-randomized within the brazikumab induction dose group, 1:1 at Week 10 to receive either brazikumab CCI CCI every 4 weeks during the Maintenance Period.

The study will be unblinded and the primary analysis for the study will be conducted after the last participant has completed the Week 10 visit. AstraZeneca personnel who are directly involved with the conduct of the study, study site personnel, as well as participants will remain blinded to the treatment assignment for individual participants until the completion of the study. Details on what roles will remain blinded and how trial integrity will be maintained will be documented separately.

A study schematic is provided in Section 1.2.

Study Duration: Following a Screening Period of up to 5 weeks, the study duration is up to 68 weeks, consisting of a 54-week Treatment Period (last dose of study intervention is at Week 50) and an 18-week post-last brazikumab/brazikumab placebo dose (Week 50) Safety Follow-up Period.

Approximately 255 participants will be randomized to the study.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) that would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity. Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note: in the case of verbal consent/reconsent, the ICF should be signed according to local regulations).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the sponsor Study Physician/designee.
- Home or remote visit: Performed by a site-qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home study intervention administration: Performed by a site-qualified HCP or HCP provided by a TPV. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix I.

4.2 Scientific Rationale for Study Design

Several design features have been incorporated in the current study to minimize bias, including double-blind and random assignment of participants, helping to ensure that both known and unknown risk factors are distributed evenly among intervention groups. The comparison of placebo to a standard of care drug provides internal evidence of assay sensitivity.

Traditional study designs that assess 'induction of remission' and 'maintenance of remission' as separate studies require that a specific time point is established that defines when induction treatment ends and maintenance treatment begins. Disadvantages of these traditional separate study designs include the potential of selecting an inappropriate timepoint that may not reflect the optimal time at which the PD properties of the treatment occurs, highly variable response rates that encumber estimation of the sample size needed for re-randomization, treatment carryover effects, and difficulties assessing whether the underlying disease process is still active. Typically, participants who demonstrate a clinical response in a traditional induction study are re-randomized into a separate maintenance study and since only responders are allowed to continue, they may not be the most appropriate population to evaluate long-term remission or evaluate participants who may have responded at a later timepoint with continued treatment. However, the current study design will make it possible to evaluate long-term maintenance of remission in participants receiving continuous treatment who have achieved remission at an earlier specified timepoint.

The current study is designed to combine both initial intervention (induction) and maintenance phases into a single study, in a 'treat-straight-through' approach. Using this design, participants are randomized to receive induction therapy with study intervention or placebo and are then treated straight through for the remainder of the study, which includes both an assessment of clinical remission at Week 10 and an assessment of sustained remission in participants who were in remission at both Week 10 and Week 54. The major advantage of this naturalistic design is that it allows evaluation of both induction and maintenance intervention in a single study and avoids some of the complexities noted above that are associated with a traditional re-randomization maintenance design. Also, the consolidation of the benefits of initial intervention can be evaluated with continued intervention, especially for those participants who have responded to the initial treatment but did not meet the remission criteria at Week 10 but could be converted to a responder/remitter with continued treatment. This naturalistic design also mimics clinical practice as patients would continue to be treated along a continuum and not have their intervention truncated into an artificially selected time point. Furthermore, preserving the initial randomization assignment to intervention would ensure that long-term maintenance intervention was not biased in favor of participants that achieved remission during the Induction Period because those who achieved remission with their intervention would still be on the same intervention in the maintenance phase, without any influence of withdrawal or discontinuation of the intervention. Additionally, those who responded to placebo during the induction phase would still be on placebo in the maintenance phase, without any influence of discontinuation of placebo.

4.3 Justification for Dose

CCI doses of up to CCI brazikumab were well tolerated by healthy white and Japanese male and female participants in Phase 1 Study 3150-101-008 and multiple CCI CCI and CCI doses were shown to be well tolerated and efficacious in patients with CD

in Phase 2a Study D5170C00001. The CCI doses as part of the induction intervention and the CCI doses as part of the maintenance intervention in this Phase 2b study are therefore expected to be well tolerated. Dose-ranging assessments will also be performed during the maintenance intervention period; participants who received CCI brazikumab during the Induction Period will then be randomized 1:1 to receive either CCI brazikumab every 4 weeks. Participants in the placebo group will undergo the same study assessments as the brazikumab-treated participants.

There are considerable exposure margins between what would be expected from participants in Study D5272C00001 (Legacy #3151-201-008) receiving multiple CCI doses of CCI brazikumab/multiple CCI doses of CCI brazikumab and animals in the pivotal toxicology studies exposed to brazikumab at the NOAEL. The NOAEL of CCI for brazikumab was established in cynomolgus monkeys in 3 studies in which brazikumab was administered CCI weekly for up to 14 weeks and CCI weekly up to 6 months. At this dose, no toxicologically significant effects were observed. Based on C_{max} and AUC values in these pivotal toxicology studies in cynomolgus monkeys and comparable PK parameter values from Phase 1b Study 20090519 and Phase 1 Study 3150-101-008 in healthy participants, the margins of exposure margins are presented in Table 6.

Table 6 Summary of Brazikumab Cynomolgus Monkey to Human Margins of Exposure

Study	NOAEL dose (mg/kg/week)	C_{max} (µg/mL)	$AUC_{0\text{-}tau}$ (µg•day/mL)	Human exposure margins	
				C_{max}	AUC [a]
3-Month with 12-month recovery period (109075)	CCI			8.1 [b]	11 [b]
3-Month with 12-month recovery period (109075)				168 [c]	172 [c]
6-Month with 11-week recovery period (109184)				132 [c]	133 [c]

[a] The monkey $AUC_{0\text{-}tau}$ was multiplied by 4 to adjust for the 28-day dosing interval in humans.
[b] Safety margins were calculated based on predicted exposures in humans (C_{max} = 1828 µg/mL; $AUC_{0\text{-}28day}$ = CCI for an CCI dose of CCI brazikumab. Predicted exposure estimates were based on human exposures following an CCI dose of CCI brazikumab multiplied by 2 (Source Data Study 3150-101-008).
[c] Safety margins were calculated based on exposures in humans following a CCI dose of CCI Source Data Study 20090519). Human C_{max} CCI and $AUC_{0\text{-}tau}$ CCI were measured at steady state.
AUC = area under the serum concentration versus time curve; $AUC_{0\text{-}tau}$ = area under the serum concentration-time curve from time zero to the end of the dosing interval; $AUC_{0\text{-}28day}$ = area under the curve from time zero to 28 days; C_{max} = maximum serum drug concentration; CCI ; NOAEL = no-observed-adverse-effect-level; CCI .

In conclusion, the results from toxicology studies with brazikumab support the proposed clinical study and provide data that indicate that brazikumab is considered safe for its intended use in humans.

4.4 End of Study Definition

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

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3). For participants who proceed to the OLE study, the last scheduled study visit is at Week 54. For participants who do not proceed to the OLE study, the last scheduled study visit occurs 18 weeks after the last dose of study intervention (Week 68).

5 STUDY POPULATION

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

Each participant should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures; refer to Section 5.4. In this protocol, enrolled participants are defined as those who sign informed consent. Randomized participants are defined as those who undergo randomization and receive a randomization number.

5.1 Inclusion Criteria

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

1 Ability to provide written informed consent prior to any study procedures and willing and able to attend all study visits, comply with the study procedures, read and write in order to complete questionnaires, and be able to complete the study period.

2 Aged 18 to 80 years of age, inclusive, at the time of signing the informed consent.

3 Diagnosis of UC with an onset of symptoms for a minimum of 3 months prior to Screening as determined by the investigator based on clinical history, exclusion of infectious causes, and characteristic endoscopic and histologic findings.

4 Evidence of UC extending proximal to the rectum (≥ 15 cm of involved colon).

5 Moderately to severely active UC as defined by (5a and 5b must be met):

   (a) Stool Frequency and Rectal Bleeding subscores will be obtained during Screening on an eDiary. The calculation of Stool Frequency and Rectal Bleeding for eligibility will be based on the participant's evening diary data that will be collected daily. Diary data from the days for familiarization with the device, bowel prep, and the endoscopy procedure will not be used for eligibility calculations. The eligibility calculation is to be based on a 7 consecutive day period that includes at least 3 days of evening diary entries. The following criteria must also be met:

      i. Average daily mMS Stool Frequency subscore ≥ 1 AND

      ii. Average daily mMS Rectal Bleeding subscore ≥ 1

   (b) Modified Mayo endoscopic subscore of ≥ 2 based on a full colonoscopy within 14 days prior to initial IRT randomization.

6 Participant had an inadequate response or intolerance to intervention with conventional treatment (oral aminosalicylates, oral CS, azathioprine, methotrexate, or 6-mercaptopurine) or prior biological treatment or demonstrated CS dependence for the treatment of UC. For participants who have previously used biological treatment, a

participant may have failed up to 3 biologics that include up to 2 different mechanisms of action. To fulfill this criterion, the participant must meet at least one of the following:

(a) Had an inadequate response to 1 of these agents, ie, defined as persistent signs and/or symptoms of active UC judged by the investigator's overall clinical assessment of the participant's history taking into consideration a lack of clinical improvement or inability to maintain previously achieved clinical improvement despite treatment with medication(s) used according to the local label and generally considered to be safe and effective in treating UC.

(b) Was intolerant to 1 of these agents, defined as the inability to continue treatment due to adverse effects, regardless of treatment dose.

(c) Has CS dependence, defined as the daily or regularly scheduled use of CS to manage UC signs/symptoms and inability to discontinue CS use without the prompt return of UC signs/symptoms.

7 Where applicable, participants taking any of the following medications must be at a stable dose or discontinued as defined:

(a) Oral 5-aminosalicylates must be at a stable dose for 2 weeks prior to the Screening colonoscopy.

(b) Oral prednisone up to CCI or equivalent, must be at a stable dose for 2 weeks prior to the Screening colonoscopy and kept stable until the Week 10 assessment.

(c) Oral budesonide up to 9 mg/day, must be at a stable dose for 2 weeks prior to the Screening colonoscopy and kept stable until the Week 10 assessment. Please see Section 6.5.3 for additional details for CS.

(d) Topical (rectal) aminosalicylic acid (eg, mesalamine) or topical (rectal) steroids should be discontinued within 2 weeks prior to Screening colonoscopy. Rectal therapies should not be restarted after the Screening colonoscopy.

(e) An immunomodulator: participants must have been on treatment for a minimum of 8 weeks and must be kept at stable doses as below:

i. Azathioprine, must be at a stable dose for 4 weeks prior to Screening, OR

ii. 6-mercaptopurine, must be at a stable dose for 4 weeks prior to Screening, OR

iii. Methotrexate, must be at a stable dose for 4 weeks prior to Screening.

8 Female participants of childbearing potential must have a negative urine pregnancy test prior to administration of study intervention and must agree to use a highly effective method of birth control (confirmed by the investigator) from randomization throughout the study duration and for at least 18 weeks after last dose of study intervention; cessation or continuation of contraception after this point is to be discussed with a responsible physician in accordance with local regulations and guidelines. Highly effective methods

(those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation— oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation— oral, injectable, or implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Sexual abstinence, ie, refraining from heterosexual intercourse (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant)
- Vasectomized sexual partner, provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success

9 Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

(a) Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range. Until FSH is documented to be within menopausal range, treat the participant as having childbearing potential.

(b) Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

If these criteria are not met, the participant should be regarded as having childbearing potential.

10 Non-sterilized males who are sexually active with a female partner of childbearing potential should use condoms during treatment and until the end of relevant systemic exposure in the male participant, plus a further 18 weeks. For a female partner of childbearing potential, contraception recommendations should also be considered (as described in Inclusion Criterion 8).

11 Participant must have the QFT-TB test performed and meet the following TB criteria. A TB worksheet must also be completed (see Appendix F):

(a) Participant has no known history of active TB.

(b) Participant has no known history of latent TB without completion of an appropriate course of intervention.

(c) Meets 1 of the following acceptable TB test results:

i. Negative QFT-TB obtained from central laboratory during Screening, OR

For a positive QFT-TB test obtained during Screening from the central laboratory, active TB must be ruled out or treated and negative QTF-TB confirmed by central laboratory, OR

ii. Indeterminate QFT-TB test obtained during the Screening Period from the central laboratory with ongoing QFT-TB testing as outlined in Appendix F . Participants with an indeterminate QFT-TB test can continue with Screening if they have all of the following:

1. No symptoms/risk factors per TB worksheet provided by the sponsor.
2. No known recent exposure to a case of active TB.
3. No evidence of active TB on chest x-ray within 8 weeks prior to Screening or during Screening.
4. Confirmed QTF-TB negative by central laboratory.

(d) Participants with a history of using anti-TNFα agents for a treatment course of 1 year or longer who have discontinued an anti-TNFα agent within 6 months prior to Screening must obtain a chest x-ray showing no evidence of active TB within 8 weeks prior to Screening or during Screening.

5.2 Exclusion Criteria

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

1 Participant has UC limited to the rectum (ie, not beyond 15 cm of the anal verge).

2 Current diagnosis of fulminant colitis, a diagnosis of CD or indeterminate colitis, presence or history of a fistula consistent with CD, primary sclerosing cholangitis, celiac disease, or untreated bile acid malabsorption. Participants with a history of toxic megacolon within 12 months of Screening are excluded.

3 History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, ileostomy, or other prior colonic resection, or need for surgical intervention for control of UC anticipated within 6 months.

4 Participant has received the following treatment:

(a) Infliximab: within 8 weeks prior to randomization (Day 1).

(b) Adalimumab, certolizumab pegol, or golimumab: within 8 weeks prior to randomization (Day 1).

(c) Vedolizumab or ustekinumab within 12 weeks of randomization (Day 1).

(d) Other prohibited medication, biologic or small molecule treatment within 5 half-lives prior to randomization (Day 1).

(e) Fecal microbiota transplantation: within 8 weeks prior to randomization (Day 1).

5 *[Criterion deleted as part of Amendment 5]*

6 Except for ustekinumab, prior exposure to any biologic agent targeting IL-12 or IL-23 (risankizumab, brazikumab, mirikizumab, guselkumab, tildrakizumab).

7 Known history of allergy to the study intervention formulation or any of its excipients or components of the delivery device, or to any other biologic therapy.

8 Participant received cyclosporine, mycophenolate mofetil, sirolimus (rapamycin), thalidomide, tacrolimus (FK-506), or tofacitinib within 2 weeks prior to Screening.

9 Participants who received CCI or CCI steroids within 2 weeks prior to Screening.

10 Participant is currently enrolled in another investigational device or drug study, or is within 35 days or 5 half-lives, whichever is longer, since ending another investigational device or drug study(s), or receiving other investigational agent(s), with the exception of "registry" or "cohort" trials, which may include periodic biological sampling and/or participant questionnaires but in which no other unlicensed IP is administered. In the event that a participant has received an investigational agent, the elimination half-life of which is not known, then the last dose must have been received at least 6 months prior to randomization (Day 1).

11 Participant received a transfusion of blood, plasma, or platelets within 30 days prior to Screening.

12 Participant received a Bacille Calmette-Guérin vaccination within 12 months of randomization (Day 1) or any other live vaccine less than 4 weeks prior to randomization (Day 1) or is planning to receive any such vaccine over the course of the study.

13 Participant has any of the following criteria related to infections:

(a) Evidence of a recent (within 6 months of randomization [Day 1]) systemic fungal infection, requiring inpatient hospitalization, and/or antifungal treatment. Participants treated for localized fungal infections (eg, oral, vaginal and skin candidiasis, onychomycosis) are not excluded.

(b) Any infection requiring hospitalization or treatment with CCI anti-infectives (including antiviral treatment) within 4 weeks of Screening.

(c) Cytomegalovirus or EBV infection that has not resolved within 8 weeks prior to Screening.

(d) Clinically significant chronic infection (eg, osteomyelitis) that has not resolved within 8 weeks of Screening.

(e) Nonserious infection requiring oral anti-infectives within 2 weeks prior to randomization must be further discussed with study medical monitor. Chronic

suppressive antiviral treatment for herpes simplex virus in the absence of active lesions or uncomplicated urinary tract infections are not considered exclusionary.

(f) Clinical evidence of or suspected to have an abscess during Screening. Cutaneous and perianal/perirectal abscesses are not exclusionary if drained and adequately treated at least 3 weeks prior to Screening.

(g) Any underlying condition that predisposes the participant to infections.

(h) Participant had previous allogenic bone marrow transplant or history of organ or cell-based transplantation (eg, islet cell transplantation or autologous stem cell transplantation) with the exception of corneal transplant.

(i) Clinically significant active infection or signs/symptoms of infection that has the potential to worsen with immunosuppressive therapy.

(j) Signs or symptoms of ongoing infection due to intestinal pathogens.

14 Participant has known or suspected history of chronic use of NSAIDs (defined as at least 3 times per week for more than 3 months; not applicable to daily aspirin use up to CCI CCI and/or opiates, drug, or alcohol abuse. Participants who use marijuana for medicinal purposes, including treatment of symptoms associated with UC and improving quality of life, will be permitted in the study. Marijuana use should be documented as a concomitant medication. Participants who abuse marijuana (ie, interferes with aspects of the participant's life) as judged by the investigator are excluded.

15 History of cancer with the following exceptions:

(a) A history of basal cell carcinoma and/or squamous cell carcinoma of the skin, with apparent successful curative therapy, greater than 12 months prior to Screening, would not be exclusionary.

(b) Carcinoma in situ of the cervix, with apparent successful curative therapy, greater than 12 months prior to Screening.

If there is evidence of dysplasia on endoscopy, and confirmed on biopsy, the participant must be excluded.

16 Clinically significant cardiovascular conditions including recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure within 6 months of Screening.

17 Prolonged QTcF interval (QTc > 450 msec or QTc > 480 msec for participants with bundle branch block; determined on central ECG), or conditions leading to additional risk for QT prolongation (eg, congenital long-QT syndrome). Participants with electrolyte abnormalities such as hypokalemia and hypomagnesemia that would increase the risk of QT prolongation should be corrected prior to randomization; the ECG for these participants may be repeated after electrolyte correction for determination of eligibility if needed.

18 Clinically significant kidney disease including but not limited to:

(a) Acute kidney injury within 6 weeks of Screening. Corrected pre-renal azotemia with serum creatinine at the participant's baseline value during Screening would not be excluded.

(b) Chronic kidney disease with an estimated glomerular filtration rate of less than 30 mL/min calculated by MDRD equation at Screening by the central laboratory are excluded.

19 Abnormal laboratory results at Screening:

(a) Liver tests: either AST, ALT, or alkaline phosphatase > 2.0 × ULN or total bilirubin > 1.5 × ULN (except for participants with Gilbert's Syndrome; pathological evidence of conjugated [direct] hyperbilirubinemia per investigator and/or sponsor discretion is exclusionary).

(b) Neutrophil count CCI

(c) Hemoglobin CCI

(d) Platelet count CCI

(e) Evidence of acute or chronic HBV or HCV infection defined as:

- Hepatitis B: (1) positive for hepatitis B surface antigen or (2) positive for anti-hepatitis B core antibody (HBcAb+) and positive confirmatory PCR for HBV, regardless of anti–hepatitis B surface antibody status
- Hepatitis C: positive result for hepatitis C antibody and positive confirmatory PCR test for HCV

(f) Positive central laboratory result for HIV.

(g) *C. difficile*–positive stool testing (antigen and toxin) by central laboratory. For indeterminate results (antigen-positive and toxin-negative), a positive *C. difficile* stool PCR is exclusionary.

(h) Any other abnormal laboratory results at Screening that, in the opinion of the investigator, will prevent the participant from completing the study or will interfere with the interpretation of the study results.

20 Participant is pregnant or breastfeeding or plans to become pregnant during the study.

21 Other concurrent medical conditions: Participant has known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurologic, renal, gastrointestinal, hepatic, hematological, respiratory, or any other system abnormalities that are not associated with UC and are uncontrolled with standard treatment. Any clinically significant abnormal findings in physical examination, vital signs, laboratory, or endoscopic assessments during the Screening Period, that in the opinion of the investigator may put the participant at risk because of his/her participation in the study; may influence the results of the study; compromise the ability of the participant to give written informed consent and/or complete the entire duration of the study. If eligible concurrent conditions have been treated, the participant may be eligible to enter the study.

22 Participant has any disorder that, in the opinion of the investigator, may compromise the ability of the participant to give written informed consent and/or to comply with all required study procedures.

23 Employees of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals.

Rationale for Inclusion and Exclusion Criteria

Participants in this study will be 18 to 80 years of age, inclusive, with moderately to severely active UC who, as determined by the investigator, have failed or are intolerant to conventional therapy. This includes participants who have not received a biologic agent (biologic naïve) or have received a biologic agent (eg, anti-TNFα) at a dose approved for the treatment of UC and did not respond initially (ie, primary non-response), or responded initially but then lost response with continued therapy (ie, secondary non-response), or were intolerant to the medication. This also includes participants who have previously received a biologic agent with a successful response without subsequent treatment failure.

The inclusion criteria are designed to enroll a patient population that is sufficiently symptomatic to demonstrate a clinically meaningful change from baseline to support a treatment benefit for patients with moderately to severely active UC. The participants are required to have a full colonoscopy within 14 days of randomization to ensure that the appearance of their colonic mucosa is consistent with moderately to severely active UC, to examine and document the extent of colonic surface area that is affected, and to assess if changes in colonic mucosa can reasonably be attributed to the study intervention. Furthermore, the extent of disease assessed by the baseline full colonoscopy may be used to determine if a flexible sigmoidoscopy would be appropriate for the subsequent endoscopic assessments.

5.3 Lifestyle Considerations

The following restrictions apply while the participant is receiving study intervention and for the specified times before and after:

1 Women of childbearing potential must use highly effective contraceptive methods from enrollment throughout the study and at least for 18 weeks after last administration of the study intervention, as stated in inclusion criterion 8 in Section 5.1. Cessation or continuation of contraception after this point is to be discussed with a responsible physician in accordance with local regulations and guidelines.

2 Participants should not donate blood or blood components while participating in this study and through 18 weeks after the last dose of study intervention.

5.3.1 Meals and Dietary Restrictions

There are no meal, dietary, or activity restrictions in this study.

5.3.2 Caffeine, Alcohol, and Tobacco

1 Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit during study intervention administration. Use of nicotine replacement therapy should be recorded as concomitant medication.

2 Participants are to be encouraged to avoid caffeine intake for a minimum of 1 hour prior to their clinic visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. These participants should have the reason for study withdrawal recorded as ‘Screen Failure’ (ie, does not meet the required inclusion/exclusion criteria) in the eCRF. This reason for study withdrawal is only valid for screen failures and not randomized participants.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened once with the sponsor’s prior approval. Rescreened participants should be assigned the same participant number as for the initial Screening. Rescreened participants should sign a new ICF. All procedures from the Screening Period should be repeated.

If a participant is not eligible to continue Screening based on a laboratory parameter, retesting of the laboratory value is allowed once during the Screening Period.

6 STUDY INTERVENTION

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

Where allowable by local health authorities and ethics committees, participants may have the option for at-home study intervention administration and visit assessments performed by a qualified HCP.

6.1 Study Interventions Administered

Participants who satisfy all inclusion and exclusion criteria (Sections 5.1 and 5.2) will receive study intervention, defined as any investigational treatment or placebo intended to be administered to a study participant according to the study protocol. Table 7 presents details regarding study intervention and administration.

Table 7 Study Interventions

Study intervention name	Brazikumab CCI	Brazikumab CCI	Placebo CCI	Placebo CCI
Route of administration	CCI	CCI	CCI	CCI
Dose (mg)	CCI CCI	CCI CCI	Not applicable	Not applicable
Dosing Instructions [a]	CCI	CCI	CCI	CCI
Packaging and Labelling	Study intervention will be provided in kits. Each kit will be labelled as required per country requirement.	Study intervention will be provided in kits. Each kit will be labelled as required per country requirement.	Study intervention will be provided in kits. Each kit will be labelled as required per country requirement.	Study intervention will be provided in kits. Each kit will be labelled as required per country requirement.
Provider	AstraZeneca	AstraZeneca	AstraZeneca	AstraZeneca

[a] Instructions for the preparation of all doses is provided in the Pharmacy Manual. For IV infusions, contents of vials will be added to an IV bag of dextrose solution to a total volume of CCI then administered by CCI CCI.

Brazikumab for CCI

Brazikumab for CCI will be supplied as a CCI The label-claim volume is CCI

Brazikumab for CCI .

Brazikumab for CCI

Brazikumab for CCI . The label-claim volume is CCI

Brazikumab for CCI

Placebo for CCI

Placebo for CCI he label-claim volume is CCI

Placebo for CCI

Placebo for CCI The label-claim volume is CCI

All formulations

Study intervention CCI are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Study intervention must be kept in original packaging until use to prevent prolonged light exposure.

6.1.1 Dosing Regimen

Brazikumab is CCI and CCI for all subsequent doses. Details regarding dosage formulation and dosing procedures for the study intervention may be found in the CCI

For the double-blind Maintenance Period, all participants will receive CCI every 4 weeks per the administration schedule (Table 7). Please refer to the Pharmacy Manual for additional details regarding the administration schedule for study intervention.

All study interventions will be handled by a pharmacist (or appropriately qualified individual) and handed over to the qualified site staff who will administer the study intervention to participants according to the brazikumab investigational directions for use. Due to viscosity differences between brazikumab and placebo, the person who administers subcutaneous IP must not be involved in performing assessments on participants. A study monitor will perform study intervention accountability. In the event that the treatment allocation for a participant becomes known to the investigator or other blinded study staff involved in the management of study participants, the sponsor's study monitor must be notified immediately.

6.1.1.1 CCI Administration

All participants will receive 1 CCI of study intervention (brazikumab or placebo) on Days 1, 15, and 43 of the Induction Period. An experienced and qualified staff member will place the CCI access. The total volume administered will be recorded in the eCRF.

All visit procedures (including sample collection, urine pregnancy tests) are to be completed prior to study intervention administration unless otherwise specified.

Vital signs (BP, temperature, pulse rate, and respiration rate) will be obtained before CCI study intervention administration at all treatment visits. In addition, participants will be monitored for changes in vital signs and/or new symptoms approximately every CCI during CCI administration, CCI and at approximately CCI CCI or until stable, whichever is later. The first and last vital signs are to be recorded on the eCRF. Participants will be discharged from the site when they are deemed clinically stable by the investigator and after completion of PK sampling, a minimum of 2 to 4 hours after completion of CCI administration for the CCI CCI (Week 0) and a minimum of 1 hour after completion of CCI administration for the second and third infusions (Weeks 2 and 6).

Infusion reactions have been reported with the administration of CCI monoclonal antibodies. As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs, such as epinephrine, antihistamines, CSs, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, or procedures for emergency treatment must be in place. Study personnel must be trained to recognize and take appropriate action for emergency measures according to local guidelines. Any infusion-related reaction and/or hypersensitivity reaction is to be reported as an AESI (see Section 8.3.10.1 and Section 8.3.10.3).

6.1.1.2 CCI

Brazikumab or placebo will be administered to all participants during the Maintenance Period by CCI Each CCI dose will be administered by an experienced and qualified staff member who must not be involved in performing assessments on participants. The

brazikumab or placebo dose will be administered as CCI according to the dosing administration table. Injections will be over no more than 10 minutes total time for all CCI injections and at a distance of at least 2 cm apart.

It is advised that the site of study intervention injection be rotated such that the patient receives study intervention at a different anatomical site at each treatment visit. The suggested injection-site rotation sequence is presented below (Figure 2). The injection site must be documented in the source at each treatment visit and recorded in the eCRF. The date and time of all study intervention administrations, as well as any missed doses, should be recorded in the appropriate section of the eCRF.

CCI CCI.



If rotation of the injection site is not possible, the reason for this must be documented in the source.

Vital signs (BP, temperature, pulse rate, and respiration rate) will be obtained before and immediately after CCI study intervention administration during treatment visits outlined in the SoA (Section 1.3). In addition, for the first 2 CCI brazikumab doses (Week 10 and Week 14), participants will be monitored for changes in vital signs and/or new symptoms approximately every 30 minutes for a minimum of 1 hour CCI or until stable, whichever is longer. For the third and subsequent CCI doses of brazikumab or placebo, participants will be monitored for a minimum of 30 minutes or until stable, whichever is longer. The first and last vital signs (pre- and postdose) are to be recorded on the eCRF. Discharge from the site will be determined by the investigator. Any injection-site reaction is to be reported as an AESI (see Section 8.3.10.1).

6.1.2 Study Intervention Administration Rescheduling

Every effort should be taken to keep study intervention administration within the scheduled window. If a participant presents with a condition that requires a delay in dosing, study intervention will be withheld and administered as soon as possible thereafter, as clinically appropriate.

Study intervention should not be administered, and the dosing is to be rescheduled in the presence of any clinically significant infection or illness or SAE or laboratory abnormality that, in the opinion of investigator, contraindicates dosing.

It is recommended that the sponsor Study Physician/designee be contacted in case of any questions.

When study intervention dosing needs to be postponed, it is recommended that all scheduled treatment visit procedures (except for study intervention administration) are still performed within the visit window. Rescheduled study intervention dose can then be administered at an unscheduled visit. All required minimum procedures are to be performed at this visit. It may also include remaining visit procedures (not performed at the scheduled visit) and additional assessments as deemed necessary by the investigator.

If the visit procedures cannot be conducted within the window (eg, the participant is unable to attend the study site), then the entire visit will be rescheduled along with study intervention dose.

If a dose is significantly delayed, it is recommended to keep at least a 2-week interval before the next dose. If a postponed dose overlaps with the next treatment visit window, the postponed dose will be skipped, and the next dose of study intervention given at the regularly scheduled visit.

The visit schedule will always be calculated from randomization visit date.

If a participant misses more than 1 dose of study intervention during the Treatment Period, it is recommended that a conversation between the investigator and sponsor Study Physician/designee takes place to review the participant's adherence to treatment and decide on the participant's further disposition.

6.1.3 Study Supplies

AstraZeneca will supply the following study interventions:

(a) CCI of brazikumab for CCI
(b) CCI of brazikumab placebo for CCI
(c) Brazikumab pack containing CCI

(d) Brazikumab placebo pack containing one CCI for CCI

Additional details and instructions for study intervention use are provided in the CCI CCI

All defects in study intervention (including malfunction, use error, and inadequate labelling) shall be reported by the investigator as described in the Pharmacy Manual.

6.2 Preparation/Handling/Storage/Accountability

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. Any temperature excursions during storage must be reported and resolved before use of the study intervention.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 All unused study intervention must be stored securely. Unused study intervention should be destroyed locally at site wherever possible, once expired or at the termination of the study, by site personnel after accounted for by the monitor. Where local destruction is not possible, then return to supplying depot can be arranged.

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

Brazikumab and placebo preparation for CCI

The dose of brazikumab or placebo for CCI administration must be prepared by the investigator's or site's designated IP manager using aseptic technique. Prepared study intervention must be administered at CCI from CCI

A dose of CCI will be administered using a CCI containing CCI solution. A CCI volume of CCI will be removed from the CCI before addition of CCI (CCI of brazikumab and CCI of placebo. The bag must be mixed by gently inverting to ensure homogeneity of the dose in the bag.

A dose of CCI will be administered using an CCI containing CCI solution. A CCI volume of CCI will be removed from the CCI before addition of CCI of brazikumab. The bag must be mixed by gently inverting to ensure homogeneity of the dose in the bag.

A placebo dose will be administered using an CCI containing CCI A CCI volume of CCI solution will be removed from the CCI before addition of CCI of placebo. The bag must be mixed by gently inverting to ensure homogeneity of the dose in the bag.

Brazikumab and placebo CCI

Brazikumab and placebo infusions are to be administered through an CCI administration set with a CCI acceptable configurations include an CCI set containing an CCI CCI or the CCI the distal end of the CCI

The brazikumab and placebo infusion time is 1 hour; however, if there are interruptions, the total allowed time must not exceed 6 hours after removal of CCI from refrigeration.

Other drugs must not be co-administered through the CCI .

The CCI will be CCI according to local practices to ensure the full dose is administered. Infusion time does not include the CCI

If either preparation time or CCI exceeds the time limits, a new dose must be prepared from new vials. Brazikumab does not contain preservatives, and any unused portion must be discarded immediately after use.

Brazikumab and placebo preparation for CCI

One brazikumab CCI and 1 placebo CCI are required for CCI . Two brazikumab CCI are required for CCI Two placebo CCI are required for placebo CCI should be kept at CCI for at least 40 minutes inside the carton prior to administration. The dose of brazikumab or placebo for CCI must be administered at CCI CCI

Brazikumab and placebo CCI

For CCI the person administering the dose will wipe the skin surface of the CCI with alcohol and allow the skin to air dry. The skin will be pinched to isolate the CCI from CCI . Avoiding the CCI , the needle will be inserted at CCI . Brazikumab or placebo will be slowly injected (at least CCI) into the CCI CCI . The area is not to be massaged CCI are

to be rotated and noted in the source documents only. The total volume of dose administered will be recorded in the eCRF.

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the log-in information and directions for the RTSM will be provided to each site.

The randomization assignment procedure will take place only after all eligibility criteria have been satisfied, including the central reader's assessment of the Mayo endoscopy score and the calculation of Mayo scores for Stool Frequency and Rectal Bleeding.

Study intervention will be administered at the study visits summarized in the SoA (Section 1.3). Refer to the Pharmacy Manual for additional details.

Participants will be randomized in a 1:1:1 ratio for brazikumab CCI brazikumab CCI and placebo group. Participants will be stratified according to prior treatment experience: biological treatment-naïve (or biological treatment non-refractory) OR prior biological use (failed or were intolerant to prior biological treatment) at randomization prior to receiving Induction Period dosing and at re-randomization prior to receiving Maintenance Period dosing. Participants who were assigned to receive CCI brazikumab during the Induction Period will be re-randomized within the brazikumab induction dose group, 1:1 at Week 10 to receive either brazikumab CCI or CCI every 4 weeks during the Maintenance Period.

The study will be unblinded, and the primary analysis will be conducted, after the last participant has completed the Week 10 visit. AstraZeneca personnel who are directly involved with the conduct of the study, study site personnel, as well as participants will remain blinded to the treatment assignment for individual participants until the completion of the study. Details on what roles will remain blinded and how trial integrity will be maintained will be documented separately.

The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator is encouraged to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. If the blind is broken, the participant will be disqualified from the study.

Colonoscopy video clips will be read centrally by independent gastroenterologists experienced in IBD who are blinded to the participant's clinical activity and treatment allocation.

Regular transfers of the randomization schema will be performed from the IxRS vendor to the bioanalytical lab until randomization is complete for correct identification of brazikumab participants for PK analyses.

Pharmacokinetics drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the qualified staff, under medical supervision. Due to viscosity differences between brazikumab and placebo, the person who administers subcutaneous IP must not be involved in performing assessments on participants. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the participant's eCRF at each visit along with the reason the medication is taken.

6.5.1 Prior Medications Requiring Stable Dose Regimen

Participants must be on a stable dose of any of the medications listed in Table 8 for the specified period. Other medications being used at Screening may be continued.

Table 8 Medications Requiring Stable Dose Regimen

Medication	Stable dose required
CCI	[redacted]

Medication	Stable dose required
Immunomodulators (participants must have been on treatment for a minimum of 8 weeks)	
Azathioprine	CCI
6-mercaptopurine	
Methotrexate	

The immunomodulators and 5-aminosalicyclate listed above in Table 8 should remain at stable doses throughout the study from the time of study enrollment except for cases of toxicity related to the medication. In cases of toxicity, the medication dose may be decreased or discontinued; however, the medication dose should not be increased or restarted once the toxicity has resolved. The doses of prednisone (or equivalent) and/or budesonide are to remain stable from 2 weeks prior to the Screening endoscopy until Week 10, and then to be tapered as per Section 6.5.3.

6.5.2 Permitted Concomitant Treatments

Investigators may prescribe concomitant medications or interventions deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" in Section 6.5.4. Specifically, participants should receive full supportive care during the study, including transfusions of blood and blood products; intervention with antibiotics, anti-emetics, antidiarrheals, and analgesics; and other care as deemed appropriate and in accordance with institutional guidelines or local site practice.

In addition to permitted medications requiring a stable dose regimen (Table 8), the following concomitant treatments/interventions used in the care of IBD participants are permitted during the study, with adherence to the details described in Table 9:

Table 9 Permitted Concomitant Treatments

Treatment	Details
Probiotics (eg, Culturelle® and *Saccharomyces boulardii*)	Permitted only if being taken at Randomization.
Antidiarrheals (eg, loperamide and diphenoxylate with atropine)	Permitted as needed for controlling chronic diarrhea and if taken at Randomization.
NSAIDs	Limited to occasional short courses for less than 7 days. The use of NSAIDs is generally discouraged for IBD patients due to the risk of flares. Chronic NSAID use is exclusionary.
Inactivated/killed vaccination (eg, inactive influenza)	Not allowed within the 7 days before or within 7 days after any study intervention dosing study visit.

IBD = inflammatory bowel disease; NSAID = nonsteroidal anti-inflammatory drug.

The dose of the permitted concomitant medications listed above should remain stable during the study Treatment Period. Antidiarrheal agents may be stopped if the participant has had no stools in 3 consecutive days. After any such stopping of antidiarrheal agents during the double-blind period, if any recurrence of loose stools occurs, antidiarrheal use is permitted to be immediately resumed.

The use of NSAIDs is generally discouraged for IBD patients due to the risk of flares. Use of NSAIDs should be limited to occasional short courses for less than 7 days. Chronic NSAID use is exclusionary (as per Section5.2).

Background UC medication (eg, those listed in Table 8) is not regarded as study intervention and will not be provided by the sponsor.

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

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/intervention is in question, please contact the sponsor or designee.

6.5.3 Corticosteroid Study Guidelines

Participants may continue treatment with CS during the Screening and treatment periods of the study according to the study guidelines below:

- The following doses of oral prednisone, oral budesonide, or equivalent dose should be kept stable from at least 2 weeks prior to the Screening colonoscopy through Week 10 (see Section 6.5.1):
  - Oral prednisone up to CCI [redacted] or equivalent
  - Oral budesonide up to CCI [redacted]
- Participants receiving oral CS must attempt CS tapering as per guidelines in Table 10. Corticosteroid tapering should be initiated at least by Week 14.

Table 10 Corticosteroid Tapering Guidelines

Initial corticosteroid dose	Dose reduction
CCI	

MMX = Multi-Matrix System.

General tapering guidelines:

- If there are worsening symptoms of UC attributed to the steroid tapering per the investigator's judgment, the participant may be instructed to return to the baseline dose. These situations would not represent the use of rescue medication. The increase in steroid dose should be recorded in the appropriate eCRF along with the indication for increase.
- If an oral steroid dose is temporarily increased back to the previous dose due to worsening UC symptoms, tapering should be attempted again within 2 weeks after symptoms have improved and remain stable.

The target goal is to discontinue steroids prior to or by Week 42, if clinically appropriate.

6.5.4 Prohibited Interventions During the Study

Participants must be instructed to not take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications or interventions are considered exclusionary and are not permitted during the study. The sponsor or designee must be notified if a participant receives any of these, and study intervention must simultaneously be discontinued:

- Natalizumab
- Anti-TNFα agents
- Vedolizumab

- Any commercially available or experimental biologic agent (eg, risankizumab, mirikizumab, guselkumab)
- Tofacitinib
- Calcineurin inhibitors (eg, cyclosporine and tacrolimus)
- Mycophenolate mofetil
- Sirolimus (rapamycin)
- Thalidomide
- Live attenuated vaccine
- Intra-abdominal surgery
- Any experimental product or device as specified in Sections 5.1 or 5.2.
- Fecal microbiota transplantation
- The use of alternative or complementary treatments must be discussed with the Study Physician/designee. Treatments such as Chinese herbal therapies are considered prohibited interventions.
- Any experimental product or device as specified in Section 5.2.

Note: Topical (rectal) aminosalicylic acid (eg, mesalamine) or topical (rectal) steroids are prohibited from 2 weeks prior to the Screening colonoscopy through Week 54 and will be considered as rescue therapy if taken during this time period. Participants will continue to receive study intervention. The use of other immunosuppressant therapies not listed above will require discussion with the medical monitor to determine whether study intervention must be discontinued.

The decision to administer a prohibited medication/intervention during the study period is done with the safety of the study participant as the primary consideration. When possible, the sponsor is to be notified before the prohibited medication/intervention is administered. If the study intervention is discontinued and the participant does not enroll in the OLE study, the participant should be encouraged to continue with all applicable study assessments through the end of the study, including the Safety Follow-up Period. The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the participant's eCRF at each visit along with the reason the medication is taken.

6.5.5 Rescue Treatment

For study purposes, any new concomitant medication or any increase in dose of a baseline medication required to treat new or unresolved UC symptoms, except for antidiarrheal medications already used at baseline, will be considered rescue treatment. Other investigational products are not permitted to be used as rescue treatment. An increase in CS dose back to baseline dose level for participants undergoing CS tapering within the guidelines

in Section 6.5.3 is not considered rescue treatment. Initiation of rectal steroids or rectal aminosalicylates after randomization until the end of Week 54 will be considered rescue treatment.

The **new** initiation of medications or interventions listed below will be considered as rescue treatment and will not require stopping study intervention:

- 5-Aminosalicylates
- Parenteral, oral, or rectal CS
- Oral steroid doses above initial baseline dose
- Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)
- IV immunoglobulin

Administration of rescue treatment constitutes treatment failure. Participants requiring rescue treatment will continue to receive study intervention unless a prohibited treatment is administered as listed in Section 6.5.4. Participants are expected to continue through study completion. Rescue treatment should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety.

The use of rescue treatment is to be considered by the investigator at Week 18 and Week 38 if there is worsening or no improvement in UC symptoms compared to the baseline Stool Frequency or Rectal Bleeding scores used for eligibility. The need for rescue treatment may also be considered at any other visit at the investigator's discretion.

The following guidelines must be followed prior to the use of rescue treatment:

- Lack of improvement compared to the baseline average daily Stool Frequency or Rectal Bleeding scores used for eligibility
- Lack of improvement or worsening of other UC signs/symptoms not specifically used for eligibility may also be considered for the use of rescue therapy
- Lack of improvement must be confirmed for at least 2 visits at least 2 weeks apart and no improvement in confirmatory centrally read modified endoscopy score by at least 1 point from baseline.

If the participant meets the guidelines for use of rescue treatment, the participant may be eligible for the OLE study, as applicable, if all other eligibility criteria are also met (eg, participant does not meet clinical response, modified Mayo endoscopic subscore greater than 1, etc). An unscheduled endoscopy visit may be performed at the investigator's discretion and may be used for the ET endoscopy requirement, as applicable.

6.6 Dose Modification

No dose modification of study intervention is permitted during this study.

6.7 Intervention After the End of the Study

No interventions will be dispensed after the end of the study unless the participant enters the OLE study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

A premature discontinuation will occur if a participant who signs the ICF and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used terms:

- Adverse event
- Completed
- Death
- Lack of efficacy
- Lost to follow-up
- Noncompliance with study intervention
- Other
- Physician decision
- Pregnancy
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by participant

The reason for discontinuation should be clearly documented on the appropriate eCRF (see Appendix H for Standard Discontinuation Criteria/Definitions).

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

It is the right and the duty of the investigator or subinvestigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual participant. In addition, the investigator or subinvestigator is to stop treatment of any participant with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results. Participants who are discontinued from study intervention and are not eligible for the

OLE study are to be encouraged to remain in the study and continue all other applicable study assessments.

A participant must be discontinued from study intervention for any of the following reasons:

1 Participant requires intra-abdominal surgery during study participation.
2 Participant receives any live vaccine during study participation.
3 Mycobacterial infections, systemic fungal infections, or viral infections requiring hospitalization or parenteral anti-infective therapy.
4 Sepsis (CTCAE Grade 3 or higher).
5 Any worsening of an infection (beyond CTCAE Grade 2).
6 New diagnosis of malignancy with the exception of non-melanocytic, non-metastatic skin cancer at the investigator's discretion with sponsor agreement.
7 Participant receives prohibited medication listed in Section 6.5.4.
8 Participant becomes pregnant.

Discontinuation of study intervention for abnormal liver function is to be considered by the investigator when a participant meets criteria for Hy's Law (See Section 8.3.6 and Appendix E) or 1 of the conditions outlined or if the investigator believes that it is in best interest of the participant.

Abnormal liver function is defined as meeting one of the conditions outlined below, and confirmed by repeat testing within 48 to 72 hours of awareness or if the investigator believes that it is in the best interest of the participant:

- 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 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%)

Potential Hy's Law should be reported as an AE as outlined in Section 8.3.6.

If a clinically significant finding is identified (including, but not limited to changes from Baseline in QTc interval after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an AE.

Discontinuation of a participant from study intervention is to be considered if there is a marked prolongation of the QT/QTc interval during treatment, especially if the measurement

is obtained from more than 1 ECG. Increases in QT/QTc to > 500 msec or of > 60 msec over baseline require study drug discontinuation. This review of the ECG printed at the time of collection must be documented.

If the study intervention is discontinued, the participant should be encouraged to continue with all applicable study assessments through the end of the study, including the Safety Follow-up Period. If the participant is unwilling to continue through the end of the study, the participant is to be encouraged to complete the Early Termination Visit and Safety Follow-up Period. See the SoA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

- If the participant is unwilling or unable to attend the scheduled site visits until the end of the study, he/she will be offered a follow-up option that includes monthly telephone contact instead. During follow-up telephone contact, the investigator will collect information about concomitant medications, information on UC, and AE/SAE(s).
- Participants who discontinue study intervention during the Treatment Period and are unwilling to attend scheduled visits or have telephone contact will exit the study after completion of the ED/ET visit.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, compliance, or administrative reasons.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the global study team.
- See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site by the time the study is completed (as defined in Section 4.4).

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts are to be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of A 9.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- Participant compliance with scheduled protocol assessments including eDiary completion will be a part of investigator and sponsor judgment when participant transition to OLE study is planned.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- The investigator will ensure that data are recorded on the eCRFs. The web-based data capture system will be used for data collection and query handling. The investigator will ensure the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed approximately CCI Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Modified Mayo Score (mMS)

Efficacy will be assessed using the Mayo Scoring System for assessment of UC (Mayo score) as described by Schroeder et al, 1987. The Mayo score assesses stool frequency, rectal bleeding, endoscopic findings, and the physician's assessment of disease activity. The Mayo score has been modified to specify no friability in the endoscopy subscore of 1 (mild disease). Stool frequency and rectal bleeding will be assessed daily by the participant using the electronic device provided. The Mayo item for stool frequency has been operationalized as bowel movement frequency to improve clarity and facilitate consistent interpretation of this item among participants. The calculation of the Stool Frequency and Rectal Bleeding scores for Mayo scores will be based on the participant's average nightly diary data recorded over the

most recent 3 days of allowable data, within 7 days of the colonoscopy. These should not include any days in which bowel preparation are administered or the day of endoscopy. For the Screening colonoscopy, an additional 7 days of evening diary data are required (a total of 14 days data prior to colonoscopy) as a run-in period for participants to gain familiarity with eDiary device use prior to the 7-day period used for calculating the Mayo score.

The mucosal appearance during the endoscopic examination will be assessed for the modified Mayo endoscopic subscore (ie, findings of endoscopy item). The endoscopic appearance will be examined by both the investigator and the central reader. Centrally read endoscopic subscores will be used for all eligibility and efficacy analyses.

The PGA acknowledges the participant's symptoms as well as the participant's general sense of well-being and other observations, such as endoscopic and laboratory findings. The endoscopic subscore and the PGA must be performed by a qualified physician, and it is recommended that the same physician performs all assessments for a particular participant throughout the course of the study.

The Mayo Scoring System is shown in Table 11.

Data for the primary and secondary efficacy assessments and diary data will be collected via eDiary.

Table 11 Mayo Scoring System for Assessment of Ulcerative Colitis Activity

Stool frequency [a]
0 = Normal number of bowel movements for this participant
1 = 1 to 2 bowel movements more than normal
2 = 3 to 4 bowel movements more than normal
3 = 5 or more bowel movements more than normal
Rectal bleeding [b]
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passed
Findings of endoscopy [c]
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, no friability)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

Physicians' Global Assessment
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

[a] Each participant serves as his or her own control to establish the degree of abnormality of the stool frequency.
[b] The daily bleeding score represented the most severe bleeding of the day.
[c] Subscore of 1 (mild disease) modified to reflect no friability for modified Mayo score as described above.
Source: Amended from Schroeder et al, 1987.

8.1.2 Partial Mayo Score (pMS)

The pMS uses the 3 non-invasive components of the full Mayo score (Table 11): stool frequency, rectal bleeding, and PGA. Because the endoscopic score is excluded, the maximum score is 9 points. The pMS will be assessed at the timepoints described in the SoA (Section 1.3) and may also be used (at any scheduled or unscheduled visit) to evaluate clinical response when signs and symptoms are attributed to IBD and an endoscopic evaluation is not available. It may also be utilized if needed to assess the participant's clinical condition at any time.

The calculation of the Stool Frequency and Rectal Bleeding scores will be based on the participant's average nightly diary data completed over the most recent 3 days within a 7 consecutive day period, that does not include any days on which bowel preparation was conducted in preparation for endoscopy/colonoscopy or any days on which endoscopy/colonoscopy was conducted. The Screening Visit 1 pMS will follow the same rules as above but will be based upon participant recall.

The PGA evaluates the participant's symptoms, as well as the participant's general sense of well-being, and other observations, such as laboratory findings. The PGA must be performed by a qualified physician, and it is recommended that the same physician performs all assessments for a particular participant throughout the course of the study. The PGA score may be performed once all applicable data are available to the qualified physician.

8.1.3 Endoscopy

A full colonoscopy is required at Screening for all participants. All remaining endoscopic assessments during the study can be performed via a flexible sigmoidoscopy as clinically indicated. Endoscopic assessments should be performed in accordance to the time window described in the SoA (Section 1.3).

The risks for endoscopy procedures may include perforation, bleeding after collection of biopsy samples, and complications related to sedation when administered. Individual risks and

benefits of the endoscopy procedure should be further discussed with participants and consent for the procedure should be obtained per local guidelines.

All colonoscopy or flexible sigmoidoscopy procedures for the assessment of endoscopic findings for the mMS will be recorded using a video capture kit as supplied by the central reading facility. The video clips will be read centrally for endoscopic severity based on the modified Mayo endoscopy score by independent gastroenterologists experienced in IBD who are blinded to the participants clinical activity and intervention allocation.

In all cases, video recordings are to be performed with biopsies taken upon endoscopic withdrawal. Technical instructions for making the video recording will be provided separately (these instructions will include how to capture the depth of insertion).

The central readers should promptly notify both the sponsor and the investigator of the detection of any clinically significant bowel lesions that are not manifestations of UC.

8.1.4 Colon Mucosal Biopsies

Mucosal biopsies will be collected at each study endoscopy (see SoA in Section 1.3). The biopsies will be used to support assessments of changes over time in:

- Geboes Histological Index
- Robarts Histopathology Index
- Molecular profile of colonic inflammation

Detailed instructions for biopsy collection kits for processing, handling, and shipping will be provided to the sites to support the centralized testing for each of the various exploratory objectives. A central laboratory will be used to process, stain, and analyze BMs from the biopsy specimens.

8.1.5 Geboes Histological Index

The GHI is a measure of the degree of mucosal inflammation as follows: 0 = structural change only; 1 = chronic inflammation; 2a = lamina propria eosinophils; 2b = lamina propria neutrophils; 3 = neutrophils in epithelium; 4 = crypt destruction; and 5 = erosions or ulcers (Geboes et al, 2000). The biopsies that are obtained during the endoscopy will be scored according to the GHI by the central pathologist.

8.1.6 Robarts Histopathology Index

The RHI incorporates 4 histological descriptors (severity of chronic inflammatory infiltrate, the number of lamina propria neutrophils, the number of neutrophils in the epithelium, and the severity of erosions or ulceration), each of which is objectively graded between 0 and 3 (Mosli et al, 2017). The RHI will be calculated based on information from the GHI.

8.1.7 PRO Assessments

Participants will complete all PRO assessments using an electronic provisioned device. The electronic device (eDiary) will be the only accepted source of PRO data.

Patient-reported outcomes assessments used within this study will include, but not be limited to, the following:

- IBDQ
- SF-36v2
- FACIT-F
- EQ-5D-5L
- PGIC-UC and PGIS-UC
- Real-time bowel movement diary
- Evening daily diary, including NRS symptom items and mMS PRO components

The investigator will ensure that participants are properly trained on the use of this device and the importance of completing assessments as scheduled.

The device will be programmed at the first Screening visit, and participants will be required to complete a training module on the device at the site. Site staff must verify the training has been completed before the participant takes the device home.

The investigator or designee will be responsible for monitoring participant adherence with the PROs and follow-up as necessary to minimize missing data. Monitoring of participant adherence to the daily PROs (mMS) is especially critical between the first visit and second (endoscopy) visit during Screening to ensure that the participant meets applicable criteria for mMS eligibility calculation. A minimum of 2 consecutive weeks of ePRO data is required prior to Screening colonoscopy. If the participant does not meet the eligibility requirements, the device will be deactivated and retained at the site for future use. Participants are expected to bring the device to every site visit. Review of participant compliance with the assessment schedule and completion of any available assessments should be completed prior to any other study procedures.

8.1.8 Bowel Movement eDiary

The Bowel Movement eDiary assessment is a real-time entry assessment available on the device 24/7 throughout the duration of the study. The assessment is to be completed by participants after each bowel movement, which is defined as a trip to the toilet when the participant passes stool, blood, or mucus. They will record bowel movement components

(stool, blood, or mucus), presence or absence of urgency, and the stool consistency using the BSFS.

The BSFS classifies the form of stools into 7 types, each with an accompanying visual aid and text description. The BSFS will be used to measure the form of individual stools, with loose/liquid stools characterized by either Type 6 or Type 7 (all liquid) on the scale (Appendix G 1).

It is important that the participant be instructed to complete this assessment after every bowel movement each day, even during times when awakened from sleep and as close to the as possible to the time the bowel movement occurred.

8.1.9 Evening Diary

The evening eDiary assessment will be available every evening throughout the duration of the study.

The participant will be instructed to complete the evening eDiary every night and will be prompted to report any additional bowel movements that they did not enter already in real time for that day. Participants will also be prompted to report bowel movements more than normal and rectal bleeding, captured by the mMS, over the past 24 hours. In the same evening assessment, participants will record the severity rating of their abdominal pain, fatigue, tiredness, weakness, lack of energy, joint pain, and flatulence (and frequency of flatulence) over the past 24 hours (Appendix G 2).

Site staff should review compliance of the evening report for each participant on a regular basis.

8.1.10 Site Visit Assessments

The PGIS-UC, PGIC-UC, FACIT-F, IBDQ, SF-36v2, and EQ-5D-5L will be scheduled to be completed at select site visit timepoints. The selection of visit confirmation by site staff will trigger the availability of the scheduled assessments. The participant will be instructed to complete the assessments at the site and prior to any study procedures occurring at the visit. Refer to Table 4 for the PRO visit assessment schedule.

The PGIS-UC (Appendix G 3.1) is a single item that assesses participants' perceptions of overall severity of UC symptoms for the last 7 days.

The PGIC-UC (Appendix G 3.2) is a single item that assesses participants' perceptions of overall change in their UC symptoms since starting treatment.

The FACIT-F (Appendix G 3.3) is a 13-item instrument developed to measure fatigue in chronic illness patients. Total score ranges from 0 to 52 based on a rating of 5-point Likert scale.

The IBDQ (Appendix G 3.4) is a disease-specific PRO instrument that measures HRQoL in patients with IBD (Guyatt et al, 1989). The IBDQ covers the following dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Items are scored on a 7-point Likert scale, yielding a global score in the range 32 to 224 (with higher scores indicating better quality of life). The IBDQ has been frequently used in drug approval applications to assess treatment efficacy in IBD. The IBDQ has been designed to be self-administered and completed in 5 minutes.

The EQ-5D-5L (Appendix G 3.5) is a standardized instrument used to measure self-reports of health status and functioning, consisting of 5 elements: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate an index measuring the value to society of his or her current health. In addition, the EQ-5D-5L includes a visual analog scale that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health.

The SF-36v2 (Appendix G 3.6) is a standardized instrument used to measure self-reports of health status and functional well-being, consisting of 8 domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Empirically derived weights can be applied to an individual's responses to the SF-36v2 descriptive system to generate an index measuring the value to society of his or her current health.

8.1.11 Participant Qualitative Interview Sub-study

Participants who complete the ICF in English will be invited to participate in a Participant Qualitative Interview sub-study. The overall goal of this sub-study is to supplement and support the interpretation of PRO quantitative trial results through qualitative exploration of the participants' disease and treatment experience. The study will highlight the meaningful changes in participant experience and feedback on the feasibility and ease of the eDiary data collection throughout the course of the trial. Up to 25 participants who complete the End of Treatment study visit (Week 54) can be enrolled in the sub-study. The sub-study consists of a one-to-one non-interventional, 60-minute telephone interview conducted in English in the US, United Kingdom, and Canada. A detailed description of sub-study procedures is available in the Participant Qualitative Interview Sub-study Manual.

Participants will be introduced to the sub-study during the informed consent process using the participant communication materials attached to the Participant Qualitative Interview

Sub-study Manual and the Sub-study ICF Addendum. Participants will be contacted according to procedures described in the Participant Qualitative Interview Sub-study Manual. The interview discussion guide is provided as an appendix to the Participant Qualitative Interview Sub-study Manual.

The interview will be audio recorded with the participant's permission (confirmed verbally prior to the start of the interview and obtained in main ICF). The recordings will be transcribed.

Participants' confidentiality and personal information will be protected throughout the sub-study to the same standard as all other coded data in the study.

Due to the qualitative nature of the data and the analysis, the results will be presented in a separate report (not in the CSR) and the data (transcriptions) will not be entered into the study database. No identifiable data will be reported.

AstraZeneca will follow standard procedures for handling AE reporting involving these participants (as described in Appendix B). At the beginning and end of each interview, participants will be advised to report any AE to the investigator or designee.

8.2 Safety Assessments

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

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- Extra-intestinal manifestation will be assessed at the timepoints indicated in the SoA (Section 1.3).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Body temperature, pulse rate, respiratory rate, and BP will be assessed.
- Blood pressure and pulse measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 BP measurement and will be recorded on the eCRF.
- Height and weight will also be measured and recorded (height will be measured at the first Screening visit only).

8.2.3 Electrocardiograms

- Single 12-lead ECGs will be obtained as outlined in the SoA (Section 1.3) using a study-provided ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1 for QTc withdrawal criteria and additional QTc readings that may be necessary.

8.2.4 Clinical Safety Laboratory Assessments

- See Table 12 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. The clinical chemistry, hematology, and urinalysis will be performed by the central laboratory.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 18 weeks after the last dose of study intervention are to be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or sponsor Study Physician/designee.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology is to be identified and the sponsor notified.
  - All protocol-required laboratory assessments, as defined in Table 12, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results will be recorded in the eCRF.

Table 12 Protocol-required Safety Laboratory Assessments

Laboratory assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV MCH % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry [a]	BUN CRP	Potassium	AST	Total and direct bilirubin
	Creatinine eGFR	Sodium	ALT	Total protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Bicarbonate
	Magnesium Uric acid	Chloride	Albumin	Phosphate
Fecal tests	• *C. difficile* • Fecal calprotectin • Fecal lactoferrin			
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (reflexively as needed)			
Other Screening tests	• QFT-TB Gold In-Tube • FSH (as needed in women of non-childbearing potential only) [b] • Serum hCG pregnancy test (as needed for WOCBP); urine hCG should be performed locally at each visit, except Week 4 • Serology (HIV antibody, HBsAg, HBc total antibody, HBc IgM antibody, and HCV antibody with reflex testing when required) • All study-required laboratory assessments will be performed by a central laboratory unless indicated (eg, local urine hCG testing).			

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix E.

[b] FSH does not need to be repeated at Week 54 if it was in the post-menopausal range at Screening. If the female participant becomes amenorrhoeic during the course of the study, FSH should be assessed at Week 54.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; *C. difficile* = *Clostridium difficile*; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgM = immunoglobulin M; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; QFT-TB = QuantiFERON-TB; RBC = red blood cell; TB = tuberculosis; WBC = white blood cell; WOCBP = women of childbearing potential.

Note: In the case in which a participant shows an AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN, please refer to Appendix E for further instructions.

8.3 AEs and SAEs

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator or designee will determine whether these meet the criteria for an AE.

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from time of signature of the ICF throughout the Treatment Period and including the Follow-up Period.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

New or updated information will be recorded in the originally completed eCRF.

AE variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped

- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess the causal relationship between IP and each AE and/or incident, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures and/or medical devices. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as *yes*.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.3.4 AEs Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: *Have you had any health problems since the previous visit/you were last asked?* or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other

signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 AEs Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the IP, or are considered to be clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, [eg, dose adjustment or drug interruption]).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.7 Disease Under Study

Symptoms of disease under study are those that might be expected to occur as a direct result of UC (eg, hemorrhagic diarrhea or defecation urgency). Events that are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

8.3.8 Reporting of SAEs

All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B of the CSP.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention

8.3.9.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day** (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.9.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 18 weeks following the last dose.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) occurring from the date of the first dose until 18 weeks following the last dose should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3.10 Adverse Events of Special Interest

8.3.10.1 CCI

CCI is commonly associated with CCI Anaphylaxis and CCI have some common manifestations and may be difficult to distinguish from each other. CCI are commonly observed during or shortly after the first exposure to therapeutic monoclonal antibodies delivered through CCI These reactions are less common following subsequent exposures. Reactions occurring at the time of or shortly after CCI of study intervention are to be judged by the investigator at his/her own discretion.

The site of injection will be assessed at every visit during the Induction and Maintenance Periods. Injection-site reactions will be recorded as AEs according to the criteria described in Section 8.3.

8.3.10.2 Malignancies

Emerging data from clinical trials with briakinumab and ustekinumab suggest a possible association between dual inhibition of IL-12 and IL-23 and the development of certain malignancies; however, it remains uncertain whether inhibition of IL-23 alone would have similar effects.

Nonclinical studies evaluating the genotoxic, mutagenic, and carcinogenic potential of brazikumab have not been conducted because brazikumab is a large protein molecule that is not expected to cross the nuclear or mitochondrial membranes and interact directly with DNA or other chromosomal materials. In preclinical toxicology studies, no effects related to tumor formation were observed in cynomolgus monkeys treated with brazikumab for 6 months that resulted in exposures greater than those used in humans. Furthermore, results from preclinical studies in mice suggest that blockade of the IL-23 pathway or deficiencies in the IL-23 or IL-23 receptor genes result in decreased tumor formation, tumor volume, and metastases and faster elimination of injected tumor cells.

Participants in this study will be monitored for the development of any malignancies by routine laboratory, physical examination, and AE assessments. In addition, participants will be advised of the potential risk of malignancy in the ICF.

Participants with a history of cancer, except for basal cell carcinoma and/or squamous cell carcinoma of the skin, or in situ carcinoma of the cervix treated with apparent success with curative therapy within the specified time period, outlined in Exclusion Criterion #15, will be excluded. Participants with evidence of dysplasia on endoscopy and confirmed on biopsy will be excluded.

8.3.10.3 Hypersensitivity Reactions (Including Anaphylaxis)

Unlike CCI [redacted] anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and/or mucosal reactions.

8.3.10.4 Infections

The use of immunomodulatory drugs, including biologic therapies, may increase susceptibility to infections. Participants should be counselled on infection risk, and a benefit/risk assessment should be considered prior to initiating treatment. Appropriate precautions should be considered, including vaccine administration for prevention prior to study enrollment, according to local guidelines.

The immunoregulatory role of IL-23 in humans is not completely understood. Nonclinical studies have suggested that IL-23 may play a role in host defense against certain extracellular and intracellular pathogens. Participants administered brazikumab may be at risk of developing, or have difficulty overcoming, certain types of infections.

Participants with certain ongoing, recent, or latent infections, or at high baseline risk of developing infections, are not to receive brazikumab and will be excluded from the study per Exclusion Criterion #13.

Occurrence of infections will be monitored during the study by routine hematology, physical examination, and AE assessments.

8.3.10.4.1 Non-opportunistic Infections

A serious non-opportunistic infection is any non-opportunistic infection that meets the SAE criteria in Appendix B 2. Any relevant culture results and diagnostic and/or therapeutic procedure results for a participant with a serious non-opportunistic infection must be provided as an SAE update. Nonserious non-opportunistic infections will not be reported as AESIs.

8.3.10.4.2 Opportunistic Infections

An opportunistic infection is an infection caused by microorganisms that are normally non-pathogenic or rarely pathogenic or result in a more severe infection not experienced in individuals with normal immune function. Examples of opportunistic infections may include *Pneumocystis jiroveci* pneumonia, *Salmonella* septicemia, and certain Cytomegalovirus infections such as encephalitis or retinitis.

Opportunistic infections are considered serious and must be reported as an SAE. Any relevant culture results and diagnostic and/or therapeutic procedure results for a participant with an opportunistic infection must be provided as an SAE update.

8.3.11 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day** (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.8) and **within 30 days** for all other medication errors.

The definition of a medication error can be found in Appendix B 5.

8.4 Overdose

For this study, any dose of brazikumab greater than CCI or CCI administration will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.8) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay, as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

Venous blood samples will be collected for measurement of serum brazikumab concentrations as specified in the SoA in Section 1.3. All predose PK samples are to be collected at 0 hours (ie, CCI).

The actual date and time (24-hour clock time) of each sample and each dose will be recorded. Samples collected may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Serum concentration data will be analyzed using a PK population approach as described in the Modeling and Simulation Analysis Plan.

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor (eg, for safety reasons). The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate bioanalytical report.

8.5.2 Immunogenicity Assessments

Serum samples to measure the presence of ADA against brazikumab will be collected prior to study intervention administration and according to the SoA (Section 1.3). Instructions for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the sites.

In brief, blood samples will be collected from all participants for the detection of anti-brazikumab antibodies (binding antibodies and neutralizing antibodies) using a validated immunoassay and a validated cell-based assay. Full details of the methods used will be described in a separate report.

Anti-drug antibody samples may also be further tested for characterization of the ADA response.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.3 Pharmacodynamics

Pharmacodynamic assessments will not be included in this study.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study, the participant consents to the mandatory research components of the study.

Blood, stool, and biopsy samples will be collected and analyzed to evaluate protein, nucleic acid, metabolic, and cellular BMs according to the SoA in Section 1.3. All samples should be collected predose and will be analyzed centrally at contracted third-party labs.

Biomarkers that may be analyzed include, but are not limited to, whole blood gene expression, gut biopsy tissue gene expression, stool microbiome composition, serum/plasma/stool proteins including, but not limited to, cytokines, chemokines, and inflammatory mediators associated with IBD, immunological function, and the pharmacology of brazikumab. The intended purpose is to evaluate the association of these BMs with observed clinical responses over the entire treatment duration of the clinical study and to enhance knowledge and understanding of UC pathogenesis.

Instructions for the collection and handling of biological samples will be provided by the sponsor. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the sites.

Venous blood samples will be collected for measurement of IL-22 serum concentration, CCI concentration, and other soluble BMs. IL-22 serum samples may also be used for development of a commercial diagnostic assay.

An additional whole blood sample will be collected for isolation of RNA and stored for future analyses. Ribonucleic acid may be used for the analyses of transcript expression using next-generation sequencing, microarray, or other suitable techniques.

All additional BM analyses are exploratory and will be described in a separate report.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement in the ICF addendum.

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

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.8 Healthcare Resource Utilization

Healthcare resource utilization data, associated with medical encounters, will be collected in accordance with the SoA (Section 1.3) in the eCRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

At randomization, retrospective IBD-related healthcare resource utilization information will be collected with a 1-year recall period. At all subsequent visits, IBD-related healthcare resource utilization information will be collected with a recall period of "since the last scheduled visit." At visits when healthcare use is being collected, the investigator should ask the participant if they have had any need to seek medical treatment for IBD or an IBD-related episode since the previous scheduled visit.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries and other selected procedures (inpatient and outpatient)
- Rate of IBD-related surgeries
- Rate of all-cause hospitalizations and IBD-related hospitalizations
- Duration of each hospitalization (total days or length of stay, including duration by units [eg, intensive care unit, emergency room, and hospitalization unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and interventions (including physician or emergency room visits, test procedures, and medications)

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary null hypothesis is that the clinical remission rates at Week 10 derived from mMS (primary efficacy endpoint) for each of the IV brazikumab 720 mg and IV brazikumab 1440 mg treatment groups is not different from that for the IV placebo treatment group. The alternative hypothesis for each of the brazikumab treatment groups is that the clinical remission rates associated with the brazikumab treatment group is different from that for the placebo treatment group.

The primary estimand is described in Table 13.

Table 13 Primary Estimand

Key elements	Description
Population	Participants with moderately to severely active UC

Variable	Clinical remission defined as:
	• mMS at Week 10:
	  ◦ Endoscopy subscore = 0 or 1, AND
	  ◦ Rectal bleeding subscore = 0, AND
	  ◦ Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline

Treatment comparison	Each brazikumab dose versus placebo
Strategy for intercurrent events:	A participant who: • discontinues treatment prematurely • takes rescue treatment • uses prohibited treatment is considered as being unsuccessfully treated ("Composite strategy" – ICH E9 [R1]).
Population-level summary	• Percentage of participants with clinical remission

ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; mMS = modified Mayo score; UC = ulcerative colitis.

9.2 Sample Size Determination

In previous studies, the clinical remission responder used was based on the Mayo Scoring System where the endoscopic subscore of 1 (mild disease) allowed the presence of friability. In this study, the endoscopic subscore of 1 was modified to specify no friability.

Brazikumab and placebo responder rates are assumed to be 22.4% and 5.4%, respectively, considering previous study results and available external data, along with the expected ratio of biologic naïve to biologic intolerant of refractory participants. Based on these assumptions, a

continuity-corrected Cochran-Mantel-Haenszel test of odds ratio = 1 for 2 × 2 tables in 2 strata will have 81% power to detect an odds ratio of 5.3 using a 2-sided 5% test level.

The total sample size of CCI account for the 3 treatment arms, brazikumab CCI brazikumab CCI and placebo CCI Participants previously randomized to the brazikumab CCI and vedolizumab CCI treatment arms under Protocol Amendment 4 and earlier are not included in the total sample size of CCI

9.3 Populations for Analyses

The analysis populations are defined in Table 14.

Table 14 Populations for Analysis

Population/Analysis Set	Description
All Patients Analysis Set	All individuals screened for the study.
Full Analysis Set	All randomized participants, excluding participants randomized to active comparator (vedolizumab) or 2100 mg brazikumab; participants will be summarized according to the randomized study intervention.
Safety population	All participants who have received at least 1 dose of investigational product. Erroneously treated participants (eg, those randomized to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A participant who has on one or several occasions received active study intervention is classified as active and is accounted for in the active study intervention treatment group. A participant who has received both active dose regimens is classified as the higher active dose regimen.
PK population	The PK population includes all participants who receive at least 1 dose of study intervention and have at least 1 PK sample containing detectable brazikumab concentrations. The Exposure-Response population will be defined in the Modeling and Simulation Plan prior to database lock.
Maintenance Period population	All participants who received at least 1 dose at or after Week 10, excluding participants randomized to active comparator (vedolizumab) or 2100 mg brazikumab. Data for participants will be summarized according to the study intervention they actually received.

PK = pharmacokinetic(s).

9.4 Statistical Analyses

The study will be unblinded, and the primary analysis for the study will be conducted, after the last participant has completed the Week 10 visit. AstraZeneca personnel who are directly involved with the conduct of the study, study site personnel, as well as participants will remain blinded to the treatment assignment for individual participants until the completion of the

study. Details on what roles will remain blinded and how trial integrity will be maintained will be documented separately. The final analysis will be performed after the last participant completes the Week 54 visit.

9.4.1 General Considerations

The efficacy analyses will be based on the Full Analysis Set. All statistical tests will be 2-sided hypothesis tests. All CIs will be 2-sided 95% CIs, unless stated otherwise.

The SAP was signed off before any review of blinded data and before Protocol Amendment 4. The SAP will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned main statistical methodology features of the primary and the key secondary endpoints. The SAP will be amended according to Protocol Amendment 5 before the first participant after amendment 4 is included in the study.

Efficacy data

All efficacy data for participants who were enrolled prior to Protocol Amendment 5 and randomized to brazikumab CCI or vedolizumab CCI will be listed only. The other pre-Amendment 5 participants (randomized to brazikumab CCI brazikumab CCI CCI will be grouped with their corresponding post-Amendment 5 dose group and included in the efficacy analysis.

Safety data

All safety data for participants who were enrolled prior to Protocol Amendment 5 and randomized to CCI will be listed only. The other pre-Amendment 5 participants will be grouped with their corresponding post-Amendment 5 dose group and included in safety summary tables. Participants in the pre-Amendment 5 high-dose brazikumab group (CCI will be included in the "overall brazikumab" category of summaries but will not be summarized separately.

Details will be provided in the SAP.

For all responder endpoints, participants who do not meet responder criteria, either due to missing assessments or ED, are considered non-responders for analysis purposes. Furthermore, the use of rescue treatment and/or prohibited treatment will be considered a failure of the study independently from the therapeutic intent. This method is referred to as NRI and will be applied to primary, secondary, and exploratory efficacy endpoints. Details will be provided in the SAP.

Unless otherwise defined, baseline for efficacy variables is defined as the last nonmissing efficacy assessment before the first dose of study intervention upon randomization. The mMS assessed at Screening will be used as baseline. Details will be provided in the SAP.

Considering that this is not a confirmatory study, no multiplicity adjustment will be planned in this study.

9.4.2 Efficacy

9.4.2.1 Efficacy Endpoints

The primary and secondary efficacy endpoints are listed below and analyses are defined in the following sections.

Table 15 Efficacy Endpoints

Endpoint	Definition
Primary	
Clinical remission at Week 10	mMS derived from the Mayo Scoring System with endoscopic friability modification Clinical remission at Week 10 requires meeting ALL of the following criteria at Week 10: • Endoscopy subscore = 0 or 1 • Rectal bleeding subscore = 0 • Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline
Secondary	
Sustained clinical remission	Clinical remission requires meeting ALL of the following criteria at both Week 10 and Week 54: • Endoscopy subscore = 0 or 1 • Rectal bleeding subscore = 0 • Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline
CS-free clinical remission at Week 54	CS-free clinical remission at Week 54 requires meeting ALL the following criteria at Week 54 and who are CS-free for at least 12 weeks before the assessment at Week 54: • Endoscopy subscore = 0 or 1 • Rectal bleeding subscore = 0 • Stool frequency subscore = 0 or 1, AND at least a 1-point decrease from baseline
Clinical response at Week 10	Clinical response at Week 10 requires meeting the following criterion at Week 10 • Reduction in mMS ≥ 2 points from baseline AND ≥ 30% from baseline AND a decrease in the rectal bleeding score ≥ 1 point from baseline or a score of 0 or 1
Endoscopic improvement at Week 10	Endoscopic improvement at Week 10 requires meeting the following criterion at Week 10: • Endoscopy subscore = 0 or 1

CS = corticosteroid; mMS = modified Mayo score.

Additional efficacy endpoints will be fully described, with corresponding analyses, in the SAP. These may include change from baseline and/or responder analyses derived from the following assessments:

- mMS
- CS use
- GHI
- RHI

- FACIT-F
- PGIC-UC
- PGIS-UC
- IBDQ
- SF-36v2
- EQ-5D-5L

9.4.2.2 Efficacy Analyses

For the Induction Period, the primary and secondary responder endpoints described in Section 9.4.2.1 will be analyzed using a Cochran-Mantel-Haenszel test, comparing each active CCI brazikumab CCI treatment groups as randomized at baseline) versus placebo, and controlling for randomization stratum which is prior biological intervention use (naïve or prior use). The responder endpoints during the Maintenance Period (sustained clinical remission, etc) will be analyzed using a Cochran-Mantel-Haenszel test controlling for randomization stratum. Analysis will be performed on the Full Analysis Set population, by induction treatment group, for the primary endpoint. For these analyses, the following statistics will be presented:

- Responder counts and estimated response rate with corresponding 95% CI for each treatment group
- Estimated treatment effect (ie, difference in response rate for active versus placebo) with corresponding 95% CI and 2-sided p-value

Any additional analyses may be defined in the SAP.

9.4.3 Safety

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs, clinical laboratory values, vital signs, physical exams, and ECG parameters. For each clinical laboratory, vital sign, and ECG parameter, the last nonmissing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter.

9.4.3.1 Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of study intervention. However, an AE that occurs more than 18 weeks after the last dose of study intervention will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criteria.

The number and percentage of participants reporting TEAEs in each study intervention will be tabulated as follows:

- By SOC and PT
- By SOC, PT, and severity

The number and percentage of participants reporting treatment-related TEAEs in each study treatment will be tabulated by SOC and PT.

If more than 1 AE is coded to the same PT for the same participant, the participant will be counted only once for that PT using the most severe occurrence for the summarization by severity.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation if 5 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

In addition, adverse events of special interest as defined in Section 8.3.6 will also be summarized.

The definitions of an AE and SAE can be found in Appendix B.

9.4.3.2 Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline and changes from baseline at each assessment will be presented by study intervention for each clinical laboratory assessment.

The criteria for PCS laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study intervention at each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.3.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, weight, respiration rate, and temperature) at baseline and changes from baseline at each assessment will be presented by study intervention.

Vital sign values will be considered PCS if they meet both the observed value criteria and the change from baseline value criteria that will be detailed in the SAP. The number and

percentage of participants who have PCS postbaseline vital sign values will be tabulated by study intervention for each assessment. The percentages will be calculated relative to the number of participants who have available baseline values or available non-PCS baseline values for parameters with only observed value criterion and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.3.4 Electrocardiograms

Descriptive statistics for ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTc) at baseline and changes from baseline at each assessment will be presented by study intervention for each ECG assessment.

The criteria for PCS ECG values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline ECG values will be tabulated by study intervention at each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetic Analyses

Descriptive statistics of brazikumab serum concentrations and immunogenicity will be presented. Pharmacokinetic and PD analyses will be specified in a separate Modeling and Simulation Analysis Plan finalized before database lock. The population PK and PK-PD analyses may be reported separately from the main CSR.

9.4.4.2 Biomarker Analyses

The primary endpoint will be further evaluated for the IL-22 BM that potentially predicts the efficacy of brazikumab with respect to the remission response. This endpoint will be evaluated for brazikumab intervention versus placebo to determine a possible subgroup based on the IL-22 BM. The cutoff will provide an optimal threshold to define a BM-positive and a BM-negative subgroup for future studies. The IL-22 concentration cutoff will be selected as the value that maximizes the difference in clinical remission between brazikumab and placebo when comparing the BM+ and BM- population for the pooled doses of brazikumab versus placebo. This cutoff will be algorithmically derived using a normalized Z-score across the population of all possible cutoff points. Should an optimal threshold be determined, it will be selected with consideration to the totality of statistical evidence in conjunction with clinical, regulatory, and commercial relevance.

The exploratory BM endpoints defined in Table 5 will be analyzed in the same way as for the all-comer population. All presentations will include results for both the BM+ and BM- participants. Further details will be included in the SAP.

Other exploratory BM analyses will be defined and presented outside of the SAP and CSR.

9.5 Interim Analyses

The primary analysis (described in Section 9.4.2) will be conducted when all participants have completed their Week 10 visit. Hence, this is an analysis prior to the time point of the formal completion of the trial.

9.6 Data Safety Monitoring Board

In addition to the above, monitoring of participant safety data will be performed by an independent DSMB. The DSMB will review interim safety data at defined intervals throughout the study. The DSMB will communicate their recommendations to the sponsor after each meeting but will serve in an advisory capacity only; the DSMB will not be empowered to stop the study or require changes in the protocol. Study conduct may be interrupted or terminated by the sponsor based on DSMB recommendation if safety data become available that appear to represent an undue risk to the study participants' health or well-being. Further details of the DSMB (composition, policy, and procedures) are specified in a separate DSMB charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The DSMB is charged with reviewing and evaluating safety for this study as agreed upon with the study sponsor. A DSMB is created to review accumulating safety data of Study D5272C00001 at scheduled time points, as agreed upon with the sponsor. The DSMB's activities will further protect the rights, safety, and well-being of the participants in this study. The DSMB will be independent from the trial sponsor, the investigators, or anyone involved in the clinical care of the study participants.

DSMB services are provided by vendor (Everest), and all activities are described in the DSMB charter.

Issues identified by DSMB will be addressed. For example, this could involve amendments to the CSP and letters to investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and nonserious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an *important medical event* that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above

Adverse events for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the *important medical event* criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **nonserious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as nonserious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity Rating Scale

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 Definition of Adverse Events of Special Interest

An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESI(s) have been identified for the study intervention(s) in this protocol:

- CCI
- Malignancies
- CCI
- Infections
  - Serious non-opportunistic infections
  - Opportunistic infections

Nonserious AESIs are to be recorded in the eCRF within 72 hours, and serious AESIs are to be reported to the sponsor within 24 hours.

B 4 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of *related* is made if following a review of the relevant data, there is evidence for a *reasonable possibility* of a causal relationship for the individual case. The expression *reasonable possibility* of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as *not related*.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 5 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion

- Dispensing error (eg, medication prepared incorrectly, even if it was not actually given to the participant)
- Drug not administered as indicated (eg, wrong route or wrong site of administration)
- Drug not taken as indicated (eg, tablet dissolved in water when it should be taken as a solid tablet)
- Drug not stored as instructed (eg, kept in the refrigerator when it should be at room temperature)
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM, including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) (eg, forgot to take medication)
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue treatment, or standard of care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

B 6 AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF within 3 days.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the ICF.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the ICF.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B, or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability or life-threatening or fatal disease in otherwise healthy humans or animals.

Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Examples of Category B pathogens include Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

Exempt – Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care, and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfill all of the inclusion criteria described in the main body of the CSP and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
  - Healthy volunteers and pediatric patient samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at Day 1 or at any other timepoint after Day 1. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the ICF for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated ICFs must be given to the participant and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, the sponsor Study Physician/designee or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations, or health insurance companies. This can be done by placing the results in scientific databases where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; eg, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated total bilirubin from a local laboratory.

The investigator will also review AE data (eg, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

Potential Hy's Law is defined as AST or ALT ≥ 3 × ULN **together with** total bilirubin ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

Hy's Law

Hy's Law is defined as AST or ALT ≥ 3× ULN **together with** total bilirubin ≥ 2 × ULN, where no other reason, other than the IP, can be found to explain the combination of increases (eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug).

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to the AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central study team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria *important medical event* and causality assessment *yes/related* according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The sponsor Study Physician/designee contacts the investigator to provide guidance and discuss and agree upon an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE page as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the sponsor Study Physician/designee. This includes deciding which tests available in the HL lab kit should be used.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the sponsor Study Physician/designee if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the sponsor Study Physician/designee contacts the investigator in order to review available data, agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP, and ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and

Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previous Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and total bilirubin elevations other than the IP:

- Update SAE page (report term *Hy's Law*) according to AstraZeneca standard processes.
  - The *Medically Important* serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of *related* should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously entered SAE of Potential Hy's Law (report term now *Hy's Law case*), ensuring causality assessment is related to IP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously entered PHL SAE page following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin [c]
Autoimmune hepatitis	ANA Anti-LKM ASMA
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
[c] Carbohydrate deficient-transferrin and transferrin are not available in China. Study teams should amend this list accordingly.

ANA = antinuclear antibody; anti-LKM = anti-liver/kidney microsomal antibody; ASMA = anti-smooth muscle antibody; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = gamma-glutamyl transferase; HAV = hepatitis A virus; HbsAg = hepatitis B surface antigen; HBc = hepatitis B core; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; RNA = ribonucleic acid.

E 6 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation.' Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix F Procedures for Tuberculosis Testing from Screening

Testing for TB will be performed as specified in the SoA (Section 1.3). The following guidelines for TB testing should be followed at Screening and during the study period:

- TB worksheet must be completed for all participants during Screening to assess risk factors for TB.
- Participants who have negative results for the QFT-TB test at Screening and have not had any known recent exposure to individuals with TB may be randomized if eligible without prophylaxis.
- Participants with a new diagnosis of latent TB at Screening are excluded.
- If the QFT-TB test at Screening is indeterminate, the QFT-TB test is to be repeated once by the central laboratory at Screening. The participant may be randomized if the following are fulfilled:
  - QFT-TB retest is negative.
  - The chest x-ray at Screening (or within 8 weeks prior to Screening) does not show evidence of active TB.
  - There are no symptoms, signs, risk factors, or medical history that are consistent with active TB per the TB worksheet.
  - No known recent exposure to a case of active TB.
- If there is a concern for increased risk for TB after randomization, an unscheduled QFT-TB test may be performed.

Appendix G Patient-reported Outcomes Questionnaires, Descriptions, and Instructions

G 1 Bowel Movement Diary

Patient Reported Outcomes Questionnaire: Bowel Movement Diary was removed due to copyrights.

G 2 Evening Diary

Patient Reported Outcomes Questionnaire: Evening Diary was removed due to copyrights.

Patient Reported Outcomes Questionnaire: Evening Diary was removed due to copyrights.

G 3 Site Visit Instruments

Note: The questionnaires presented below are an approximation of the planned final documents. The order of some questions may change. The final documents will be incorporated into the handheld electronic device for participant use.

G 3.1 Patient Global Impression of Severity – Ulcerative Colitis

Overall, how would you rate your ulcerative colitis (UC) symptoms in the past 7 days?

[0] None
[1] Mild
[2] Moderate
[3] Severe

G 3.2 Patient Global Impression of Change – Ulcerative Colitis

Compared to before you started this study, how would you rate your ulcerative colitis (UC) symptoms overall?

[1] Much better
[2] Somewhat better

[3] A little better
[4] No difference
[5] A little worse
[6] Somewhat worse
[7] Much worse

G 3.3 FACIT-F Scale (Version 4)

Patient Reported Outcomes Questionnaire: FACIT-F Scale was removed due to copyrights.

G 3.4 Inflammatory Bowel Disease Questionnaire

Patient Reported Outcomes Questionnaire: IBDQ was removed due to copyrights.

Patient Reported Outcomes Questionnaire: IBDQ was removed due to copyrights.

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Patient Reported Outcomes Questionnaire: IBDQ was removed due to copyrights.

Patient Reported Outcomes Questionnaire: IBDQ was removed due to copyrights.

G 3.5 EQ-5D-5L (US English Sample Version)

Patient Reported Outcomes Questionnaire: EQ-5D-5L was removed due to copyrights.

Patient Reported Outcomes Questionnaire: EQ-5D-5L was removed due to copyrights.

G 3.6 SF-36v2® Health Survey

Patient Reported Outcomes Questionnaire: SF-36v2 was removed due to copyrights.

Patient Reported Outcomes Questionnaire: SF-36v2 was removed due to copyrights.

Patient Reported Outcomes Questionnaire: SF-36v2 was removed due to copyrights.

Patient Reported Outcomes Questionnaire: SF-36v2 was removed due to copyrights.

Patient Reported Outcomes Questionnaire: SF-36v2 was removed due to copyrights.

Patient Reported Outcomes Questionnaire: SF-36v2 was removed due to copyrights.

Appendix H Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. [Modified from ICH E2A] Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion. (NCI)
Death	The absence of life or state of being dead. (NCI)
Disease relapse	The return of a disease after a period of remission.
Failure to meet randomization criteria	An indication that the participant has been unable to fulfill/satisfy the criteria required for assignment into a randomized group.
Lack of efficacy	The lack of expected or desired effect related to a therapy. (NCI)
Lost to follow-up	The loss or lack of continuation of a participant to follow-up
Noncompliance with study drug	An indication that a participant has not agreed with or followed the instructions related to the study medication. (NCI)
Other	Different than the one(s) previously specified or mentioned. (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to participant. (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Progressive disease	A disease process that is increasing in extent or severity. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol. (NCI)

CDISC Submission Value	CDISC Definition
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI)
Screen failure	The potential participant who does not meet one or more criteria required for participation in a trial.
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor. (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor. (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument. (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study. (NCI)

AE = adverse event; CDISC = Clinical Data Interchange Standards Consortium; ICH = International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; NCI = National Cancer Institute.

Appendix I Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor, and instructions on how to perform these procedures will be provided at the time of implementation. If participant testing is performed as a result of the public health crisis, results may be documented for this study.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions, and other measures implemented to ensure the participant's safety. If in doubt, please contact the sponsor Study Physician/designee.

Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary (eg, remote visits). Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in the SoA (Section 1.3). Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated sponsor Study Physician/designee.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrollment into the study or commencing of dosing with study intervention. If this delay is outside the Screening window specified in Table 1, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a participant in addition to that detailed in

Section 5.4. The procedures detailed in Table 1 must be undertaken to confirm eligibility using the same randomization number as for the participant.

Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the participants home or other remote location as per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix and the associated Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster or Public Health Crisis, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medications, etc to be collected according to study requirements.

At-home or Remote Location Study Intervention Administration Instructions

If a site visit is not possible, at-home or remote location administration of study intervention may be performed by a qualified site HCP, provided this is acceptable within local regulation/guidance. The option of at-home or remote location study intervention administration ensures participants safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimize interruption of study intervention administration during other study disruptions (eg, site closures due to natural disaster).

At-home or Remote Location Study Intervention Administration by a Qualified HCP or TPV Service

A qualified HCP from the study site or TPV service may administer the study intervention at the participant's home or other remote location according to the CSP and the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis, and if allowed by local SOPs, as applicable. All necessary supplies and instructions for administration and documentation of study intervention administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit. Refer to the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for step-by-step guidance including drug accountability and reconciliation requirements.

Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents.

Appendix J Abbreviations

Abbreviation or Special Term	Explanation
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANA	antinuclear antibody
anti-LKM	anti-liver/kidney microsomal antibody
aPTT	activated partial thromboplastin time
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
AUC	area under the serum concentration versus time curve
$AUC_{0\text{-}28day}$	area under the serum concentration-time curve from time zero to 28 days
$AUC_{0\text{-}tau}$	area under the serum concentration-time curve from time zero to the end of the dosing interval
BM	biomarker
BM-	biomarker serum IL-22 concentrations below a pre-established cutoff
BM+	biomarker serum IL-22 concentrations at or above a pre-established cutoff
BP	blood pressure
BSFS	Bristol Stool Form Scale
BUN	blood urea nitrogen
C. difficile	*Clostridium difficile*
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum serum drug concentration
CMV	cytomegalovirus
COVID	coronavirus disease 2019
CRO	clinical research organization
CRP	C-reactive protein
CS	corticosteroid
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or Special Term	Explanation
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
EC	European Commission
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation of study intervention
EDC	electronic data capture
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EIM	extra-intestinal manifestation
EMA	European Medicines Agency
ePRO	electronic patient-reported outcomes
EQ-5D-5L	5-level European Quality of Life – 5 Dimensions
ET	early termination
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	US Food and Drug Administration
FSH	follicle-stimulation hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GHI	Geboes Historical Index
HAV	hepatitis A virus
HBc	hepatitis B core
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCP	health care provider
HCV	hepatitis C virus
HEV	hepatitis E virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hy's Law
HRQoL	health-related quality of life

Abbreviation or Special Term	Explanation
HSV	herpes simplex virus
IATA	International Airline Transportation Association
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
IEC	independent ethics committee
IFNγ	interferon-gamma
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
CCI	CCI
IWRS	interactive web response system
IxRS	interactive voice/web response system
CCI	CCI
LDH	lactate dehydrogenase
MACE	major adverse cardiac events
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
mMS	modified Mayo score
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect-level
NRI	non-responder imputation
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension

Abbreviation or Special Term	Explanation
PCR	polymerase chain reaction
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PGA	Physician's Global Assessment
PGIC-UC	Patient Global Impression of Change – Ulcerative Colitis
PGIS-UC	Patient Global Impression of Severity – Ulcerative Colitis
PHL	potential Hy's Law
PII-BMF	Patient Impression of Interference – Bowel Movement Frequency
PIS-RB	Patient Impression of Severity – Rectal Bleeding
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
pMS	partial Mayo score
PR	time from beginning of the P wave until the beginning of the QRS complex
PREGREP	pregnancy report
PREGOUT	pregnancy outcome report
PRO	patient-reported outcomes
PT	preferred term
QFT-TB	QuantiFERON-TB
QRS	time from beginning of the Q wave to end of the S wave in heart's electrical cycle
QT	time from beginning of the Q wave to end of the T wave in heart's electrical cycle
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RBC	red blood cell
RHI	Robarts Histopathology Index
RNA	ribonucleic acid
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
CCI	CCI
SF-36v2	36-item Health Survey Version 2
SI	International System of Units
SoA	schedule of activities
SOC	system organ class

Abbreviation or Special Term	**Explanation**
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNFα	tumor necrosis factor-alpha
TPV	third-party vendor
UC	ulcerative colitis
ULN	upper limit of normal
UNS	Unscheduled
US	United States
W	Week
WBC	white blood cell
WOCBP	women of childbearing potential
w/v	weight/volume

Appendix K Protocol Amendment History

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

Amendment 5: (March 2021)

In 2020, AstraZeneca resumed full ownership of brazikumab clinical development. AstraZeneca re-evaluated the development plan and the CSP D5272C00001 (Legacy #3151-201-008) was consequently reviewed and amended.

As part of the changes to the development program, the highest brazikumab induction dose CCI arm and the vedolizumab arm were removed from this study. CCI induction dose was anticipated to provide limited additional benefit versus CCI in this study. The vedolizumab arm was removed to expand the study population to include vedolizumab failures and reduce study complexity, which decreases participant burden by eliminating the need for the double-dummy design.

In addition, changes were made to improve clarity and consistency across the protocol resulting from changes in the study design and the application of the AstraZeneca protocol template.

Section # and Name	Description of Change	Brief Rationale
Throughout	The protocol was transferred to the AstraZeneca protocol template.	The sponsor of the study has changed to AstraZeneca. The protocol was transferred to the AstraZeneca template to align the study with AstraZeneca processes and approved language, including alignment across brazikumab protocols.
Throughout	The vedolizumab treatment arm was removed.	The vedolizumab arm was removed to expand the study population to include vedolizumab failures and reduce study complexity, which decreases participant burden by eliminating the need for the double-dummy design.
Throughout	The 2100 mg brazikumab IV treatment arm was removed.	As a result of the sponsor change, the development program has been re-evaluated. Based on re-evaluation of data, limited benefit of CCI over CCI is expected (CCI is predicted to give maximal effect).

Section # and Name	Description of Change	Brief Rationale
Throughout	Changes to the study intervention doses throughout have been changed accordingly: • The [redacted] brazikumab [redacted] treatment arm was changed to [redacted] the [redacted] brazikumab [redacted] arm was changed to [redacted] • The [redacted] brazikumab [redacted] treatment arm was changed to [redacted] the [redacted] brazikumab [redacted] arm was changed to [redacted]	As a result of the sponsor change and process batch material changes, nominal doses in both induction and maintenance are changing, aligning doses across all brazikumab studies (UC and CD). Study intervention for this study has been changed to the following: • Brazikumab [redacted] solution for [redacted] which is [redacted] per [redacted] Dosing has been matched to the [redacted] concentration. • Brazikumab [redacted] prefilled syringe for [redacted] in a [redacted] Dosing has been matched to the [redacted] concentrations. The dose change is regarded as minor in relation to variability in exposure.
Throughout	Study visit numbers were replaced by week numbers, starting with the Treatment Period.	To improve clarity regarding the timing of study activities.
Throughout	"Baseline (Visit 2)" was replaced with "Week 0 (Day 1)."	To align with new language for visits within the amended CSP.
Throughout	[redacted]	To align with MedDRA terminology.
Throughout	Replaced "study physician" with "sponsor Study Physician/designee."	To allow flexibility in the sponsor contact person.
Title page	Deleted "Treatment," "Double-dummy," and "Active-controlled" from the study title.	To reflect the removal of the active comparator treatment arm from the study design.
Title page	Added the study acronym Expedition Lead-in.	To align with the AstraZeneca template.
Title page	Added international coordinating investigator.	To align with the AstraZeneca template.
Synopsis	Revised to align with changes to the protocol and the AstraZeneca template.	To align with changes to the protocol and the AstraZeneca template.
Study schema	Revised study schema.	To reflect study design changes.

Section # and Name	Description of Change	Brief Rationale
SoA	• Separated the SoA into 4 tables: Screening Period, Treatment Period, Safety Follow-up Period, and PROs. • Added language at beginning of Section 1.3 that study procedures are to be completed prior to study intervention administration if possible and PROs should be completed prior to other assessments. • Added sentence with hyperlinks cross-referencing to each SoA table. • Reformatted tables (including updating explanatory notes) and grouped assessments by category.	Revised for clarity for investigators and to align across brazikumab protocols.
SoA – Screening	Expanded Screening Period up to 35 days (5 weeks) for all participants.	To decrease site and participant burden and to provide flexibility for endoscopy scheduling.
SoA – Screening	Removed assessment for hemoglobin A1c.	Hemoglobin A1c value does not impact study eligibility and may be evaluated by local laboratory at the investigator's discretion. To align with other brazikumab protocols.
SoA – Screening and Table 12	Removed urine drug testing.	Removed to reduce participant and site burden. Aligns with AstraZeneca procedures; testing is not required for all participants.
SoA – Screening	Removed sample for CCI	CCI has been changed to an exploratory BM and will be measured at Day 1 to align with treatment outcome measures.
SoA – Screening	Added stool sample for fecal calprotectin and fecal lactoferrin.	To evaluate BMs with efficacy variables to understand correlation with response.
SoA – Screening	Revised language regarding PRO assessments.	To include providing PRO device and instructions and checking PRO compliance.
SoA – Screening	Added assessments for partial and mMSs.	To clarify the timing of assessments with respect to PRO assessments.
SoA – Treatment	Added a column to the Treatment Period for unscheduled visits.	Added to provide guidance to the investigator on assessments to be performed at any unscheduled visit.
SoA – Treatment	Changed Baseline visit to W0.	To improve clarity and avoid confusion with baseline values from the Screening Period.

Section # and Name	Description of Change	Brief Rationale
SoA – Treatment	Removed 1-week delay between randomization and first dose of study intervention.	Delay stated in legacy protocol allowed for shipment of study intervention to site after initial randomization. Change in treatment arms now permits the first dose of study intervention to occur on the same day as randomization.
SoA – Treatment	Revised language regarding PRO assessments.	To clarify what will be done at PRO visits.
SoA – Treatment	Added row for qualitative sub-study interview.	To align with addition of the Participant Qualitative Interview Sub-study.
SoA – Treatment	Added Mayo score to endoscopy and colon mucosal biopsies.	To emphasize that the endoscopy is part of the Mayo score; colon mucosal biopsies will be performed at the same time.
SoA – Treatment	Added PGA to Week 0.	Since endoscopies may be performed at specialist centers and not at the primary site for all other assessments, collection of PGA scores will be undertaken both pre- and post-baseline colonoscopy to enable determination of any changes at either side of the procedure and subsequent determination of the complete (4-domain) Mayo score. This also allows for alignment with PRO assessments (eg, FACIT-F).
SoA – Treatment	Added physical examination at Weeks 0, 2, and 30.	For assessment of participant safety.
SoA – Treatment	Revised presentation of PK sampling.	To align with other brazikumab protocols.
SoA – Treatment	Added fecal lactoferrin and exploratory biomarkers to stool sample.	To expand possible stool biomarkers.
SoA – Treatment	CCI and CCI administration rows.	For simplification and clarity.
SoA – Safety Follow-up Period	Added 12-lead ECG to both Safety Follow-up visits.	For assessment of participant safety in the Follow-up Period. To align with other brazikumab protocols.
SoA – Safety Follow-up Period	Added injection-site reaction assessments to both Safety Follow-up visits.	For assessment of participant safety in the Follow-up Period. To align with other brazikumab protocols.
SoA – Safety Follow-up Period	Removed PAXgene for whole blood RNA transcript profiling assessment.	Not required during follow-up; additional samples for RNA profiling will be taken during OLE study.
SoA – PRO Assessments	Reduced the number of timepoints at which PROs are assessed.	To reduce site and participant burden.

Section # and Name	Description of Change	Brief Rationale
SoA – PRO Assessments and Sections 8.1.7 and 9.4.2.1	Removed PIS-RB and PII-BMF.	Not relevant as specific symptoms to the primary endpoint. The removal of these 2 measures supports reduction of non-essential PRO collection, reducing patient burden.
SoA – PRO Assessments and Section 8.1.10	Changed SF-12v2 to SF-36v2.	The SF-36v2 is more robust as it incorporates more items than the SF-12v2. Aligns assessment within brazikumab program.
SoA – PRO Assessments and Section 8.1.11	Added a Participant Qualitative Interview Sub-study.	Interview was added to supplement and support the interpretation of PRO quantitative trial results through qualitative exploration of the participant disease and treatment experience.
Sections 2 and 2.2	Added text (with citation) about anti-IL-23p19 antibodies inducing a clinical response in UC.	To update background information with latest published information.
Sections 2.2 and 2.3	Text was revised to update information from the recently completed Study 3150-101-008.	To include most recent data.
Section 2.3	Added conclusion regarding the benefit/risk balance.	To align across brazikumab protocols.
Section 3	Changed “primary objective” in first sentence to “purpose.”	To avoid confusion with study objectives and endpoints.
Section 3	Expanded Objectives and Endpoints table to include information for population, intercurrent event strategy, and population-level summary (analysis).	To align with AstraZeneca template.
Sections 3 and 9.4.2.1	For clinical remission definition, expanded stool frequency subscore to be 0 or 1, AND at least 1-point decrease from baseline.	This amended definition is an acceptable component of the clinical remission definition as outlined in regulatory guidances. This expanded definition has been used in previously approved biologics for UC, and therefore allows for better comparison across therapeutics for achieving clinical remission based on the mMS.
Sections 3 and 9.4.2.1	Added secondary endpoints of clinical response and endoscopic improvement.	Data for sub-components of the Mayo clinical remission score and alternate levels of improvement are to be evaluated to facilitate Phase 3 planning.

Section # and Name	Description of Change	Brief Rationale
Section 3	Added exploratory objectives for IL-22 biomarker cutoff determination and efficacy in BM+ population.	To explore the relationship of biomarkers with the efficacy of brazikumab.
Section 4.1	Updated study design description, number of treatment arms, doses, study duration, and planned number of participants. Added language on stratification and unblinding for the primary analysis.	To align with study design changes. To align with AstraZeneca SOPs.
Section 4.1	Removed sentence on pooling data from IND and non-IND sites for analysis, a paragraph that defines study completion, and a sentence about an independent DSMB monitoring participant safety data.	To align with other brazikumab protocols.
Section 4.1.1 and Appendix I	New section on study conduct mitigation is added that would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue while minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.
Section 4.2	Deleted paragraph that study was designed to comply with FDA and EMA guidances for UC.	To align with other brazikumab protocols.
Section 4.3	Updated data from Study 3150-101-008, which have been finalized.	Study 3150-101-008 has completed.
Section 4.4	Added language to the end-of-study definition.	To align with AstraZeneca template.
Section 5	Added text to specify that participants have to meet all of the inclusion and none of the exclusion criteria.	Added for clarification.
Section 5.1	Revised introductory sentence from “are met” to “apply” for all eligibility criteria.	To align with AstraZeneca template.
Section 5.1, Inclusion criterion #2	Revised age criterion to be at timing of signing of the informed consent instead of at Screening.	To be more precise regarding the age cutoff point.

Section # and Name	Description of Change	Brief Rationale
Section 5.1, Inclusion criterion #5a	Removed information regarding timing of colonoscopy and requirements for colonoscopy in the case of rescreening.	To allow flexibility for study sites.
Section 5.1, Inclusion criterion #5a and Section 8.1.1	Changed duration of eligibility calculation period for Stool Frequency and Rectal Bleeding subscores from 5 days to 7 days.	To conform with regulatory authority guidance.
Section 5.1, Inclusion criterion #5b	Changed timing of full colonoscopy from within 35 days to within 14 days before first dose of study intervention.	To keep the timing from Screening colonoscopy to the Week 10 visit more uniform and decrease potential for variability during the extended Screening Period given the relapsing/remitting nature of the disease.
Section 5.1, Inclusion criterion #6	Revised language on inadequate response or intolerance to intervention with conventional treatment or prior biological treatment.	To specify stability of participants on immunomodulators and to align with other brazikumab protocols.
Section 5.1, Inclusion criteria #7b and #7c	Revised language regarding stable dose of oral prednisone and oral budesonide.	To avoid impacting efficacy deltas during induction by keeping steroid dosing stable.
Section 5.1, Inclusion criterion #7e	Added that participants on immunomodulators must have been on treatment for a minimum of 8 weeks and must be kept at stable doses.	To ensure that participants are on a stable dose to not confound efficacy endpoints and to align with other brazikumab protocols.
Section 5.1, Inclusion criteria #8-10	Revised the criteria for reproduction and contraception use.	Criteria are consistent with prior requirements but provide additional specificity and clarity regarding acceptable contraception; revised wording aligns with standard AstraZeneca template.
Section 5.1, Inclusion criterion #11 and Appendix F	Excluded participants with newly-identified latent TB. Added a requirement for the QFT-TB test to be performed and removed Exclusion criterion 6 (c) iv, which had required a negative TB skin test if the QFT-TB test was not approved/registered in that country.	Revised in consideration for participant safety in countries with high burden of TB. Revised the criterion to reflect the QFT-TB testing that was already required; the negative skin test requirement was removed because it was redundant with the required QFT-TB test.
Section 5.2	Revised introductory sentence from “are met” to “apply” for all eligibility criteria.	To align with AstraZeneca template.
Section 5.2, Exclusion criterion #2	Revised language regarding other medical conditions.	To exclude other conditions that may potentially confound assessments.

Section # and Name	Description of Change	Brief Rationale
Section 5.2, Exclusion criterion #4a	Changed language of timepoint for prior treatment with infliximab from randomization to randomization (Day 1).	To align with new language in CSP.
Section 5.2, Exclusion criterion #4b	Changed timepoint for prior treatment with adalimumab, certolizumab pegol, or golimumab from randomization to randomization (Day 1) and changed window from 10 weeks to 8 weeks.	To align with new language in CSP and to better align window with clinical practice and other clinical studies in UC.
Section 5.2, Exclusion criterion #4c	Added washout time period for ustekinumab; changed timepoint for prior treatment with vedolizumab from randomization to randomization (Day 1); changed window from 18 weeks to 12 weeks.	To align with new language in CSP and be more consistent with real-world use and other clinical studies in UC. Revised according to acceptable half-life washout period for specified biologics and to minimize impact on efficacy and safety assessments.
Section 5.2, Exclusion criterion #4e	Added criterion for fecal microbiota transplantation within 8 weeks prior to Screening colonoscopy.	To avoid impact on PROs, colonoscopy, and stool testing.
Section 5.2, Exclusion criterion #5	Deleted criterion on previous treatment with vedolizumab.	Criterion no longer applies with the removal of the vedolizumab treatment arm.
Section 5.2, Exclusion criterion #6	Revised language on prior exposure to any biologic agent targeting IL-12 or IL-23 to allow prior use of ustekinumab.	Ustekinumab has an expanded indication that presently includes UC. Clarification included to allow prior ustekinumab use into the study and to align with other brazikumab protocols.
Section 5.2, Exclusion criterion #10	Revised language on enrollment in another investigational device or drug study.	To align with AstraZeneca template.
Section 5.2, Exclusion criterion #12	Changed language of timepoint for Bacille Calmette-Guérin vaccination from “Baseline (Visit 2)” “to randomization (Day 1)”.	To align with new language in CSP.
Section 5.2, Exclusion criterion #13	Revised language on infections.	For participant safety and to align with other brazikumab protocols.
Section 5.2, Exclusion criterion #14	Revised language on chronic use of NSAIDs and/or opiates, drug, or alcohol abuse.	For participant safety and to avoid confounding effect of chronic NSAID use. To align with other brazikumab protocols.
Section 5.2, Exclusion criterion #15	Revised language on cancer history.	To specify ‘of the skin’ and to align with other brazikumab protocols.

Section # and Name	Description of Change	Brief Rationale
Section 5.2, Exclusion criterion #17	Revised language on prolonged QTcF interval.	To align with other brazikumab protocols.
Section 5.2, Exclusion criterion #18	Added "including but not limited to" to clinically significant kidney disease criterion.	To clarify that clinically significant kidney disease could entail other criteria.
Section 5.2, Exclusion criterion #19	Revised language on abnormal laboratory results.	To add clarity to viral hepatitis and *C. difficile* testing and to align with other brazikumab protocols.
Section 5.2, Exclusion criterion #21	Revised language on other concurrent medical conditions.	Revised for clarity and specificity. To exclude conditions that may impact safety and efficacy. To align with other brazikumab protocols.
Section 5.2	Changed language from "within 35 days" to "within 14 days" of randomization.	To be as close to randomization as able so that disease activity at mMS calculation is as similar as possible to first dosing visit.
Section 5.3	Restructured the section and added restrictions regarding contraception and donation of blood.	To align with standard AstraZeneca template wording.
Section 5.3.2	Added information on recording the use of nicotine replacement therapy and avoiding caffeine intact for at least 1 hour prior to a clinic visit.	To align with standard AstraZeneca template wording and align with other brazikumab protocols.
Section 5.4	Added text regarding screen failures and rescreening.	Added for clarification.
Section 6	Added language regarding an option for at-home study intervention administration and visit assessments.	To reduce burden for participants and sites and align with brazikumab program.
Section 6.1	Revised study intervention table and text (removal of information on high-dose brazikumab, vedolizumab, and double-dummy dosing). Added details on the brazikumab and placebo CCI and CCI formulations.	To align with removal of high-dose brazikumab and vedolizumab from the revised study. Added for clarity and to align with AstraZeneca template and SOPs.
Former Section 6.1.1	Removed section on double-dummy dosing regimen.	Section is no longer applicable because the vedolizumab treatment arm was removed.
Section 6.1.1	Added new Dosing Regimen section.	To align with study design changes, operational changes, and other brazikumab protocols.
Section 6.1.2	Added section for study intervention administration rescheduling.	To provide guidance for missed doses/when not to administer and window when dose is delayed.

Section # and Name	Description of Change	Brief Rationale
Section 6.1.3	Revised description of study supplies.	Revised for clarity and to align with available supplies.
Section 6.2	Revised text regarding study intervention handling. Provided details on preparation and administration of brazikumab and placebo CCI and CCI dosing.	Revised to align with AstraZeneca template and to provide clarification of existing text. Added for clarity and to align with AstraZeneca template and SOPs.
Section 6.3	Changed randomization ratio to 1:1:1.	To reflect the removal of 2 treatment arms (vedolizumab and high-dose brazikumab).
Section 6.3	Revised language on measures to minimize bias. Replaced "IWRS" with "IRT/RTSM".	To align with other brazikumab protocols and AstraZeneca processes.
Section 6.4	Included language to describe how study intervention will be administered to preserve the double-blind and ensure participant compliance.	To clarify how study intervention will be administered in double-blind fashion.
Section 6.5.1	Revised Table 8 Medications Requiring Stable Dose Regimen and updated accompanying text.	To simplify prednisolone and budesonide dosing so doses remain stable from Screening colonoscopy to Week 10 and do not affect the primary endpoint.
Section 6.5.2	Added a table for Permitted Concomitant Treatments and updated subsequent text.	To clarify permitted concomitant treatments to study site personnel and align with other brazikumab protocols.
Section 6.5.3	Revised CS taper instructions and added table for corticosteroid tapering guidelines.	Revised to align steroid tapering during maintenance. Steroid tapering aligns broadly with clinical guidelines.
Section 6.5.4	Added language regarding over-the-counter products.	To clarify what types of medications participants should not take without first consulting with the investigator.
Section 6.5.4	Added fecal microbial transplantation as a prohibited intervention. Noted that alternative or complementary treatments must be discussed with the Study Physician/designee, and clarified that Chinese herbal therapies are prohibited interventions.	Fecal microbial transplantation could affect PROs and other efficacy assessments. Updated prohibited treatments to include alternate/complementary therapeutic treatments that may impact efficacy and/or safety assessments.
Section 6.5.5	Revised restrictions and actions regarding the use of rescue treatment.	To capture late responders while preventing potential bias of entry into the OLE study.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.5	Added new initiation of 5-aminosalicylates as a rescue treatment.	To clarify that the new use of 5-aminosalicylates treatment for UC is considered rescue treatment as this treatment was not previously included in this section.
Section 6.5.5	Updated rescue treatment guidelines to require confirmation from a centrally read modified endoscopy score.	Endoscopy added to avoid bias by allowing rescue treatment based only on PROs.
Section 6.5.5	Added language regarding participants meeting rescue guidelines being potentially eligible to roll over into the OLE study.	To show potential for enrollment into the OLE study and to align with other brazikumab protocols.
Section 6.7	Revised language regarding study intervention after the end of the study.	To recognize that participants who enroll in the OLE study will continue to receive study intervention.
Section 7.1	Added sentence that discontinuation from study intervention is not the same thing as withdrawal from the study.	To clarify that discontinuation from study intervention and withdrawal from the study are separate processes.
Section 7.1	Revised wording regarding hospitalization and treatment of infections to include antimicrobial and antiviral therapies.	To broaden the range of therapies for infections that would result in a participant discontinuing study intervention.
Section 7.1	Added language regarding meeting criteria for Hy's Law and discontinuation of study intervention.	To clarify that abnormal liver function includes meeting criteria for Hy's Law.
Section 7.1	Added language that the investigator can perform repeat testing of abnormal liver function if he or she believes it is interest of the participant.	To protect participant safety.
Section 7.1	Added language that permits telephone follow-up visits in the case of discontinuation of study intervention and the participant being unwilling or unable to attend scheduled site visits.	To give the participant options for follow-up if they are unwilling or unable to attend scheduled site visits.
Section 7.1	Added language that participants who discontinue study intervention during the Treatment Period and are unwilling to attend scheduled visits or have telephone contact will exit the study after completion of the ED/ET visit.	To clarify the process when a participant discontinues study intervention and does not want to participate in additional visits.
Section 7.2	Revised language regarding participant withdrawal from the study.	To align with AstraZeneca template.

Section # and Name	Description of Change	Brief Rationale
Section 7.3	Revised definition of lost to follow-up to include the participant is unable to be contacted by the study site by the time the study is completed.	To clarify the limit of the period for lost to follow-up.
Section 8	Added general information regarding study assessments and procedures.	To align across brazikumab protocols.
Section 8.1.1	Deleted 2 sentences about the PGA score.	To improve clarity and decrease misinterpretation among study sites.
Section 8.1.1	Deleted table for Planned Efficacy Assessments by Timepoint.	To streamline the protocol by having timepoints only in the SoA and reduce the potential for inconsistencies.
Section 8.1.2 (new)	Added section for pMS.	To describe the pMS, which was added to the SoA.
Section 8.1.4	Revised colon mucosal biopsy language.	To highlight that biopsies will be used for BM analysis and molecular characterization of local inflammation.
Sections 8.1.7, 8.1.8, 8.1.9, and 8.1.10	Restructured PRO sections and revised content.	To improve clarity.
Section 8.2.4	Revised the description of clinical laboratory assessments.	To align with the AstraZeneca template.
Sections 8.3 and 8.3.2	Added new text to describe collection of AEs and SAEs.	To align with AstraZeneca template; new content is consistent with the previous text.
Section 8.3.2	Removed prior Section 8.3.2 Method of Detecting AEs and SAEs. Replaced prior text regarding follow-up of AEs and SAEs with standard AstraZeneca template text.	Prior Section 8.3.2 text is not needed per AstraZeneca template and SOPs. New text regarding follow-up of AEs and SAEs is consistent with prior information and includes more details. Provides alignment with AstraZeneca template and SOPs.
Section 8.3.3	Added new section on assessment of AE causality.	Revised to align with AstraZeneca template and SOPs; consistent with text that was in the prior Appendix 3.
Section 8.3.4	Removed prior Section 8.3.4 Regulatory Reporting Requirements for SAEs; replaced with new section to inform the sites of how to handle AEs based on signs and symptoms.	New information; added to align with AstraZeneca template and SOPs.
Section 8.3.5	Added new section to inform the sites of how to handle AEs that were identified through examinations and tests.	New information; added to align with AstraZeneca template and SOPs.

Section # and Name	Description of Change	Brief Rationale
Former Sections 8.3.6 and 8.3.7	Removed prior Section 8.3.6 Cardiovascular and Death Events and Section 8.3.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events.	To align with AstraZeneca template and across brazikumab protocols.
Section 8.3.6 and Appendix E	Text on Hy's Law replaces prior Section 8.3.8.1 and Appendix 8.	AstraZeneca standard template text was added to align with AstraZeneca template and SOPs. The new content is consistent with the prior text.
Section 8.3.7	New section was added to inform the sites how to handle AEs due to the disease under study.	New information; added to align with AstraZeneca template and SOPs.
Section 8.3.8	Added new section to inform the sites how to report SAEs; this information was previously provided in Appendix 3.	Added to align with AstraZeneca template and SOPs; content is similar to the information that was removed from Appendix 3.
Section 8.3.9	Replaced previous Section 8.3.5 with standard AstraZeneca template text on the handling of pregnancies. Removed the requirement to report elective abortions without complications as AEs or SAEs.	Added to align with AstraZeneca template and SOPs; except as noted, the content is similar to the information that was removed from previous Section 8.3.5.
Section 8.3.10	Reordered AESI sections.	To align with other brazikumab protocols.
Section 8.3.10	Removed the AESI of Hy's Law in Section 8.3.8.1. Hy's Law is now included in Section 8.3.6.	Section 8.3.6 Hy's Law aligns with AstraZeneca Protocol Template. No need to duplicate as an AESI because it is not a specific risk for brazikumab.
Section 8.3.10.1	Updated language CCI reactions and CCI .	To align across brazikumab protocols.
Section 8.3.10.2	Updated language for malignancies.	To align across brazikumab protocols.
Section 8.3.10.3	Updated language for hypersensitivity reactions (anaphylaxis).	To align across brazikumab protocols.
Section 8.3.10.4	Updated language for infections.	To align across brazikumab protocols.
Section 8.3.11	Replaced legacy text in Section 8.3.9 with AstraZeneca template text regarding the handling of medication errors. Together with Appendix B 5, provides additional information on the handling of medication errors.	Revised to align with AstraZeneca template and SOPs; provides additional information to the sites on recognizing and reporting medication errors.

Section # and Name	Description of Change	Brief Rationale
Section 8.4	New text replaces prior Section 8.4 with AstraZeneca standard template text on overdose. Added details on overdose of [redacted] brazikumab. Removed details on underdosing. Removed standard Allergan text on the handling of overdose and replaced with standard AstraZeneca text.	Details on overdose of [redacted] brazikumab were added to provide more information to the sites. Remaining changes were for alignment with AstraZeneca template and SOPs.
Prior Section 8.5 Pharmacokinetics and Prior Section 8.7 Biomarkers	Prior section was renamed "Human Biological Samples" and restructured to include subsections for PK, immunogenicity assessments, and pharmacodynamics; prior Section 8.7 Biomarkers was removed.	To align with AstraZeneca template.
Section 8.5	Text was added to describe standard AstraZeneca process regarding the handling of biological samples.	Added to align with AstraZeneca template and SOPs.
Section 8.5.1	Removed PK sampling timepoints from text and referred to SoA. Revised PK collection details; added template text.	To simplify text and reduce possibility of inconsistency between text and SoA. To align with the AstraZeneca protocol template and with other brazikumab protocols.
Section 8.6	Added text to support new samples (stool samples and biopsies). Noted that biopsies will be used for BM analysis.	Stool and biopsy BM analysis is crucial to provide data on: • The link between IL-23–driven inflammation in the gut and circulating IL-22 levels. • The PD effect of brazikumab on local inflammation and associated BM.
Section 8.7	Replaced legacy "Collection of Optional Biomarker Samples" with AstraZeneca template "Optional Genomics Initiative Sample."	To standardize language regarding the use of DNA samples for genetic analysis across AstraZeneca trials.
Section 8.8	Replaced "Health Economics" section with "Healthcare Resource Utilization."	Revised to standardize language around the use of DNA samples for genetic analysis across AstraZeneca trials.
Section 9.1	Revised entire section, including adding a table for the primary estimand and updating the treatment groups and doses.	To reflect changes in study design.
Section 9.2	Updated brazikumab and placebo responder rates assumptions and power calculation.	To reflect new information on responder rates and subsequent effect on power calculation.

Section # and Name	Description of Change	Brief Rationale
Section 9.2	Removed Sample Size Assumptions table.	To streamline protocol since information in the table was already in the text.
Section 9.2	Added text describing that the total sample size of CCI participants does not include the brazikumab high-dose and vedolizumab treatment arms in previous protocol amendments.	To clarify that the participants previously randomized to these treatment arms are not included in the total sample size of CCI.
Section 9.3	Updated information in Populations for Analysis table.	To align with AstraZeneca template and SOPs and with other brazikumab protocols.
Section 9.4	Updated language regarding statistical analyses.	To align with other brazikumab protocols.
Section 9.4.1	Revised general statistical considerations language.	To align with other brazikumab protocols, to clarify how the use of rescue and/or prohibited treatment will be handled in statistical analyses, and to define what will be considered baseline values in the case of missing data.
Section 9.4.2.1	Updated Efficacy Endpoints table.	To align with updated Objectives and Endpoints table in Section 3.
Section 9.4.4	Revised language regarding PK and biomarker analyses.	To provide flexibility, to align with AstraZeneca SOPs, and to align with other brazikumab protocols.
Section 9.5	Revised interim analyses language.	To align with other brazikumab protocols.
Section 9.6	Moved data monitoring committee information from legacy Section 9.5.1 to new Section 9.6.	To align with AstraZeneca template.
Appendices	Reordered the appendices.	To order the appendices according to the AstraZeneca template; additional appendices were added after the template-ordered appendices.
Appendix A, Appendix B, Appendix C, Appendix D, Appendix E, Appendix F	Revised content.	To align with AstraZeneca template and other brazikumab protocols.
Appendix G	Revised bowel movement diary, evening diary, PGIS-UC, and PGIC-UC content. Replaced SF-12v2 with SF-36v2.	To reflect study design change and align with other brazikumab protocols. To use the 36-item version of the questionnaire.
Appendix J, Section 11	Updated the list of abbreviations and references.	To align with prior sections of the protocol.

AE = adverse event; AESI = adverse event of special interest; BM = biomarker; *C. difficile* = *Clostridium difficile*; COVID-19 = coronavirus disease 19; CD = Crohn's disease; CS = corticosteroid; CSP = clinical study protocol; DNA = deoxyribonucleic acid; DSMB = Data Safety Monitoring Board; ECG = electrocardiogram; ED = early discontinuation; EMA = European Medicines Agency; ET = Early Termination; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; FDA = Food and Drug Administration; GCP = Good Clinical Practice; IL = interleukin; IND = Investigational New Drug; IRT = interactive response technology; CCI [redacted] IWRS = interactive web response system; CCI [redacted] MedDRA = Medical Dictionary for Regulatory Activities; NSAID = nonsteroidal anti-inflammatory drug; mMS = modified Mayo score; OLE = open-label extension; PD = pharmacodynamics; PGA = Physician's Global Assessment; PGIS-UC = Patient Global Impression of Change – Ulcerative Colitis; PII-MBF = Patient Impression of Interference – Bowel Movement Frequency; PIS-RB = Patient Impression of Severity – Rectal Bleeding; PK = pharmacokinetics; pMS = partial Mayo score; PRO = patient-reported outcomes; QFT-TB = QuantiFERON-TB test; QTcF = QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)⅓); RNA = ribonucleic acid; RTSM = Randomization and Trial Supply Management; SAE = serious adverse event; CCI [redacted] SF-36v2 = 36–item Health Survey Version 2; SoA = schedule of activities; SOP = standard operating procedure; TB = tuberculosis; UC = ulcerative colitis; W = week.

Amendment 4: (August 2020)

The protocol was updated to change the sponsor from Allergan to AstraZeneca. This included changes to the sponsor name, study number, and SAE reporting information.

Section # and Name	Description of Change	Brief Rationale
Throughout	Change sponsor to AstraZeneca and change study number to AstraZeneca study number	The sponsor of the study is changing to AstraZeneca and an AstraZeneca study code will be used moving forward
Throughout	Change Medical Safety Physician (MSP) to study physician.	This changed is being made to align with AstraZeneca terminology.
Title Page	Change in Sponsor Name and Legal Registered Address	The Sponsor name and address were changed to AstraZeneca AB
Title Page	Emergency Telephone number removed	The Allergan emergency number was removed from the title page. This will be provided directly to investigators
Title Page	SAE Reporting Fax Number/email removed	The Allergan SAE reporting Fax number/email were removed. Safety reporting information will be provided directly to investigators.
Title Page	Sponsor signatory was removed	The Allergan sponsor signatory was removed
Section 6.1, Study Intervention	AstraZeneca will be providing study interventions.	With the sponsor change, AstraZeneca will be providing study interventions.
Section 6.1.2, Study Supplies	Allergan was changed to AstraZeneca	AstraZeneca will supply the test articles for the study.

Section # and Name	Description of Change	Brief Rationale
Section 7.1: Discontinuation of Study Intervention	Added: Any worsening of an infection (beyond CTCAE Grade 2)	This withdrawal criteria was added for consistency with the brazikumab Crohn's Disease program.
Section 8.3.1, Time Period and Frequency for Collecting AE and SAE information Section 8.3.3, Follow-up of AEs and SAEs Section 8.3.8.1 Potential Hy's Law Cases	The Allergan specific AE reporting information was removed.	AstraZeneca will provide safety reporting information directly to investigators.
Section 10.3, Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The Allergan specific AE reporting information was removed. AstraZeneca protocol language was added.	AstraZeneca language was added due to change in Sponsor. AstraZeneca will provide safety reporting information directly to investigators.
Section 10.8, Appendix 8: Liver Safety: Suggested Actions and Follow-up Assessments	The Allergan specific AE reporting information was removed.	AstraZeneca will provide safety reporting information directly to investigators.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

Amendment 3: (March 2019)

This protocol amendment includes updates based on regulatory requests and to clarify eligibility criteria and study procedures.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Changed the study duration from 72 to 73 weeks to allow up to 7 additional days of Screening	Up to 7 additional days of Screening permitted for extenuating circumstances in order to complete all required Screening assessments
1.1 Synopsis	Added DSMB	Due to the limited data and the complexity of the proposed study design, the DSMB was added
Figure 1-1	Replaced with updated schema to include a note that blinded sham placebo will be administered CCI and CCI at applicable visits for all intervention groups and to clarify additional 7 days	Updated for clarity and as noted above

Section # and Name	Description of Change	Brief Rationale
	may be added to Screening Period for extenuating circumstances	
Table 1-1	Added an investigative biomarker blood sample at Screening	Updated for clarity and to align with other studies in the program
Table 1-1	Clarified intent of language in footnote k	Updated for clarity and patient centricity
Table 1-1	Added footnote o, including consent and exclusions based on previous blood transfusion for PAXgene testing	Updated for clarity and to align with other studies in the program
Table 1-1	Added footnote p to allow for up to 7 additional days of Screening for extenuating circumstances	As noted above
Table 1-1	Added QFT-TB testing should be repeated at Visit 17 if QFT-TB is negative in Table and footnote g	Updated procedure for participant safety
Table 1-1	Added hemoglobin A1C blood sample at Screening	To obtain additional baseline study population information
Table 1-1	Footnote e updated to HIV instead of HIV-1	Currently testing for both HIV-1 and HIV-2 so aligns with program of studies
Table 1-2	Added an investigative biomarker blood sample at 8 weeks post-last dose and 18 weeks post-last dose	Updated as for clarity and to align with other studies in the program
Table 1-2	Clarified language in footnote a	Updated for clarity and patient centricity
2.2 Background	Included additional information about the choice of vedolizumab as an active comparator	Updated for clarity
2.3 Benefit/Risk Assessment	Updated to include additional benefit/risk information	To improve clarity
4.1 Overall Design	Added text to include re-randomization	To improve clarity and to align with Section 6.3
4.1 Overall Design	Changed the study duration to increase the total number of weeks from 72 to up to 73	As noted above
4.3 Justification for Dose	Updated the safety information from the ongoing Phase 1 tolerability study (3150-101-008)	To provide further data on the tolerability of high doses of brazikumab
5.1 Inclusion Criteria	Added clarification to criterion 5.b	To improve clarity
5.1 Inclusion Criteria	Aligned criterion 11.c.iv with SoA	As noted above
5.2 Exclusion Criteria	Updated criterion 2, so that participants that had toxic megacolon within 12 months of Screening would be excluded	To align with other studies in the program

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Added update to criterion 5.c to include example of PML in text	To improve clarity
5.2 Exclusion Criteria	Criterion 9 updated so participants using steroids 2 weeks prior to Screening were excluded instead of prior to Baseline	To align with other studies in the program
5.2 Exclusion Criteria	Criterion 12 was updated exclude Bacille Calmette-Guérin vaccination	Updated for clarity and to align with other studies in the program
5.2 Exclusion Criteria	Criterion 13, bullet b was updated to specifically include sepsis and listeriosis as examples in text	To improve clarity
5.2 Exclusion Criteria	Criterion 13, bullet e was updated with clarified language, reformatted, and modified so uncomplicated urinary tract infections would not be exclusionary	To align with other studies in the program
5.2 Exclusion Criteria	Criterion 13, bullets f and h were added	To align with other studies in the program
5.2 Exclusion Criteria	Updated criterion 15 to include tofacitinib	To align with other studies in the program
5.2 Rationale for Inclusion and Exclusion Criteria	Updated time for full colonoscopy from 21 to 35 days	To align with eligibility criteria in Inclusion criterion 5.b
5.4 Screen Failures and Laboratory Re-testing	Updated text to only allow rescreening once	To align with other studies in the program
Table 6-1	Correction that CCI dosing of study intervention will be provided	Correction to protocol
6.1.1.2 Subcutaneous Administration	Added that any injection-site reaction considered worse than expected is to be reported as an AE.	To align with other studies in the program
6.2 Preparation	Changed to guidance for the final disposition study interventions are in the Pharmacy Manual.	To improve clarity and align with language in protocol
6.3 Measures to Minimize Bias	Included additional information on stratification and clarified the randomization “assignment” procedure	To improve clarity
6.3 Measures to Minimize Bias	Added language around discontinuing participants if blind is broken	To improve clarity
6.5.1 Prior Medications	Added 5-aminosalicyclate should remain at stable doses	To align with other studies in the program
6.5.4 Rescue Therapies	Updated list of therapies “for the treatment of UC after randomization”	To improve clarity and align with other studies in the program

Section # and Name	Description of Change	Brief Rationale
6.5.4 Rescue Therapies	Clarified text regarding guidelines that must be followed prior to the use of rescue therapy	To improve clarity and to align with other studies in the program
7.1 Discontinuation of Study Intervention	Added to list of discontinuing criteria, diagnosis of PML or other demyelinating condition	To improve clarity and risk mitigation
8.1.2 Endoscopy	Added language regarding the risks	Updated to improve clarity and to align with Section 2.3
8.3.1 Time Period	Added that AEs will be collected at timepoints specified in SoA that SAEs will be recorded on SAE form and faxed or emailed to sponsor	To align with other studies in the program
8.3.3 Follow-up of AEs and SAEs	Added investigator will submit SAE date via the SAE form	To align with other studies in the program
8.3.8.1 Potential Hy's Law Cases	Added reference to Section 10.8 and that a potential Hy's Law case must be reported on an SAE form	To improve clarity
8.3.8.2 CCI [redacted]	Removed CCI [redacted] as an AESI	To align AESI with other studies in the program
8.3.8.3 Hypersensitivity	Added (Anaphylaxis) to heading	To be consistent with other changes to protocol and align with other studies in the program
8.3.8.5 Infections	Updated to refer back to Exclusion criterion #13 instead of listing criteria	To clarify and align with other studies in the program
9.4.1 Efficacy Analyses	Added that the "method will be applied to both primary and secondary efficacy endpoints"	To improve clarity
9.4.1.2 Efficacy Analyses	Replaced prior anti-TNFα with prior biological intervention	To improve clarity and to align with other studies in the program
9.5 Interim Analyses	Added more detail including a list of potential analysis	To improve clarity
9.5.1 Data Monitoring Committee	Added DSMB	Due to the limited data and the complexity of the proposed study design, the DSMB was added
Table 10-1	Added hemoglobin A1c to list of clinical laboratory tests and stool *C. difficile* and fecal calprotectin to the list of other Screening tests, made correction to spelling for eGFR	To obtain additional safety information and to align with SoA
Table 10-1	Added clarification to footnote a	To align with other studies in the program

Section # and Name	Description of Change	Brief Rationale
10.2.1 Procedures for Tuberculosis Testing	Added additional language regarding QFT-TB testing to align with changes made to SoA	As noted above
10.3 Appendix 3	Removed injection-site reactions as an AESI and added information on forms for reporting Hy's Law cases and updated recording instructions for AESIs	To align AESI with other studies in the program and to improve clarity
10.4 Appendix 4	Added eGFR, PML, and DSMB to list of abbreviations	Updated abbreviations as needed
10.6 Appendix 6	Changed the study duration to increase the total number of weeks from 72 to up to 73 and updated the stratification factor	As noted above and to align with other changes to the protocol
10.8 Appendix 8	Added Hy's Law cases to be reported on SAE form	To align with other studies in the program
10.13	Added summary of changes for Protocol Amendment 2	Moved SOC for amendment 2 from beginning of document to Section 10.13

AE = adverse event; AESI = adverse event of special interest; *C. difficile* = *Clostridium difficile*; DSMB = Data Safety Monitoring Board; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; IV = intravenous; PML = progressive multifocal leukoencephalopathy; QFT-TB = QuantiFERON-TB; SAE = serious adverse event; SC = subcutaneous; SoA = schedule of activities; TNFα = tumor necrosis factor-alpha; UC = ulcerative colitis.

Amendment 2: (October 2018)

This amendment is considered to be nonsubstantial 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 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

This protocol amendment includes changes and clarification of eligibility criteria, clarification to procedures, and changes made to reduce participant burden.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized
Title Page	Address updated from Ireland to United Kingdom	To correct the name and address of the sponsor

Section # and Name	Description of Change	Brief Rationale
Synopsis, Intervention Groups and Study Duration	Added text to clarify the timing of the Treatment Period and Safety Follow-up Period	For clarity
1.2 Schema, Figure 1–1	Replaced schema to clarify that safety follow-up is done at Week 68.	For clarity
1.3 Schedule of Activities (SoA), Table 1-1	Deleted exploratory biomarkers from "Stool for fecal calprotectin"	Exploratory biomarkers no longer applicable
1.3 Schedule of Activities (SoA), Table 1-1	Added text to footnote i to clarify the timing of PK sample collection	For clarity
1.3 Schedule of Activities (SoA) Table 1-2	Deleted exploratory biomarkers from "Stool for fecal calprotectin"	Exploratory biomarkers no longer applicable
4.1 Overall Design	Added text to clarify the timing of the Treatment Period and Safety Follow-up Period	For clarity
5.1 Inclusion Criteria, criterion 3	Changed text to clarify the timing of diagnosis	For clarity and to align with other studies in the program
5.1 Inclusion Criteria, criterion 5	Changed text to clarify the definition of moderately to severely active UC	For clarity
5.1 Inclusion Criteria, criterion 8	Replaced "tubal ligation" with "salpingectomy"	To use the proper terminology
5.1 Inclusion Criteria, criterion 11	Add text about participants in countries with high multidrug-resistant TB burden	For clarity and to align with other studies in the program
5.2 Exclusion Criteria, criterion 3	Changed text to clarify that prior colonic resection is excluded	For clarity
5.2 Exclusion Criteria, criterion 15	Added text to include relevant subpopulations	For clarity
5.2 Exclusion Criteria, criterion 21	Added text to provide an example	For clarity
6.1.1.1 Intravenous Administration	Added text about recording vital signs on the eCRF	For clarity
6.1.1.2 Subcutaneous Administration	Added text about recording vital signs on the eCRF	For clarity
6.3 Measurement to Minimize Bias: Randomization and Blinding	Changed text about how and when the blind should be broken in case of an emergency	To address regulatory body comments

Section # and Name	Description of Change	Brief Rationale
6.5.1 Prior Medications Requiring Stable Dose Regimen	Added text about maintaining a stable dose of permitted concomitant medications	For clarity
6.5.3 Corticosteroid Study Guidelines	Deleted text to clarify guidelines for steroid tapering	For clarity
6.5.4 Rescue Therapies	Added text to clarify when rescue therapy must be considered	For clarity
6.5.5 Prohibited Treatments During the Study	Added text to discuss the use of concomitant immunosuppressants with medical monitor	For clarity and safety
7.1 Discontinuation of Study Intervention	Added text to clarify reasons for discontinuation of study intervention	For clarity and to align with other studies in the program
8 Study Assessments and Procedures	Deleted text to disallow procedures conducted prior to signing the ICF	For clarity
8.1.1 Modified Mayo Score (mMS)	Changed text to align with changes to Inclusion criterion 3	For clarity and consistency
8.5 Pharmacokinetics	Added text to clarify the timing of PK sample collection	For clarity
8.5 Pharmacokinetics	Changed “a PK-PD Analysis Plan” to “the Modeling and Simulation Analysis Plan”	For clarity
8.6 Pharmacodynamics	Deleted section	Pharmacodynamics are not applicable
9.1 Statistical Hypotheses	Changed the alternative hypothesis from “greater than” to “different from”	For clarity
9.3 Population for Analyses	Changed the name of “PK-PD” population to “Exposure-Response” population and changed “a PK-PD Analysis Plan” to “the Modeling and Simulation Analysis Plan”	For clarity and consistency
9.3 Populations for Analyses	Added Maintenance Period population	For clarity
9.4.1.1 Efficacy Endpoints	Changed “Mayo scoring” to “modified Mayo score”	For clarity and consistency
9.4.1.2 Efficacy Analyses	Deleted examples of additional analyses	For clarity

Section # and Name	Description of Change	Brief Rationale
9.4.2.1 Adverse Events	Changed the AE reporting window from 30 days to 18 weeks after the last dose of study intervention	To align with timing of safety follow-up visit
9.4.3 Pharmacokinetic Analyses	Changed text to clarify that PK and PD analyses will be described in a separate Modeling and Simulation Analysis Plan	For clarity and consistency
10.2 Appendix 2: Clinical Laboratory Tests, Table 10-1	Added text to clarify that urine hCG is not performed at Visit 4	For clarity
10.2.1 Procedures for Tuberculosis Testing from Screening	Added text to clarify procedures for TB worksheet, indeterminate QFT-TB value in countries with high multidrug-resistant TB burden, and noncompliance with latent TB treatment	For clarity and to align with other studies in the program
10.4 Appendix 4: Abbreviations	Added CTCAE	CTCAE was added to the document
10.4 Appendix 4: Abbreviations	Added MP	MP was added to the document
10.12 Protocol Amendment 1 Summary	Moved to Appendix	For clarity

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; hCG = human chorionic gonadotropin; ICF = informed consent form; PD = pharmacodynamics; PK = pharmacokinetics; QFT-TB = QuantiFERON-TB test; TB = tuberculosis; UC = ulcerative colitis.

Amendment 1: (June 2018)

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.

Overall Rationale for the Amendment

This protocol amendment includes changes and clarification of eligibility criteria, including the alignment of active comparator prescribing information and changes made to reduce participant burden.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Section # and Name	Description of Change	Brief Rationale
Synopsis, Objectives and Endpoints	Text revised to clarify definition of CS-free clinical remission	For clarity
1.3 Table 1-1	Text added for FSH testing at Screening Added "as applicable" for predose collection of immunogenicity and biomarker samples Text added for collection of extra-intestinal manifestation history. Text added for collection of a sample for IL-22 and CCI at Screening (Visit 1) Text added for PAXgene for whole blood DNA analysis at Baseline (Visit 2)	For clarity
1.3 Table 1-1	Added footnote b to describe collection of UC-related history and timepoints for completion of the EIM eCRF	For clarity
1.3 Table 1-1	Footnote f revised to clarify that pregnancy testing is not required for post-menopausal women.	For clarity
1.3 Table 1-1	Footnote i modified to reflect the timing of PK sample collection.	For accuracy
1.3 Table 1-1	Footnote k modified to reflect additional instructions for stool studies at all visits where colonoscopy is needed.	For accuracy
1.3 Table 1-1	Footnote l removed from PGA. Footnote l moved to "Endoscopy, colon mucosal biopsy". Text in footnote l changed to reflect acceptable window for procedures. Visit 11 endoscopy and biopsy assessment was removed.	Decrease participant and site burden
1.3 Table 1-1	Text deleted in footnote n to allow flexibility in timing for patient-reported measures.	Decrease participant's study burden and provide flexibility for study staff
1.3 Table 1-2	Text added for collection of extra-intestinal manifestation history.	For clarity
1.3 Table 1-2	PRO eDiary and IBDQ removed from safety follow-up visits 1 and 2.	Assessments not required during Safety Follow-up Period
1.3 Table 1-2	Footnote b added to reflect acceptable window for procedure.	For clarity

Section # and Name	Description of Change	Brief Rationale
1.3 Table 1-2	Text deleted in footnote d to allow flexibility in timing for patient-reported measures.	Decrease participant's study burden and provide flexibility for study staff
3 Table 3-1	Text revised to clarify definition of CS-free clinical remission	For clarity
4.1 Overall Design	Text revised to reflect the definition of study completion	For clarity
4.2 Scientific Rationale for Study Design	Added a reference to the EMA guidelines for the treatment of ulcerative colitis	To align with both FDA and EMA guidances
4.3 Justification of Dose	Text discussing rationale for control groups was deleted	Redundant text deleted
5.1 Inclusion Criteria #2	Age for eligibility modified to 18 to 80 years, inclusive.	To align with comparator prescribing information
5.1 Inclusion Criteria #5	Changes made to the number of days required prior to bowel prep and colonoscopy for: 1) completion of nightly diaries 2) calculation of scores for eligibility Changed the number of days prior to randomization in the definition of UC	To decrease participant burden.
5.1 Inclusion Criteria #6	Added definition of inadequate or failed response and intolerance. Added guidance for specific drug classes.	For clarity
5.1 Inclusion Criteria #7	Added clarification of prednisone dosing	For clarity
5.1 Inclusion Criteria #9	Text added to FSH testing	For clarity
5.1 Inclusion Criteria #10	Text modified in Inclusion 10 to align with requirements in Appendix 7.	For accuracy
5.1 Inclusion Criteria #11	Added that a TB worksheet should be completed for all participants.	For clarity and accuracy
5.2 Exclusion Criteria #3	Text added "or need for surgical intervention for control of UC anticipated within 6 months" to exclusion criteria	Exclude participants requiring early surgical intervention and need to stop study intervention
5.2 Exclusion Criteria #4	Added exclusionary timeframe for prior use of vedolizumab, other biologics and small molecules	For clarity and accuracy
5.2 Exclusion Criteria #8	Tofacitinib added as exclusionary medication with respective timeframe for discontinuation relative to study visits	To clarify discontinuation parameters for recently approved treatment for UC

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria #9	Modified allowable timing of [redacted] or intramuscular steroids relative to study visit	For clarity and accuracy
5.2 Exclusion Criteria #14	Added opiates	To clarify drugs with potential for abuse as exclusionary
5.2 Exclusion Criteria #15	Added dysplasia on endoscopy and confirmed on biopsy	For clarity and accuracy
5.2 Exclusion Criteria #18	Added text to clarify that eGFR should be calculated by MDRD equation at Screening by the central lab	For clarity
5.2 Rationale for Inclusion and Exclusion Criteria	Age for eligibility modified to 18 to 80 years, inclusive. Deleted text referring to the Week 30 endoscopy	To align with comparator prescribing information To align with SoA revisions
6 Study Intervention	Removed medical device(s) from the definition of study intervention	For accuracy, as no devices will be included in this study
6.1.1.2 [redacted]	Text discussing allergic or [redacted] and/or hypersensitivity was deleted	Redundant text deleted
6.2 Preparation/ Handling/Storage/ Accountability	Revised the drug accountability text to be consistent with IWRS options	For accuracy
6.3 Measures to Minimize Bias: Randomization and Blinding	Deleted reference to eCRF field for reason for blind breaking	For accuracy
6.5.1 Table 6-4	Added text for clarification of prednisone dosing Removed “colonoscopy” from immunomodulators	For clarity For accuracy
6.5.3 Corticosteroid Study Guidelines	Added text for clarification of prednisone dosing	For clarity
6.5.5 Prohibited Treatments During the Study	Added “applicable” to study assessments that should be continued in cases where study intervention is discontinued. Moved text describing participant withdrawal to Section 7.1	For clarity
7.1 Discontinuation of Study Intervention	Modified text discussing participants who are discontinued from study intervention	For clarity

Section # and Name	Description of Change	Brief Rationale
8.1.1 Modified Mayo Score (mMS)	Changed the number of days required for nightly diary completion Added text to PGA assessment for clarity. Removed Visit 11 endoscopy from text and Table 8-1	To reduce participant burden For clarity To align with the SoA
8.1.2 Endoscopy	Added text stating that endoscopic assessments should be performed at the timepoints specified in the SoA	For clarity
8.1.3 Colon Mucosal Biopsies	Deleted Visit 11 Removed assessment of cellular composition of the inflammatory infiltrate	To align with the SoA For accuracy
8.1.4 Geboes Histological Index (GHI)	Text changed to include degree of mucosal inflammation Added a reference for the GHI	For accuracy
8.1.5 Robarts Histopathology Index (RHI)	Text changed to reflect that biopsies will be evaluated according to RHI.	For accuracy
8.1.6 Bowel Movement Diary	Heading title changed from “Event-Driven Diary” to “Bowel Movement Diary” Text added to provide additional direction for event-driven diary.	For clarity
8.1.7 Nightly Diary	Text added to provide additional direction for nightly diary	For clarity
8.1.8 Weekly Diary	Section added to provide instruction for weekly diaries	For accuracy
8.1.9 Site Visit Patient-Reported Outcomes (PROs)	Text deleted to allow flexibility in timing for patient-reported measures.	Decrease participant’s study burden
8.2.5 Immunogenicity Assessments	Text related to blood volume deleted as this information will be provided within the Laboratory Manual.	For clarity
8.3.8.1 Potential Hy’s Law Cases	Text included to clarify additional reflexive testing for potential Hy’s Law cases.	For clarity
8.3.8.4 Malignancies	Added “dysplasia on endoscopy and confirmed on biopsy”	To align with exclusion criteria related to dysplasia
8.7 Genetics	Text was added describing the study procedures to evaluate genetics	For accuracy

Section # and Name	Description of Change	Brief Rationale
8.8 Biomarkers	Text related to blood volume deleted as this information will be provided within the Laboratory Manual.	For clarity
9.2 Sample Size Determination	Anti-TNF changed to biologic	To align with text in regard to stratification at randomization in Section 6.3
9.4.1 Efficacy Analyses	Text revised to clarify definition of CS-free clinical remission	For clarity
9.4.2.1 Adverse Events	Modified definition of TEAE	For clarity
9.5 Interim Analysis	Text added indicating that interim analysis will be performed according to the sponsor's SOP	For clarity
10.1.5 Study Site and Institutional Review Board	Subsections deleted	Template text that is only applicable to studies being conducted in Japan.
10.2 Table 10-1	Coagulation panel included in table as reflexive test for potential Hy's Law, additional hepatitis testing (Hepatitis B Core Ab Total, Hepatitis B Core IgM Ab) added, estradiol removed Revised text related to pregnancy testing Footnote b deleted Reflexive microscopic examination for urinalysis modified.	For clarity
10.2.1 Procedures for Tuberculosis testing from Screening	Added that a TB worksheet should be completed for all participants. Added option for an unscheduled QFT-TB if there is a concern for increased risk of TB	For accuracy For clarity and accuracy
10.5 Appendix 5	Deleted definition of "withdrawal by parent/guardian"	Not applicable for this study as no minors will be enrolled.
10.6 Appendix 6	Updated to reflect changes throughout the protocol	For accuracy
10.8 Appendix 8	Text included to clarify additional reflexive testing for potential Hy's Law cases.	For clarity
10.10 Appendix 10	Text deleted as this information will be provided within the Laboratory Manual. Summary of analysis included	For clarity

Section # and Name	Description of Change	Brief Rationale
10.11.1 Bowel Movement Diary	Heading changed from "Event-driven assessment items" to "Bowel Movement Diary" Revised text and added additional questions	For accuracy
10.11.2 Nightly Diary	Minor text revisions	For clarity
10.11.2.1 Weekly Recall Instruments	The order of the subheadings was revised	For clarity
11 References	Added the Geboes reference	To include a reference added in text

CS = corticosteroid; DNA = deoxyribonucleic acid; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EIM = extra-intestinal manifestation; EMA = European Medicines Agency; FDA = US Food and Drug Administration; FSH = follicule-stimulation hormone; GHI = Geboes Historical Index; IBDQ = Inflammatory Bowel Disease Questionnaire; IgM = immunoglobulin M; IL = interleukin; IWRS = interactive web response system; CCI MDRD = Modification of Diet in Renal Disease; PGA = Physician's Global Assessment; PK = pharmacokinetic(s); PRO = patient-reported outcomes; QFT-TB = QuantiFERON-TB; RHI = Robarts Histopathology Index; SoA = schedule of activities; SOP = standard operating procedure; TB = tuberculosis; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

11 REFERENCES

Bettelli et al, 2007
Bettelli E, Korn T, Kuchroo VK. Th17: the third member of the effector T cell trilogy. Curr Opin Immunol. 2007;19:652-657.

Brazikumab, 2021
Brazikumab (MEDI2070) Investigator's Brochure, 2021; Edition 8.

Burton et al, 2007
Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, et al. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nature Genet. 2007;39:1329-1337.

Cargill et al, 2007
Cargill M, Schrodi SJ, Chang M, Garcia VE, Brandon R, Callis KP, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J of Human Gen. 2007;80:273-290.

Duerr et al, 2006
Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science. 2006;314:1461-1463.

Farago et al, 2008
Farago B, Magyari L, Sáfrány E, Csöngei V, Járomi L, Horvatovich K, et al. Functional variants of interleukin-23 receptor gene confer risk for rheumatoid arthritis but not for systemic sclerosis. Ann Rheum Dis. 2008;67:248-250.

Feagan et al, 2016
Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016;375:1946-1960.

Feagan et al, 2017
Feagan BG, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet. 2017;389:1699-1709.

Geboes et al, 2000
Geboes K, Riddell R, Öst A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000;47:404-409.

Gordon et al, 2012
Gordon K, Langley R, Gottlieb, Papp KA, Krueger GG, Strober BE, et al. A Phase III, randomized, controlled trial of the fully human IL-12/23 mAb briakinumab in moderate-to-severe psoriasis. J Invest Dermatol. 2012;132:304-314.

Gottlieb et al, 2011
Gottlieb AB; Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol. 2011;165:652-660.

Guyatt et al, 1989
Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989;96:804-810.

Illes et al, 2008
Illes Z, Safrany E, Peterfalvi A, Magyari L, Farago B, Pozsonyi E, et al. 3'UTR C2370A allele of the IL-23 receptor gene is associated with relapsing-remitting multiple sclerosis. Neurosci Lett. 2008;431:36-38.

Kimball et al, 2012
Kimball AB, Papp KA, Wasfi Y, Chan D, Bissonnette R, Sofen H, et al. Long-term efficacy and safety of ustekinumab in patients with moderate to severe psoriasis through 5 years of follow-up: results from the PHOENIX 1 long-term extension. Br J Dermatol. 2012;167(Suppl. 1):64 (Abstract P94).

Langley et al, 2012
Langley RG, Williams D, Papp K, Olds M. Long-term safety and efficacy of ABT-874 for the treatment of moderate to severe psoriasis: Interim analysis from an open-label extension study. J Am Acad Dermatol. 2012;66:AB195 (Abstract 4779).

Lee et al, 2004
Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, et al. Increased expression of interleukin 23p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med. 2004;199:125-130.

Leonardi et al, 2008
Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76 week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371:1665-1674.

Li et al, 2007
Li Y, Chu N, Hu A, Gran B, Rostami A, Zhang GX. Increased IL-23p19 expression in multiple sclerosis lesions and its induction in microglia. Brain. 2007;130:490-501.

Mannon et al, 2004
Mannon PJ, Fuss IJ, Mayer L, Elson CO, Sandborn WJ, Present D, et al. Anti-interleukin 12 antibody for active Crohn's disease. N Eng J Med. 2004;351:2069 2079.

Mosli et al, 2017
Mosli MH, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R, et al. Development and validation of a histological index for UC. Gut. 2017;66:50–58.

Papp et al, 2008
Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371:1675-1684.

Reich et al, 2011
Reich K, Langley RG, Papp KA, Ortonne J-P, Unnebrink K, Kaul M, et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. N Engl J Med. 2011;365:1586-1596.

Sandborn et al, 2012
Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012;367:1519-1528.

Sandborn et al, 2020
Sandborn WJ, Ferrante M, Bhandari BR, et al. Efficacy and safety of mirikizumab in a randomized Phase 2 study of patients with ulcerative colitis. Gastroenterology. 2020;158(3):537-549.

Sands et al, 2017
Sands BE, Chen J, Feagan BG, Penney M, Rees WA, Danese S, et al. Efficacy and safety of MEDI2070, an antibody against interleukin 23, in patients with moderate to severe Crohn's disease: a Phase 2a study. Gastroenterology. 2017;153:77-86.

Schmidt et al, 2005
Schmidt C, Giese T, Ludwig B, Mueller-Molaian I, Marth T, Zeuzem S, et al. Expression of interleukin-12-related cytokine transcripts in inflammatory bowel disease: elevated interleukin-23p19 and interleukin-27p28 in Crohn's disease but not in ulcerative colitis. Inflamm Bowel Dis. 2005;11:16-23.

Schroeder et al, 1987
Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid 548 therapy for mildly to moderately active ulcerative colitis. N Engl J Med. 1987;317:1625-1629.

Sofen et al, 2011
Sofen H, Smith S, Matheson R, Leonardi C, Calderon C, Bouman E, et al. Results of a single ascending dose study to assess the safety and tolerability of CNTO 1959 following intravenous or subcutaneous administration in healthy subjects and in subjects with moderate to severe psoriasis. Br J Dermatol. 2011;165:e10 (Abstract FC-21).

Strober et al, 2011
Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a Phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol. 2011;165:661-668.

Vaknin-Dembinsky et al, 2006
Vaknin-Dembinsky A, Balashov K, Weiner HL. IL-23 is increased in dendritic cells in multiple sclerosis and down regulation of IL-23 by antisense oligos increases dendritic cell IL-10 production. J of Immunol. 2006;176:7768-7774.

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