Clinical Study Protocol

Study Intervention	Brazikumab
Study Code	D5272C00002 (Legacy #3151-202-008)
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A Phase 2 Open-label, Long-term Extension Safety Study of Brazikumab in Participants with Moderately to Severely Active Ulcerative Colitis

(EXPEDITION OLE)

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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.

Redacted for Public Disclosure

Protocol Number: D5272C00002

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Study Intervention: Brazikumab
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Short Title: Open-label Extension Study of Brazikumab in Ulcerative Colitis

Acronym: EXPEDITION OLE

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

AstraZeneca Protocol D5272C00002 (Legacy #3151-202-008)

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	May 2022
Amendment 2	March 2021
Amendment 1	August 2020
Original Protocol	December 2019

Amendment 3 (13-May-2022)

This amendment is considered non-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 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 amendment removes unnecessary assessments related to study entry, collection of assessments throughout the study, and provides further clarity on protocol text. Previously omitted exploratory objectives and endpoints are also included.

All changes have been classified as non-substantial. The granular summary of changes in the tabular format is included below:

Section # and name	Description of change	Brief rationale
Throughout	Minor editorial and document formatting revisions.	Minor corrections were made to improve interpretation.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	Added an omitted exploratory endpoint to include PRO questionnaires.	Correction to ensure PROs were included as an endpoint for an exploratory efficacy objective.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	Added an exploratory objective for evaluating the PK and immunogenicity of brazikumab.	PK and immunogenicity sampling is mandatory per the SoA, and planned sample analysis is well defined (Section 8.5). This addition is to ensure intended use is appropriately reflected in study objectives.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	Added an additional exploratory objective needed to cover any/all biomarker analyses to be completed.	Biomarker sampling is mandatory per the SoA, and planned sample analysis is well defined (Section 8.5). This additional objective is to ensure intended use is appropriately reflected in the study objectives.
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 5.1 Inclusion Criterion 1(b), Section 6 Study Intervention	Revised text to clarify that participants with suboptimal response at Week 54 of lead-in study will rollover to CCI in this study.	Clarification to enable non-responders at Week 54 of the lead-in study to potentially benefit from CCI
Section 1.1 Synopsis, Section 9.2 Sample Size Determination	Modified text to include the maximum number of participants that may enter the study based on the number in the lead-in study.	Revisions were made for accuracy.
Section 1.1 Synopsis, Section 9.3 Populations for Analyses	Added Screened Analysis Set.	To facilitate reporting of disposition.
Section 1.3 SoA, Table 1, Section 8.2.2 Vital Signs	Removed collection of height measurement at Visit 1.	Height is collected in the lead in study, and safety assessments are not impacted by measurement of height.
Section 1.3 SoA Table 1, Table 3	Removed exploratory efficacy assessment (PGA, PRO) at Weeks 24 and 36 and indicated Week 12 only for participants who have CCI	Decreased exploratory assessments to reduce site and participant burden.
Section 1.3 SoA, Table 1, Table 3, Section 8.1.4 Patient-Reported Outcomes-Evening Diary	Clarified that PRO paper diary will be collected for 7 days before visit, excluding days of bowel prep and endoscopy.	To provide clear guidance for PRO data collection for sites and maintain data quality.

Section # and name	Description of change	Brief rationale
Section 1.3 SoA, Table 1	Reduced timepoints for urinalysis to screening and Week 52.	Frequency of urinalysis reduced during the study. Investigators to take a risk-based approach to urinalysis based upon clinical presentation, thereby maintaining participant safety.
Section 1.3 SoA, Table 1, Table 2, Section 5.2 Exclusion Criterion 4.01, Section 8.2.4 Clinical Safety Laboratory Assessments, Table 10	Removed testing of stool for *C. difficile* at all timepoints (including study entry).	*C. difficile* testing occurs upon study entry in the lead-in study, and the brazikumab mechanism of action is not associated with an increased risk of infection. Investigators will assess and manage the risk of *C. difficile*, as per local standard of care.
Section 1.3 SoA, Table 1, Section 5.2 Exclusion Criterion 1.07, 1.08, Section 8.2.4 Clinical Safety Laboratory Assessments, Table 10	Removed hepatitis B and C and HIV testing at all timepoints (including study entry).	Hepatitis B and C and HIV testing occur upon study entry in the lead-in study, and the brazikumab mechanism of action is not associated with an increased risk of infection. Investigators will assess and manage the risk of hepatitis B and C and HIV, as per local standard of care.
Section 1.3 SoA, Table 1	Removed note for urine pregnancy test row.	Serum hCG testing is performed at screening and mandatory urine hCG testing is required prior to dosing throughout the lead-in study; additional screening serum hCG testing for the OLE study will not be obtained. Urine hCG testing will be performed prior to dosing throughout the OLE study.
Section 1.3 SoA, Table 1, Table 2, Section 5.1 Inclusion Criterion 1.03, Section 8.2.4 Clinical Safety Laboratory Assessments, Table 10, Previous Appendix B Procedure for Tuberculosis Testing	Removed chest x-ray, QFT-TB, and TB testing at all timepoints (including study entry).	TB testing occurs upon study entry in the lead-in study, and the brazikumab mechanism of action is not associated with an increased risk of infection. Investigators will assess and manage the risk of TB, as per local standard of care.
Section 1.3 SoA, Table 1	Added PK sampling at Week 12 for participants who have CCI	To align PK and PD timepoints to facilitate PK/PD modelling.
Section 1.3 SoA, Table 1	Removed biomarker sampling (exploratory biomarkers, stool for lactoferrin and FCP, and PAXgene RNA) at Week 24.	Decreased exploratory assessments to reduce site and participant burden.
Section 1.3 SoA, Table 1	Moved biomarker sampling (exploratory biomarkers, stool for lactoferrin and FCP, and PAXgene RNA) from Week 0 to Screening. Samples will	Biomarker assessments from the last visit in the lead-in study will be used as baseline.

Section # and name	Description of change	Brief rationale
	only be collected from participants if not collected at the lead-in study end-of-study visit.	
Section 1.3 SoA, Table 1	Clarified PAXgene RNA collection notes that it should not be collected if whole blood transfusion within 120 days.	Added clarification to align with lead-in CSP and to ensure necessary sample quality.
Section 1.3 SoA, Table 1	Added a column and footnote to the SoA for unscheduled visits.	Added to provide guidance to the investigator on assessments to be performed at an unscheduled visit.
Section 1.3 SoA, Table 1, Section 8 Study Assessments and Procedures	Added text to footnote 'b' to indicate that a repeat colonoscopy is not required for participants that discontinued from the lead-in study between Weeks 10 to 14.	The Week 10 colonoscopy acquired in the lead-in study will be used for the screening assessment in this OLE study to reduce participant burden.
Section 1.3 SoA, Table 1, Section 8 Study Assessments and Procedures, Appendix G	Added text (Notes column and footnote 'c') to clarify window for Week 0 dose administration from the last dose in the lead-in study.	Added to maintain participant safety by keeping at least a 14-day gap between doses and to minimize potential delay in dosing of participants.
Section 1.3 SoA, Table 1	Added footnote 'd' regarding visit schedule calculation.	Added additional clarity for the sites in scheduling visits.
Section 1.3 SoA Table 2	Added follow-up visit window.	Added flexibility to visit window for site and participant benefit.
Section 1.3 SoA Table 2	Added PK blood sample at ET and follow-up visits.	Aligned PK and ADA assessments as PK information is essential for the interpretation of ADA sampling.
Section 1.3 SoA Table 2	Added PAXgene RNA at ET.	Correction to ensure PAXgene RNA is collected at ET visit.
Section 1.3 SoA, Table 3	Indicated which PRO assessments are to occur at ET.	Revisions were made to maintain data integrity by aligning ET PRO data collection at Week 52 visit.
Section 4.3 Justification of Dose, Table 5	Added omitted exposure margin from Phase 1b Study 20090519.	Correction to provide exposure margins for CCI [redacted].
Section 5.3 Lifestyle Consideration	Added text to describe restrictions that apply while receiving study intervention.	Added to align with standard AZ safety restrictions.
Section 6.1.3 Dosing Regimen	Revised the language describing the IP.	Modified to clearly describe the IP formulation.

Section # and name	Description of change	Brief rationale
Section 6.1.3.2 Subcutaneous Administration, Figure 2, Section 6.2 Preparation/Handling/ Storage/Accountability,	Additional CCI for CCI were added.	Additional injection sites were added to reduce the risk of AEs when the same site is repeatedly used, and to collect safety and tolerability information for different CCI
Section 6.2 Preparation/Handling/ Storage/Accountability	Revised the language for the equilibration time and temperature of the CCI CCI . Included a standard clause regarding storing the CCI in the inner carton during temperature equilibration.	Further investigation has determined that an equilibration time of at least CCI at room temperature is required for CCI CCI
Section 6.5.2 Corticosteroid Study Guidelines	Reduced specifications in regards to corticosteroid doses in this study.	To enable investigators to manage corticosteroid dose to maintain safety of participants.
Section 6.5.4 Prohibited Interventions During the Study	Removed language regarding exemptions to live attenuated vaccine usage.	To maintain participant safety during the study and clarity for sites.
Section 6.6 Dose Modification	Added section and description for dose modification	To describe that there is no provision for brazikumab dose modification in this study.
Section 8.1.1 Endoscopy	Revised the endoscopy assessment procedure explanation.	Confirms that endoscopic procedures are centrally read, maintaining data integrity, and provides site guidance on timing of biopsy so not to negatively impact video capture.
Section 8.1.2 Modified Mayo Score	Revised the language to state that the score will be based on the average evening diary data recorded over the most recent 3 days of allowable data within 7-day period prior to visit, exclusive of bowel prep and endoscopy.	Clarification for sites to maintain data integrity.
Section 8.1.4 Patient-Reported Outcomes-Evening Diary	Urgency added to the description of the diary. Clarified when diary should be completed and the appropriate scale for the assessment.	Modified text for accuracy and clarity.
Section 8.2.4 Clinical Safety Laboratory Assessments, Table 10	Removed coagulation group assessment from the hematology panel for the	Coagulopathy is adequately assessed by the remaining Hy's Law kit.

Section # and name	Description of change	Brief rationale
	clinical laboratory assessments.	
Section 8.2.4 Clinical Safety Laboratory Assessments, Table 10	Added FCP and fecal lactoferrin to fecal tests.	Specific analyses added to ensure accuracy and transparency with intended use in the study.
Section 8.3 Adverse Events and Serious Adverse Events	Revised the language for collecting and reporting AE information.	Revisions were made to align with current AZ standard safety reporting.
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Revised the language for collecting AE information before the start of study intervention.	Revisions were made to align with current AZ standard safety reporting.
Section 8.3.9 Reporting of Serious Adverse Events	Revised the language of safety reporting via EDC.	Revision was made to align with migration from legacy EDC to AZ EDC and standard safety reporting.
Section 8.3.10.1 Maternal Exposure	Revised the language of pregnancy reporting.	Revision was made to align with migration from legacy EDC to AZ EDC and standard safety reporting.
Section 8.3.10.2 Paternal Exposure	Added paternal exposure language.	Revision was made to align with migration from legacy EDC to AZ EDC and standard safety reporting.
Section 9.2 Sample Size Determination, Table 11	Modified description of Full Analysis Set.	Modified to accurately describe the Full Analysis Set and to streamline the text.
Appendix A 3	Added text to describe rescreening procedures.	Revisions were made for clarity and consistency with AZ policies.
Appendix F 2	Removed electronic device text.	Correction made as all PROs will be administered on paper.

ADA = anti-drug antibody; AE = adverse event; AZ = AstraZeneca; *C. difficile* = *Clostridium difficile*; CSP = clinical study protocol; EDC = electronic data capture; ET = Early Termination Visit; FCP = fecal calprotectin; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; IB = Investigator's Brochure; IP =investigational product; CCI OLE = open-label extension; PD = pharmacodynamic(s); PGA = Physician's Global Assessment; PK = pharmacokinetic(s); PRO = patient-reported outcomes; QFT-TB = QuantiFERON-TB test; RNA = ribonucleic acid; SAE = serious adverse event; CCI ; SoA = schedule of activities; TB = tuberculosis; WOCBP = women of childbearing potential.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 Open-label, Long-term Extension Safety Study of Brazikumab in Participants with Moderately to Severely Active Ulcerative Colitis (EXPEDITION OLE)

Short Title: Open-label Extension Study of Brazikumab in Ulcerative Colitis

Rationale:

Brazikumab, a human immunoglobulin that selectively binds to human IL-23 with high affinity and prevents IL-23 from interacting with the IL-23 receptor, is being studied for the treatment of UC in Study D5272C00001 (Legacy #3151-201-008).

The purpose of this OLE Study D5272C00002 (Legacy #3151-202-008) is to permit participants who previously enrolled in the double-blind Study D5272C00001 (Legacy #3151-201-008) to receive brazikumab, allowing for long-term observation of safety and efficacy in these participants treated with brazikumab. There are no formal hypotheses to be tested. Safety and efficacy data obtained in this study will be included in regulatory product submissions as appropriate.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety of long-term treatment with brazikumab in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008).	• AEs • Clinical laboratory values • Vital signs • Physical exams • ECGs
Exploratory	
To assess the efficacy of long-term treatment with brazikumab in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008).	• mMS assessments • PRO
To evaluate the PK and immunogenicity of brazikumab.	• Serum concentration of brazikumab • Serum ADAs
To explore transcriptional, histological, protein, microbiome, and clinical biomarkers in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008), and the effect of long-term brazikumab treatment on these biomarkers.	• Serum, plasma, fecal, or gut tissue proteins; whole blood or gut transcriptional changes; histological, microbiome, and clinical assessments

ADA = anti-drug antibody; ECG = electrocardiogram; mMS = modified Mayo score; PK = pharmacokinetic(s); PRO = patient-reported outcome; UC = ulcerative colitis.

Overall Design

The study is a global, multicenter, OLE study of brazikumab limited to participants previously enrolled in the lead-in Study D5272C00001 (Legacy #3151-201-008). Participants in the lead-in study are eligible to enroll in Study D5272C00002 (Legacy #3151-202-008) provided they continue to meet eligibility criteria and have not had adverse experiences considered to be related to study medication that resulted in discontinuation of the initial lead-in study intervention, or that in the judgment of the investigator, would disqualify them from participating. Eligible participants do not need to complete the 18-week Safety Follow-up Period of the lead-in study if they rollover into this study after they complete the final visit of the lead-in study.

It is anticipated that the enrolled population will consist of participants who have had varying endoscopic and clinical symptom responses during the lead-in study, ranging from complete clinical remission to no response or worsening of their signs and symptoms of UC. Participants who completed the lead-in Study D5272C00001 (Legacy #3151-201-008) and met criteria for clinical response at Week 54, will continue with maintenance brazikumab dosing, while participants who did not meet criteria for clinical response at Week 54 or who met criteria for early termination (rescue treatment) prior to Week 54 in the lead-in study will be CCI dosing with brazikumab.

Disclosure Statement:

This is an open-label, parallel group treatment extension study with 2 arms.

Number of Participants:

This study is an extension study and the sample size is determined by the number of participants in the lead-in study who are eligible for and choose to participate in this study. No separate sample size calculation was performed. Up to a maximum of 255 participants may enter the study, based on the expected number of participants in the lead-in Study D5272C00001.

Intervention Groups and Duration:

After meeting all eligibility criteria, participants will be assigned to 1 of 2 treatment groups based on their clinical response in Study D5272C00001 (Legacy #3151-201-008). A summary of the 2 possible assigned treatment regimens is as follows:

- Group A: Participants who completed the lead-in study and met criteria for clinical response at Week 54, will receive CCI brazikumab CCI and every 4 weeks through Day 365 (Week 52).
- Group B: Participants who did not meet criteria for clinical response at Week 54 or who met criteria for early termination (rescue treatment) prior to Week 54 in the lead-in study will receive CCI brazikumab CCI at Day 1 (Week 0), Day 29 (Week 4), and Day 57 (Week 8), followed by CCI brazikumab CCI every 4 weeks beginning at Day 85 (Week 12) through Day 365 (Week 52).

There will be an 18-week Safety Follow-up Period starting after the last dose of study treatment. No study intervention will be administered to participants during the safety follow-up.

Study Duration:

The study will consist of a maximum 52-week open-label treatment period and an 18-week safety follow-up period, for a total of up to 70 weeks.

Data Monitoring Committee: No

Statistical Methods

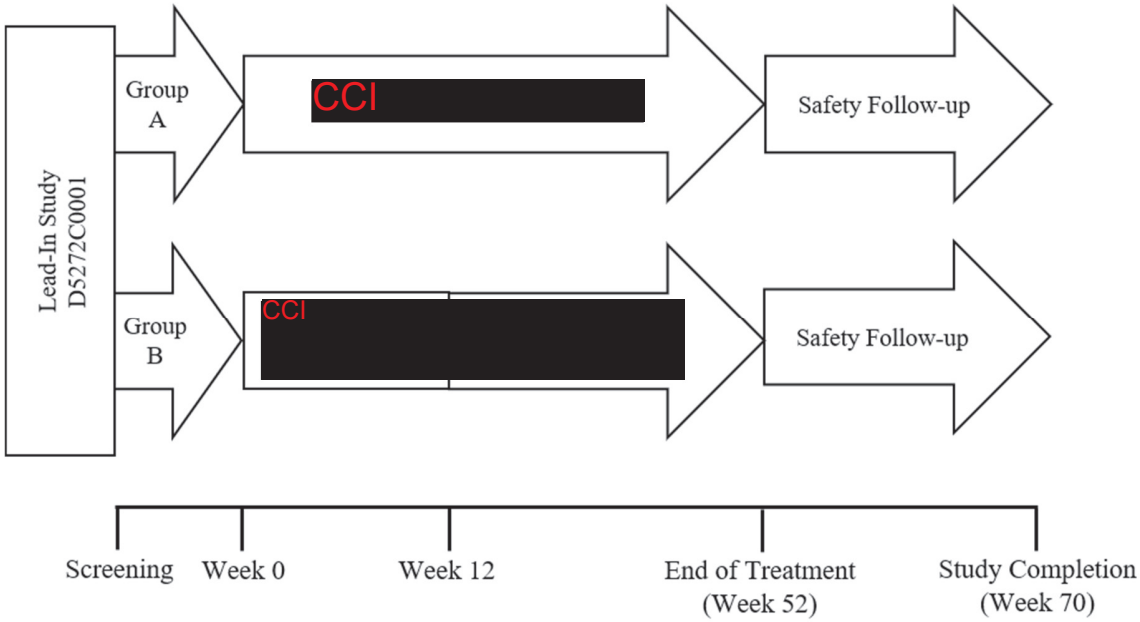
The treatment sequences in this OLE study will be presented as Brazikumab/Brazikumab for participants who received brazikumab study intervention in the double-blind, lead-in study, and Placebo/Brazikumab for participants who received placebo study intervention in the double-blind, lead-in study.

Analysis populations include the Screened Analysis Set (all participants who are screened for the study), Full Analysis Set (all participants), and the Safety Set (all participants who receive 1 or more administration of study intervention in this extension study).

All safety analyses for this study will be summarized descriptively by the visit and the treatment sequences and overall, unless stated otherwise. The baseline as defined in the double-blind, lead-in study will be used as the baseline for all data analyses in this study. Continuous variables will be summarized by the number of participants and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants. Visit time window for safety parameters and detailed statistical analyses for this study will be defined in the SAP.

1.2 Schema

Figure 1 Study Design



The safety follow-up periods are based on the last investigational dose at Week 52. Participants discontinued at any time during the study will be required to proceed to the untreated Safety Follow-up Period.

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1.3 Schedule of Activities

Study procedures are recommended to be done in sequence as listed in the below schedule, but the sequence is not mandatory.

Table 1 Schedule of Activities

Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UNS[a]**	**Notes**	**CSP Section**
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Day Visit window (days)[d]		**1**	**29 ± 7**	**57 ± 7**	**85 ± 7**	**113 ± 7**	**141 ± 7**	**169 ± 7**	**197 ± 7**	**225 ± 7**	**253 ± 7**	**281 ± 7**	**309 ± 7**	**337 ± 7**	**365 ± 7**			
General procedures																		Section 8
Eligibility criteria assessment	X	X																Section 5.1 and Section 5.2
Written ICF and participant identification assignment in IWRS	X																	
Demographics	X																	
Medical history (includes surgical and UC history)	X																	
Procedures																		
Colonoscopy	X														X	X	See note in Section 8.1.1	Section 8.1.1

Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UNS[a]**	**Notes**	**CSP Section**
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Day Visit window (days)[d]		**1**	**29 ± 7**	**57 ± 7**	**85 ± 7**	**113 ± 7**	**141 ± 7**	**169 ± 7**	**197 ± 7**	**225 ± 7**	**253 ± 7**	**281 ± 7**	**309 ± 7**	**337 ± 7**	**365 ± 7**			
Safety assessments																		
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.3
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Assessment of injection-site reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination	X	X			X			X			X				X	X		Section 8.2.1
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.2
ECG	X														X	X		Section 8.2.3
Efficacy assessments																		
mMS	X														X	X		Section 8.1.2
PGA	X				X[e]										X	X		Section 8.1.3

Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UNS[a]**	**Notes**	**CSP Section**
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Day Visit window (days)[d]		**1**	**29 ± 7**	**57 ± 7**	**85 ± 7**	**113 ± 7**	**141 ± 7**	**169 ± 7**	**197 ± 7**	**225 ± 7**	**253 ± 7**	**281 ± 7**	**309 ± 7**	**337 ± 7**	**365 ± 7**			
Provide PRO paper diary	X			X[e]										X		X	Provide the paper diary to participant and instruct them to collect the data 1 week prior to the next visit, excluding days of bowel preparation and endoscopy; W0 paper diary to be provided at last visit in lead-in Study D5272C00001 (Legacy #3151-201-008)	Section 8.1.4

Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UNS[a]**	**Notes**	**CSP Section**
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Day Visit window (days)[d]		**1**	**29 ± 7**	**57 ± 7**	**85 ± 7**	**113 ± 7**	**141 ± 7**	**169 ± 7**	**197 ± 7**	**225 ± 7**	**253 ± 7**	**281 ± 7**	**309 ± 7**	**337 ± 7**	**365 ± 7**			
PRO assessments (paper)		X			X[e]										X	X	Evening diary to be completed every evening for 1 week prior to the indicated scheduled visits	Section 8.1.4
Site visit PROs		X			X[e]										X		Will be completed at site visit	Section 8.1.5
Laboratory assessments																		
Serum chemistry, hematology, and CRP	X				X			X			X				X	X		Section 8.2.4 and Section 8.6.1
Urinalysis	X														X	X		Section 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		Section 8.2.4

Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UNS[a]**	**Notes**	**CSP Section**
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Day Visit window (days)[d]		**1**	**29 ± 7**	**57 ± 7**	**85 ± 7**	**113 ± 7**	**141 ± 7**	**169 ± 7**	**197 ± 7**	**225 ± 7**	**253 ± 7**	**281 ± 7**	**309 ± 7**	**337 ± 7**	**365 ± 7**			
Brazikumab concentration sample (pre-dose)		X			X[e]			X							X			Section 8.5.1
Brazikumab ADA immune-genicity (pre-dose)		X						X							X			Section 8.5.2
Biomarker sampling																		
Stool sample for fecal lactoferrin, FCP, and exploratory biomarkers	X				X[e]										X	X	Collect prior to bowel preparation for colonoscopy if applicable	Section 8.6.1
Blood for exploratory biomarkers	X				X[e]										X			Section 8.6.1
PAXgene RNA	X				X[e]										X		Do not collect if whole blood transfusion within 120 days	Section 8.6.1

Visit number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	UNS[a]	Notes	CSP Section
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Day Visit window (days)[d]		**1**	**29 ± 7**	**57 ± 7**	**85 ± 7**	**113 ± 7**	**141 ± 7**	**169 ± 7**	**197 ± 7**	**225 ± 7**	**253 ± 7**	**281 ± 7**	**309 ± 7**	**337 ± 7**	**365 ± 7**			
Investigational product administration																		
CCI																		

[a] Not all assessments indicated for the UNS need to be performed. The assessments are to be performed at the discretion of the investigator, as clinically indicated.

[b] All assessments made at the final visit of Study D5272C00001 (Legacy #3151-201-008) will be utilized as screening assessments for this study, unless Week 0 for this study occurs greater than 28 days from the final assessment(s) of the lead-in study, in which case the participant will need to complete all required screening assessments, except the colonoscopy. A repeat colonoscopy is not required for participants who discontinue from the lead-in study after Week 10 and prior to Week 14.

[c] Week 0 dose administration must occur no earlier than 14 days and no later than 56 days from the last dose administration in Study D5272C00001 (Legacy #3151-201-008).

[d] The visit schedule will always be calculated from Week 0 date.

[e] Collect Week 12 samples and data for Group B (induction) participants only.

[f] Participants who receive CCI dosing will be administered brazikumab CCI at 4-week intervals starting Week 12 through Week 52.

ADA = antidrug antibody(ies); AE = adverse event; CRP = c-reactive protein; CSP = clinical study protocol; ECG = electrocardiogram; eCRF = electronic case report form; FCP = fecal calprotectin; FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; ICF = informed consent form; CCI ; IWRS = interactive web response system; mMS = modified Mayo score; PGA = Physician's Global Assessment; PRO = patient-reported outcome; RNA = ribonucleic acid; SAE = serious adverse event; CCI ; Scr = screening; UC = ulcerative colitis; UNS = unscheduled visit; W = week; WOCBP = woman of childbearing potential.

Table 2 Schedule of Activities: Early Termination Visit and Safety Follow-up Period

Study period	**Open-label**	**18-week follow-up**		**Notes**	**CSP Section**
Visit name	**Early Termination Visit**	**Follow-up 1 (Week 60)**	**Follow-up 2 (Week 70)**	Study intervention will not be administered during the 18-week Safety Follow-up Period	
Visit timing (and window)	**At study withdrawal or premature discontinuation of study intervention**	**8 weeks post last dose (± 7 days)**	**18 weeks post last dose (± 7 days)**		
Safety assessments					
AE/SAE assessment	X	X	X		Section 8.3
Concomitant medications	X	X	X		
Assessment of injection-site reactions	X	X	X		
Physical examination, vital signs, and weight	X	X	X		Section 8.2.1
ECG	X				Section 8.2.3
Efficacy assessments					
mMS and PROs	X				Section 8.1.3
Colonoscopy including colon mucosal biopsies	X				Section 8.1.1
Laboratory assessments					
Serum chemistry, hematology, CRP, and urinalysis	X	X	X		Section 8.2.4
Urine pregnancy test	X	X	X		
PK blood sample	X	X	X		Section 8.5.1
Serum brazikumab and ADA immunogenicity	X	X	X		Section 8.5.2

Serum brazikumab concentration sample	X				Section 8.5.1
Biomarkers					
Stool sample for fecal lactoferrin, FCP, and exploratory biomarkers	X				Section 8.6.1
Blood for exploratory biomarkers	X				Section 8.6.1
PAXgene RNA	X			Do not collect if whole blood transfusion within 120 days	Section 8.6.1

ADA = antidrug antibody(ies); AE = adverse event; CRP = c-reactive protein; CSP = clinical study protocol; ECG = electrocardiogram; FCP = fecal calprotectin; mMS = modified Mayo score; PK = pharmacokinetic; PRO = patient-reported outcome; RNA = ribonucleic acid; SAE = serious adverse event.

Table 3 Schedule of Activities – PRO Assessments

PRO assessment	Frequency of administration	Notes
Evening Diary[a] (mMS and NRS)	CCI	Paper diaries will be provided to participants at site visits prior to collection visits. Participants will be prompted to begin recording PRO data 1 week prior to the site visit (excluding days of bowel preparation and endoscopy). The night before the site visit should be day 7.
IBDQ		Collected at the site
SF-36v2		Collected at the site
EQ-5D-5L		Collected at the site

[a] Evening is defined as 18:00 to 23:59 and participants should be instructed to complete the paper diaries during this time interval each evening.
[b] Week 12 assessments for Group B (induction) only.
EQ-5D-5L = European Quality of Life-5 Dimensions; ET = Early Termination Visit; IBDQ = Inflammatory Bowel Disease Questionnaire; mMS = modified Mayo score (PRO component); NRS = Numerical Rating Scale; PRO = patient-reported outcome; SF-36v2 = 36-Item Health Survey Version 2; UNS = unscheduled visit.

2 INTRODUCTION

This study is an open-label, continued-access study for participants with UC who previously completed or discontinued due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008). The nature of UC and the rationale for studying brazikumab in this disorder have been discussed previously in the protocol for Study D5272C00001 (Legacy #3151-201-008) and in the current Brazikumab IB (Brazikumab/MEDI2070).

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 United States 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 IBDs. In preclinical models and studies in patients, anti-IL-12/23 p40 antibodies (eg, ustekinumab [approved for treatment of CD, UC, 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). 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

Brazikumab, a human immunoglobulin that selectively binds to human IL-23 with high affinity and prevents IL-23 from interacting with the IL-23 receptor, is being studied for the treatment of UC in Study D5272C00001 (Legacy #3151-201-008).

The purpose of Study D5272C00002 (Legacy #3151-202-008) is to permit participants who previously completed or discontinued due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008) to receive open-label brazikumab in Study D5272C00002 (Legacy #3151-202-008), allowing for long-term observation of safety and efficacy in these participants treated with brazikumab. There are no formal hypotheses to be tested. Safety and efficacy data will be included in regulatory product submissions as appropriate.

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 interferon-gamma, 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-lesion skin (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 (IL-23R) component and disease (Cargill et al 2007, Duerr et al 2006). Furthermore, allelic variants of IL-23R 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 (Mannon et al 2004, Sandborn et al 2012, Feagan et al 2016, Feagan et al 2017), UC (Sandborn et al 2020) and psoriasis (Phase 2 and Phase 3 studies; Leonardi et al 2008, Papp et al 2008, Gottlieb et al 2011, Reich et al 2011, Strober et al 2011, Gordon et al 2012, Kimball et al 2012, Langley et al 2012). Phase 1 and Phase 2 clinical studies with anti-IL-23p19 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 IB (Brazikumab/MEDI2070) for details.

Brazikumab is a human, Chinese hamster ovary cell-derived, IgG2 mAb consisting of 2 heavy chains of the IgG2 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 14% (4 of 28) of the brazikumab-treated animals developed binding ADAs during the dosing period and 25% (1 of 4) of animals at CCI developed binding ADA in the recovery period. No NAbs were detected in animals that tested positive for binding ADA, and binding ADA did not decrease brazikumab exposure. The no observed adverse effect level following 26 weekly CCI of brazikumab was CCI the maximum dose tested, corresponding to a C_{max} of CCI and an area under the serum concentration versus time curve 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 D5170C0001, and Phase 1 Study 3150-101-008.

Study D5170C0001 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 CCI of brazikumab (CCI 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 study intervention 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 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 D5170C0001, CDAI response at Week 8 (defined by either a CDAI score of less than 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% vs 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% vs 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% vs 15.0%) that was not statistically significant.

The safety data from Study D5170C0001 CCI of brazikumab CCI and CCI dosing (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 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 infusion rate on the PK, safety, and tolerability of brazikumab in White participants. A total of 56 participants (24 Japanese and 32 White) were enrolled as planned. CCI doses of CCI and CCI and multiple CCI doses of CCI followed by an CCI CCI brazikumab or placebo were administered to 3 groups of 16 male and female study participants (CCI Japanese and CCI White). In addition, a CCI of 4200 mg was administered to a group of CCI White study participants to evaluate the safety, tolerability, and PK of brazikumab when a CCI dose was administered by a CCI compared to a CCI

CCI up to CCI brazikumab were well tolerated by healthy Japanese and White

participants; there were no SAEs or withdrawals due to AEs. The incidence of AEs was very low and was not correlated with the dose of brazikumab. No new clinically meaningful or unexpected safety results were observed during this study. In addition, there was no apparent difference in the safety profile of CCI single doses of CCI CCI of CCI brazikumab, administered to healthy Japanese participants relative to that observed in healthy White participants. Maximum and total brazikumab exposure increased approximately dose proportionally within the CCI range for brazikumab administered in a CCI to healthy White and Japanese participants. The accumulation ratio following a second CCI dose of CCI brazikumab was 1.3 to 1.5 for C_{max} and $AUC_{0\text{-}28days}$. Overall, there were no appreciable differences in maximum or total exposure between white and Japanese participants. Administration of brazikumab in a CCI resulted in lower than expected maximum and total brazikumab exposure over the 28-day dosing interval; the CCI dose should be infused over CCI

There were no incidences of positive ADA observed in post-dose samples collected from White or Japanese participants.

A detailed description of the chemistry, pharmacology, efficacy, and safety of brazikumab is provided in the IB (Brazikumab/MEDI2070).

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, and anti-TNFα (mAbs and vedolizumab). Many patients, however, have an inadequate response or loss of response over time to these medications, so 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 mAbs 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 mAb that specifically targets the IL 23p19 subunit preventing IL-23 from interacting with the IL-23R 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 less than 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 Q4W, 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 major adverse cardiovascular event 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
- Severe hypersensitivity (including anaphylaxis)
- CCI
- Immune complex disease

However, it is to be noted that, due to the fact that brazikumab is a selective IL-23 inhibitor, but not IL-12 inhibitor, its safety profile is expected to be free of IL-12 inhibitory side effects.

For additional information regarding the efficacy and safety of brazikumab, please refer to protocol Section 2.2 and the current IB for previous clinical study experience with brazikumab (Brazikumab/MEDI2070). For details of study procedures, dose, and study design justification, see Section 4. In conclusion, the sponsor considers that the benefit/risk balance is favorable and supports further clinical development of brazikumab as a treatment for UC.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety of long-term treatment with brazikumab in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008).	• AEs • Clinical laboratory values • Vital signs • Physical exams • ECGs
Exploratory	
• To assess the efficacy of long-term treatment with brazikumab in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008).	• mMS assessments • PRO
• To evaluate the PK and immunogenicity of brazikumab.	• Serum concentration of brazikumab • Serum ADAs
• To explore transcriptional, histological, protein, microbiome, and clinical biomarkers in UC participants who previously completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008), and the effect of long-term brazikumab treatment on these biomarkers.	• Serum, plasma, fecal, or gut tissue proteins; whole blood or gut transcriptional changes; histological, microbiome, and clinical lab assessments

ADA = anti-drug antibody; AE = adverse event, ECG = electrocardiogram; mMS = modified Mayo score; PK = pharmacokinetic(s); PRO = patient-reported outcome; UC = ulcerative colitis.

4 STUDY DESIGN

4.1 Overall Design

The study is a global, multicenter open-label extension study of brazikumab limited to participants previously enrolled in Study D5272C00001 (Legacy #3151-201-008). Participants in the lead-in study are eligible to enroll in Study D5272C00002 (Legacy #3151-202-008) provided they meet eligibility criteria and have not had adverse experiences considered to be related to study medication that resulted in discontinuation of the initial lead-in study intervention, or that in the judgment of the investigator, would disqualify them from participating. Eligible participants do not need to complete the 18-week Safety Follow-up Period of the lead-in study if they rollover into this study after they complete the final visit of the lead-in study.

It is anticipated that the enrolled population will consist of participants who have had varying endoscopic and clinical symptom responses during the lead-in study, ranging from complete clinical remission to no response or worsening of their signs and symptoms of UC. Participants who completed the lead-in Study D5272C00001 (Legacy #3151-201-008) and met criteria for clinical response at Week 54, will receive CCI brazikumab dosing. Participants who did not meet criteria for clinical response at Week 54 or who met criteria for early termination (rescue treatment) prior to Week 54 in the lead-in study will be CCI CCI with brazikumab.

A study schematic is presented in Section 1.2.

Intervention and Study Duration

Intervention:

The CCI dose of brazikumab will be administered every 4 weeks to all completers who met criteria for clinical response at Week 54 in the lead-in study (Group A). Participants in the lead-in study who did not meet criteria for clinical response at Week 54 or who met criteria for early termination (rescue treatment) prior to Week 54 are considered inadequate/non-responders (Group B) and will receive CCI dosing with CCI of brazikumab at Week 0, Week 4, and Week 8, followed by brazikumab CCI CCI every 4 weeks thereafter (up to Week 52).

See Section 6 for a detailed description of the criteria used to assign participants to a treatment group.

There will be an 18-week Safety Follow-up Period following the last dose of study intervention in this study. No study intervention will be administered to participants during the safety follow-up.

Study Duration:

The study will consist of a maximum 52-week open-label treatment period and an 18-week safety follow-up period, for a total of up to 70 weeks.

For studies conducted at US (IND) sites and non-US (non-IND) sites, data from IND and non-IND study sites will be pooled together for analysis.

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) which 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 designated Sponsor Study Physician/designee.
- Home or Remote visit: Performed by a site qualified 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, HCP provided by a TPV, if possible. 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 G.

4.1.2 Clinical Hypotheses

While there is no formal clinical hypothesis being tested, the current study will provide an opportunity for participants to receive brazikumab who have either completed treatment or have been discontinued due to lack of adequate therapeutic response after a minimum of 10 weeks of double-blind treatment from Study D5272C00001 (Legacy #3151-201-008). This study will provide important safety and efficacy information on long-term administration of brazikumab, and will provide preliminary, uncontrolled but descriptive information on the safety of participants who switch to brazikumab from placebo, regardless of their clinical status and prior response.

4.2 Scientific Rationale for Study Design

The sponsor proposes to conduct an open-label study to obtain data on the safety of long-term administration of brazikumab and to provide an opportunity, for participants who agree, to continue treatment with brazikumab for up to 1 year.

4.3 Justification for Dose

The main objective of this study is the evaluation of long-term safety of participants receiving brazikumab.

The no adverse effect level of CCI for brazikumab was established in cynomolgus monkeys in 3 studies in which brazikumab was CCI and CCI weekly up to 6 months. At this dose, no toxicologically significant effects were observed.

In the Phase 1 Study 3150-101-008, conducted in healthy Japanese and White participants to evaluate the PK, dose proportionality, safety, and tolerability of brazikumab, a CCI CCI brazikumab in a CCI was well tolerated by healthy White male study participants. There were no treatment-related AEs or clinically significant abnormalities in vital signs, clinical laboratory values, or ECG assessments. The administered CCI doses as part of the induction treatment and the CCI dose as part of the maintenance treatment in this study are therefore also expected to be well tolerated. Furthermore, in Study 3150-101-008, a CCI of CCI brazikumab infused over a CCI period were well tolerated. The CCI brazikumab study interventions in this study will be CCI (Section 6.1.1).

Table 5 presents the margins of exposure calculated for the doses proposed in this study, based on C_{max} and exposure values following CCI in the 14-week toxicology study, the clinical Phase 1b Study 20090519, and the clinical Phase 1 Study 3150-101-008.

Table 5 Exposure Margins Supporting Planned Doses

	Clinical [redacted]		Clinical [redacted]		Clinical [redacted]	
Parameter	$AUC_{0\text{-}28days}$	C_{max}	$AUC_{0\text{-}28days}$	C_{max}	$AUC_{0\text{-}28days}$	C_{max}
Margin of exposure	54.2	47.4	27.1	23.7	22.2	16.2

[a] Phase 1b Study 20090519.
[b] Estimated values based on exposure in Phase 1b Study 20090519.
[c] Phase 1 Study 3150-101-008.
$AUC_{0\text{-}28days}$ = area under the concentration-time curve from zero to 28 days; C_{max} = maximum serum drug concentration; [redacted]

All doses chosen were well tolerated in previous clinical and preclinical studies. For these reasons, the dosing options of brazikumab as outlined in this protocol are justified since they reflect the ultimate therapeutic use of the treatment as anticipated subsequent to product approval. This open-label study allows maintenance of the blinding of the treatment assignments in the lead-in study (see Section 6.3).

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 or last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if he/she has not been terminated early and has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

5 STUDY POPULATION

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

Participants must have been randomized and participated in Lead-in Study D5272C00001 (Legacy #3151-201-008). The inclusion and exclusion criteria are meant to create a population of participants that is well characterized as having UC that requires chronic treatment.

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

Male or female participants who:

1.01. Successfully completed or discontinued participation due to lack of efficacy after Week 10 in the lead-in Study D5272C00001 (Legacy #3151-201-008).

AND

Meets 1 of the following criteria for successful completion or early termination from Study D5272C00001 (Legacy #3151-201-008):

(a) Participant completed Study D5272C00001 (Legacy #3151-201-008), received scheduled study interventions, completed scheduled visits, and completed Week 54 assessments.

(b) Participant discontinued participation due to lack of efficacy and met criteria for rescue treatment after Week 10 in Study D5272C00001 (Legacy #3151-201-008), received scheduled study interventions, and completed Early Termination Visit assessments.

Note: Any suboptimal endoscopy result that cannot be fully assessed by the central reader and any missed doses/assessments in the lead-in study must be discussed with the Sponsor/Study Physician/designee for determination of eligibility in this study.

1.02. Deleted eligibility as part of Amendment 2

1.03. Deleted eligibility as part of Amendment 3

1.04. Deleted eligibility as part of Amendment 2

Reproduction

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

2.01. Male participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period.

Nonsterilized men who are sexually active with a female partner of childbearing potential should use condoms during treatment and for 18 weeks after the last dose of study intervention, must comply with the methods of contraception described in Criterion 2.02 below, and must not donate or bank sperm for fertilization purpose for

the same time period.

2.02. 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 signing the ICF 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 patient)
- Vasectomized sexual partner, provided that partner is the sole sexual partner of the WOCBP study patient and that the vasectomized partner has received medical assessment of the surgical success

2.03. 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 signing the ICF without an alternative medical cause. The following age-specific requirements apply:

- 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.
- 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.

Informed Consent

3.01. Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

3.02. Written informed consent from the participant has been obtained prior to any study-related procedures.

Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data Protection consent [EU sites]).

Other

4.01. Demonstration of adequate compliance with the study procedures in Study D5272C00001 (Legacy #3151-201-008), in the opinion of the investigator and/or sponsor.

4.02. Willingness and ability to attend all study visits, comply with the study procedures, and be able to complete the study period**.**

Age

5.01. Participant must be 18 to 80 years of age inclusive, at the time of signing the ICF.

5.2 Exclusion Criteria

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

Medical Conditions

1.01. Any participant with an unresolved AE from the lead-in study that, in the investigator's opinion, would limit the participant's ability to participate in or complete this study (see also Section 5.1 and Section 8). Any unresolved AE related to an infection will require further discussion with the Study Physician/designee prior to enrollment.

1.02. Current diagnosis of fulminant colitis, CD or indeterminate colitis, presence of a fistula consistent with CD, primary sclerosing cholangitis, celiac disease, or toxic megacolon. Bile acid malabsorption and other conditions that may potentially confound assessments must be treated prior to baseline.

1.03. Organ or cell-based transplantation (eg, islet cell transplantation or autologous stem cell transplantation) with the exception of corneal transplant.

1.04. Any other condition or finding that, in the investigator's or sponsor's opinion, would either confound proper interpretation of the study or expose a participant to

unacceptable risk, including but not limited to clinically significant findings on physical examination, clinical laboratory test, 12-lead ECG (including QTc prolongation), or clinically significant renal, hepatic, or cardiopulmonary disease (see also Section 8).

1.05. The following are exclusionary with regards to malignancy:

a) If there is evidence of intestinal epithelial dysplasia on endoscopy, and this is confirmed on biopsy, the participant must be excluded.

b) Any diagnosis of malignancy that requires discontinuation of study intervention from lead-in study.

c) Any new diagnosis of malignancy after completion of the lead-in study.

d) Carcinoma in situ of the cervix, with apparent successful curative therapy, is exclusionary within 12 months prior to Week 0.

Note: 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.

1.06. Participant meets criteria for discontinuation of study intervention during prior lead-in study.

1.07. Deleted exclusion criterion as part of Amendment 3

1.08. Known history of primary immunodeficiency, splenectomy, or any underlying condition that predisposes the participant to infection, including HIV infection.

1.09. Prolonged QTcF interval (QTc > 450 msec or QTc > 480 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 are to be corrected prior to enrollment; the ECG for these participants may be repeated after electrolyte correction for determination of eligibility if needed.

1.010. Clinically significant kidney disease including but not limited to:

(a) Chronic kidney disease with an estimated glomerular filtration rate of less than 30 ml/min calculated by Modification of Diet in Renal Disease equation, as applicable, by the central laboratory at screening are excluded.

Prior/Concomitant Therapy

2.01. Participant requires additional immunosuppressive therapy (aside from permitted concomitant medication), biological treatment or prohibited treatment (see Section 6.5.4)

2.02. Deleted eligibility as part of Amendment 2

2.03. Participant received a prohibited medication during participation in the D5272C00001 (Legacy #3151-201-008) study (see Section 6.5.4).

2.04. Participant received a Bacille Calmette-Guérin vaccination within 12 months of Week 0 or any other live vaccine < 4 weeks prior to Week 0, or is planning to receive any such vaccine over the course of the study. Participant agrees to refrain from receiving live vaccines during the course of the study.

2.05. Participant has received an investigational product after discontinuation from Study D5272C00001 (Legacy #3151-201-008) and prior to enrolling in this study or participant is planning to receive an investigational drug (other than study intervention) or investigational device at any time during Study D5272C00002 (Legacy #3151-202-008).

Prior/Concurrent Clinical Study Experience

3.01 Participant who discontinued participation due to lack of efficacy after Week 10 in Study D5272C00001 (Legacy #3151-201-008) and did not receive CCI of study interventions scheduled for Week 0 (Day 1), Week 2 (Day 15), and Week 6 (Day 43), and CCI at Week 10 (Day 71) in accordance with the protocol for Study D5272C00001 (Legacy #3151-201-008). All efforts to administer and complete the full induction regimen in Study D5272C00001 (Legacy #3151-201-008) must be satisfied; however, unique or unconventional circumstances may be discussed with and approved by the Study Physician/designee to make a final eligibility determination in cases where CCI were administered.

3.02 Participant who discontinued due to lack of efficacy after Week 10 in Study D5272C00001 (Legacy #3151-201-008) but currently demonstrates clinical response and/or meets endoscopic Mayo score of 0 or 1 prior to Week 54 in Study D5272C00001 (Legacy #3151-201-008):

Clinical Response 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, in Study D5272C00001 (Legacy #3151-201-008).

Note: Participants are encouraged to remain in the lead-in Study D5272C00001 (Legacy #3151-201-008) if the participant is demonstrating evidence of clinical response. Participants should not early terminate that study due to lack of efficacy if this exclusion is met.

Diagnostic Assessments

4.01. Abnormal laboratory results at screening.

The following abnormal laboratory results at screening will be exclusionary (laboratory results may be repeated once). The enrollment window may be extended to allow for obtaining laboratory results after discussion with the Study

Physician/designee:

- Liver tests: either AST, ALT, or ALP greater than 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)
- Neutrophil count < $1.0 \times 10^3/\mu L$ (or < $1.0 \times 10^9/L$)
- Platelet count < $100 \times 10^3/\mu L$ (or < $100 \times 10^9/L$)
- Hemoglobin < 8 g/dL
- Deleted exclusion criterion as part of Amendment 3

Other Exclusions

5.01. Females who are pregnant, breast feeding, or planning a pregnancy during the study OR females who are of childbearing potential and do not agree to use contraception consistently and correctly as required by the study protocol (see Inclusion Criterion 2.02).

5.02. Participant is directly or indirectly involved in the planning and/or conduct and administration of this study (applies to both AstraZeneca staff and/or staff at the study site) as an investigator, sub-investigator, study coordinator, other study staff member, or employee of the sponsor, or the participant is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study; or the participant is enrolled in this study at another clinical study site.

5.03. Judgment by the investigator or sponsor that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

5.04. Previous enrollment in the present study.

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 for at least 18 weeks after last administration of the study intervention, as stated in Inclusion Criterion 2.02, 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 during study CCI CCI 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 this open-label clinical study but subsequently do not receive open-label 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 other participants.

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) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

This is an open-label study in which the only study intervention planned is the administration of brazikumab. Administration is to be CCI and CCI CCI

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.

Dosing of brazikumab should be withheld in the case of any pending laboratory tests or other assessments.

6.1 Study Interventions Administered

6.1.1 Group A – Maintenance Dosing

Maintenance dosing of brazikumab CCI will be administered to participants who completed the lead-in Study D5272C00001 (Legacy #3151-201-008) and met criteria for clinical response at Week 54.

6.1.2 Group B – CCI

Intravenous induction dosing with CCI brazikumab at Weeks 0, 4, and 8, followed by CCI maintenance dosing every 4 weeks from Week 12, will be administered in this study to participants who did not meet criteria for clinical response at Week 54 or who met criteria for early termination (rescue treatment) prior to Week 54 in the lead-in Study D5272C00001 (Legacy #3151-201-008).

6.1.3 Dosing Regimen

Participants will receive all study intervention administrations at the investigational site. Table 6 presents details regarding study intervention and administration.

Table 6 Study Interventions

Study intervention name	**Brazikumab** CCI	**Brazikumab maintenance dosing** CCI
Route of administration	CCI	
Dosage form		
Dose (mg)		
Dosing instructions[a]		
Packaging and labeling	Study intervention will be provided in kits. Each kit will be labeled as required per country requirement.	Study intervention will be provided in kits. Each kit will be labeled as required per country requirement.
Provider	AstraZeneca	AstraZeneca

[a] CCI will be added to an CCI by CCI CCI.

Brazikumab for [redacted]

Brazikumab for [redacted] will be supplied as a [redacted] concentrate for solution for infusion. The solution contains [redacted] brazikumab, [redacted]. The label-claim volume is [redacted]

Brazikumab for [redacted] is a sterile, [redacted]

Brazikumab for [redacted]

Brazikumab for [redacted] will be supplied as a [redacted] solution for [redacted] in a [redacted] The solution contains [redacted] brazikumab, [redacted] The label-claim volume is [redacted]

Brazikumab for [redacted] administration is [redacted]

All Formulations

Investigational product [redacted] and [redacted] are stored at [redacted] and [redacted] Investigational product must be kept in original packaging until use to [redacted]

6.1.3.1 [redacted]

If criteria for induction dosing are met, Group B participants will receive brazikumab [redacted] on Days 1, 29, and 57 (Baseline [Week 0], Week 4, and Week 8). An experienced and qualified staff member will [redacted] The total volume administered will be recorded in the eCRF. All brazikumab doses must be separated by at least 2 weeks.

[redacted] (BP, temperature, pulse rate, and respiration rate) will be obtained before [redacted] intervention administration at all treatment visits. In addition, participants will be monitored for changes in vital signs and/or new symptoms approximately [redacted] during [redacted] administration, immediately after completion of infusion, and at approximately every [redacted], 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, [redacted] completion of [redacted] for the [redacted] The monitoring time after the third infusion may be reduced to a minimum of [redacted] at the discretion of the investigator.

Infusion-related reactions have been reported with the administration of [redacted] As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs, such as

epinephrine, antihistamines, CS, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and/or emergency procedures must be in place, and study personnel must be trained to recognize and treat anaphylaxis according to local guidelines. Any infusion-related reaction and/or hypersensitivity reaction is to be reported as an AESI (see Section 8.3.11).

6.1.3.2 CCI

Brazikumab will be administered to all participants by CCI at the visits specified in Section 1.3. Brazikumab CCI administration must be separated by at least 2 weeks. Each SC dose will be administered by an experienced and qualified staff member. Each SC injection will be no more than CCI in volume. Each open-label brazikumab intervention will be administered via CCI at a single visit (ie, CCI per assigned dose group). CCI for all CCI and at a distance of at least CCI

It is advised that the site of CCI such that the participant receives study intervention at a different anatomical site at each treatment visit. The suggested injection site CCI is presented below (Figure 2). The CCI 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. If rotation of the injection site is not possible, the reason for this must be documented in the source.

Figure 2 CCI



Vital signs (BP, temperature, pulse rate, and respiration rate) will be obtained before and immediately after CCI study CCI administration during treatment visits outlined in the SoA (Section 1.3). The first and last vital signs (pre- and post-dose) are to be recorded on the eCRF. For the first 2 visits in which a participant receives CCI ie, Weeks 0 and 4 for Group A and Weeks 12 and 16 for Group B, study participants will be discharged from the testing facility a minimum of 20 minutes post-dosing or until stable as determined by the investigator or designee, whichever is longer. For subsequent visits, discharge from the site will be determined at the discretion of the investigator or designee. CCI following CCI is to be reported as an AE if considered more severe than expected (eg, excessive redness, swelling, tenderness, bruising) or the expected time for resolution is delayed.

6.1.4 Study Intervention Administration Rescheduling

Every effort should be taken to keep study intervention administration within the scheduled window. If a patient 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 patient 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 CCI 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 the Week 0 date.

If a patient misses more than 2 doses of study intervention (consecutively or non-consecutively) at any time within a calendar year during the treatment period, it is recommended that a conversation between the Investigator and Sponsor Study Physician/designee takes place to review the patient's adherence to treatment and decide on the patient's further disposition.

6.1.5 Study Supplies

AstraZeneca will supply the following study interventions manufactured by a third party for the study:

(a) CCI [redacted]
(b) Brazikumab pack containing CCI [redacted]

Additional details and instructions for brazikumab use are provided in the Pharmacy Manual. All defects (including malfunctions, use error, and inadequate labeling) shall be reported as described in the Pharmacy Manual.

6.2 Preparation/Handling/Storage/Accountability

1 Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention.

2 All study interventions must be stored in a secure, monitored (manual or automated) area with access limited to the study pharmacist or appropriate designee.

3 Brazikumab is stored at CCI [redacted]) and CCI [redacted]. Brazikumab must be kept in the original packaging until use to prevent prolonged light exposure. 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.

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, after being accounted for by the site monitor. Where local destruction is not possible, return to the supplying depot can be arranged.

5 All study interventions will be accounted for and accountability will be performed for each site during the course of the study. 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).

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

Brazikumab Preparation for CCI

The dose of brazikumab for CCI must be prepared by the investigator's or site's designated IP manager using CCI Prepared study intervention must be administered CCI

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

Brazikumab does CCI

Brazikumab CCI

Brazikumab CCI through an CCI set with a CCI CCI attachment of CCI

The brazikumab infusion time is 1 hour; however, if there are interruptions, the total allowed time must not exceed CCI

Do not co-administer CCI

The CCI to local practices to ensure the CCI CCI does CCI

If either preparation CCI a new dose must be prepared from CCI

Brazikumab Preparation for CCI

CCI are required for CCI inside the carton prior to administration. The dose of brazikumab for CCI must be administered CCI after removal of CCI

Brazikumab CCI

For CCI the person CCI the dose will wipe the CCI of the CCI with alcohol and allow the skin to air dry. CCI to isolate the CCI from CCI CCI halfway into the CCI Brazikumab will be slowly injected (at least a 5-second duration is recommended) into the CCI using gentle pressure. CCI

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

This is an OLE study. Precautions will be taken so that activities conducted during Study D5272C00002 (Legacy #3151-202-008) do not unblind treatment allocation in Study D5272C00001 (Legacy #3151-201-008). It is critical that the treatment assignment(s) from the lead-in study not be unblinded.

No randomization will be performed for the present study.

6.4 Study Intervention Compliance

Participants will receive all doses under the direct supervision of study center personnel. Study intervention compliance will be assumed to be 100% when dosing has been recorded in the eCRF.

The study center will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study-site staff (refer to the Pharmacy Manual).

A record of the number of brazikumab doses dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

The IP Storage Manager is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter, prescription medicines, vitamins, herbal supplements, and/or medicinal cannabis or other specific categories of interest) 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

The Sponsor Study Physician/designee should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

6.5.1 Permitted Concomitant Treatments

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

The following concomitant medications for UC are permitted during the study:

- Probiotics (eg, Culturelle and Saccharomyces boulardii), only if being taken at screening
- Antidiarrheals (eg, loperamide and diphenoxylate with atropine) for control of chronic diarrhea
- Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)
- CS therapy (oral prednisone and oral budesonide)
- 5-ASA

Permitted concomitant medications used for the treatment of UC during the lead-in study should be continued at stable doses, except for cases of toxicity where the dose may be lowered or discontinued and should not be restarted during the study.

Concomitant UC medications (eg, CSs) are not regarded as study intervention and will not be provided by the sponsor.

The use of NSAIDs is generally discouraged for IBD patients due to risk of flares. Use of NSAIDs is to be limited to occasional short courses for less than 7 days.

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

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 7.

Table 7 Permitted Concomitant Treatments

Treatment	Details
Probiotics (eg, Culturelle and Saccharomyces boulardii)	Permitted only if being taken at Week 0 (Study Day 1).
Antidiarrheals (eg, loperamide and diphenoxylate with atropine) for control of chronic diarrhea	Permitted as needed.
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 IP dosing study visit.

IBD = inflammatory bowel disease; IP = investigational product; NSAID = non-steroidal anti-inflammatory drugs.

6.5.2 Corticosteroid Study Guidelines

Participants may continue treatment with CS during the study.

Participants receiving oral CS should initiate tapering as per local standard of care and as recommended per guidelines in Table 8. Additional details are provided in Appendix B.

Table 8 CS Tapering Guidelines

Initial corticosteroid dose	Dose reduction
CCI [redacted]	

CS = corticosteroid(s); 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 previous oral CS or oral budesonide dose. These situations would not represent the use of rescue treatment. The increase in steroid dose should be recorded in the appropriate eCRF along with the indication for increase.
- If a prior dose of CS is required due to increased UC signs or symptoms while tapering CS, returning to the prior CS dose would not be considered rescue treatment, unless the dose is greater than the screening CS dose.

6.5.3 Rescue Treatment

For study purposes, any new concomitant medication, any increase in dose of a baseline medication required to treat new or unresolved UC symptoms (except for anti-diarrheal medications already used at baseline) after Week 12 of Study D5272C00002 (Legacy #3151-202-008) will be considered rescue treatment. Other investigational products are not permitted to be used as rescue treatment.

The **new** initiation (or dose increase) of medications or interventions for the treatment of UC after Week 12 of Study D5272C00002 (Legacy #3151-202-008) listed below will be considered as rescue treatments and will not require stopping study intervention:

- 5-Aminosalicylates
- Parenteral, oral, or rectal CS
- Oral steroid doses above initial (Day 1) dose
- Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)
- IV immunoglobulin

Administration of rescue treatment constitutes treatment failure. If rescue treatment is needed, investigators should consider study discontinuation for lack of efficacy. Rescue treatments are not to be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety. The use of specific rescue treatment (eg, prohibited interventions) in the lead-in study will be exclusionary for this study (Study D5272C00002/ Legacy #3151-202-008) and may preclude participants from enrolling.

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 must be notified if a participant receives any of these during the study, and study intervention must simultaneously be discontinued:

- Natalizumab
- Anti-TNFα agents
- Vedolizumab
- Ustekinumab
- Any commercially available or experimental biologic agent (eg, risankizumab, guselkumab), including biologic agents for other indications
- Tofacitinib
- Calcineurin inhibitors eg, cyclosporine (Neoral®) and tacrolimus (FK 506/Prograf®)
- Mycophenolate mofetil (CellCept®)
- Sirolimus (rapamycin)
- Thalidomide
- Fecal microbial transplantation
- Live attenuated vaccine
- Intra-abdominal surgery
- Any experimental product or device as specified in Section 5.2
- 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.

Note: The use of other immunosuppressant therapies not listed above will require discussion with the Study Physician/designee 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, the participant is to be encouraged to continue with assessments and visit schedule for the Early Termination Visit and Safety Follow-up Period.

6.6 Dose Modification

There is no provision for brazikumab dose reduction or increase. There will be a recommended dosing window of ± 7 days for the duration of the study, but the decision to discontinue the participant from the study will be determined as stated in Section 7 or by the

investigator.

If a delay in dosing is expected within the dosing window, then all study assessments will be delayed until the day of dosing.

6.7 Intervention After the End of the Study

No study interventions will be dispensed after the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

The sponsor will be notified of early participant discontinuation from the study and the reason for the discontinuation will be clearly entered in the eCRF.

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

Commonly used terms	Other acceptable terms
Adverse event	Death
Lack of efficacy	
Lost to follow-up	
Other	
Physician decision	
Pregnancy	
Protocol deviation	
Screen failure	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by participant	

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

7.1 Discontinuation of Study Intervention

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

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will not

remain in the study. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

It is the right and the duty of the investigator or sub-investigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual participant. In addition, the investigator or sub-investigator is to stop treatment of any participant with unmanageable factors that may interfere significantly with the study procedures and/or the interpretation of results.

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

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

Discontinuation of study intervention for abnormal liver function is to be considered by the investigator when a participant meets criteria for HL (see Section 8.3.6 and Appendix E) or one of the conditions outlined below or if the investigator believes that it is in best interest of the participant.

Abnormal liver function, defined as meeting 1 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 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** TBL > 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 cases are to 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 screening in QTc 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. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding is to 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 greater than 500 msec or of greater than 60 msec over screening require study drug discontinuation.

If the study intervention is discontinued, the participant is required to complete the visit and assessments for the Early Termination Visit and Safety Follow-up Period. See the SoA (Section 1.3) for a listing of the 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 Early Termination Visit.

7.2 Participant Withdrawal from the Study

- A participant may be withdrawn from the study if the time between doses or visits exceeds 56 days.
- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- 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 ICF 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.
- At the time of withdrawal from the study, if possible, an Early Termination Visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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 will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- All assessments made at the final visit of Study D5272C00001 (Legacy #3151-201-008) will be utilized as screening assessments for this study, unless Week 0 for this study occurs greater than 28 days from the final assessment(s) of the lead-in study, in which case the participant will need to complete all required screening assessments, except the colonoscopy. A repeat colonoscopy is not required for participants who discontinue from the lead-in study after Week 10 and prior to Week 14.
- Week 0 dose administration must occur no earlier than 14 days and no later than 56 days from the last dose administration in Study D5272C00001 (Legacy #3151-201-008).
- Paper PRO collection must be initiated 7 days prior to Week 0.
- 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, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 300 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Endoscopy

A full colonoscopy or flexible sigmoidoscopy is not required for participants who roll over to this OLE study (Study D5272C00002 [Legacy #3151-202-008]) as it must be obtained at the final visit of the lead-in study (eg, the final [Week 52] or Early Termination Visit).

A full colonoscopy or flexible sigmoidoscopy may be performed at any time during this study at the investigator's discretion to assess the participant's clinical condition.

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.

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 reader is to promptly notify both the Sponsor Study Physician/designee and the investigator of the detection of any clinically significant findings (eg, bowel lesions) that are not manifestations of UC.

The risks for endoscopy procedures may include perforation, bleeding (as applicable if biopsy samples are collected for non-study purposes), 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.

8.1.2 Modified Mayo Score

The mMS may be assessed at any time during this study at the investigator's discretion when an unscheduled full colonoscopy or flexible sigmoidoscopy is performed to assess the participant's clinical condition.

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 sub-score of 1 (mild disease). Stool frequency and rectal bleeding will be assessed daily by the participant using a paper diary, which is to be provided to each participant prior to the reporting visit; the participant will be prompted when to begin recording responses. 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 will be based on the participant's average nightly diary data recorded over the most recent 3 days of allowable data within the 7-day period prior to the visit. These should not include any days in which bowel preparation are administered or the day of endoscopy.

When applicable, the mucosal appearance during the endoscopic examination will be assessed for the modified Mayo endoscopic sub-score (ie, findings of endoscopy item). The endoscopic appearance will be examined by both the investigator and the central reader.

The Mayo Scoring System is shown in Table 9.

Table 9 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] Sub-score of 1 (mild disease) modified to reflect no friability for modified Mayo score as described above.

Source: Amended from Schroeder et al, 1987.

8.1.3 Partial Mayo Score

The pMS uses the 3 non-invasive components of the full Mayo score (Table 9): stool frequency, rectal bleeding, and PGA. Because the endoscopic score is excluded, the maximum score is 9 points. The pMS 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 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.

8.1.4 Patient-reported Outcomes – Evening Diary

A paper evening diary will be provided to each participant at the visit prior to the reporting visit. Participants will be instructed to complete the diaries every day in the evening for the 7 days prior to the visit, with the last diary completed the evening prior to the study visit, excluding days of bowel preparation and endoscopy. Participants will bring the diaries to the site at the appropriate visit. Participants will be prompted as to when to begin recording these assessments.

The evening diary will be collected 1 week before select scheduled site visits (see Section 1.3). The evening diary will include the mMS items of bowel movement count from normal and rectal bleeding. The diary will also include an item to capture urgency, as well as NRS symptom items including abdominal pain, fatigue, tiredness, weakness, lack of energy, joint pain, and flatulence. The NRS measures the severity of symptoms in the past 24 hours using an 11-point scale (0-10).

8.1.5 Patient-reported Outcomes – Site Visits

The HRQoL assessments include the IBDQ, SF-36v2, and EQ-5D-5L and will be administered via paper at select site visits (see Section 1.3 and Appendix F).

The IBDQ 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 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 VAS 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 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.

8.1.6 Colon Mucosal Biopsies

Mucosal biopsies will be collected at each study endoscopy. 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 biomarkers from the biopsy specimens.

8.1.7 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.

8.1.8 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.

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA in Section 1.3 and will include the following:

- Physical examinations
- Vital signs

- Clinical laboratory assessments
- ECG
- AEs

8.2.1 Physical Examinations

- A physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA

- Body temperature, pulse rate, respiratory rate, and BP will be assessed.
- Blood pressure and pulse measurements will be assessed in the sitting position with an automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements are to be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs are to be taken before blood collection for laboratory tests and will be recorded on the eCRF.
- Weight will also be measured and recorded.
- Procedure for monitoring vital signs before, during, and after CCI [redacted] of study CCI [redacted] are further detailed in Section 6.1.3.1 and Section 6.1.3.2, respectively.
- See Section 8.3.5 for information on AEs related to vital sign measurements.

8.2.3 Electrocardiograms

- Single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an 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

- The clinical laboratory tests detailed in Table 10 will be performed by the central laboratory, in accordance with the Laboratory Manual and SoA (Section 1.3).
- For protocol-required biomarker laboratory tests, see Section 8.6.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10 Protocol-required Safety Laboratory Assessments

Laboratory assessments	Parameters		
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV MCH %Reticulocytes	WBC count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[a]	BUN C-reactive protein Creatinine eGFR Glucose (non-fasting) Magnesium Uric acid	AST ALT ALP Albumin Potassium Sodium Calcium Chloride	Total and direct bilirubin Total protein Bicarbonate Phosphate
Fecal Tests	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 Tests	• FSH (as needed in women of non-childbearing potential only) • Serum hCG pregnancy test or FSH when applicable is required at screening, as needed for women of childbearing potential. All other pregnancy testing will consist of urine pregnancy testing performed locally at each visit prior to administering study intervention and as outlined in the SoA. For participants who are postmenopausal, an FSH level is to be obtained at screening (see Section 5). • 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.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; SoA = Schedule of Activities; WBC = white blood cell.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The

laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that 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 significant during participation in the study or within 18 weeks after the last dose of study intervention should 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 should be identified and the sponsor notified.
- See Section 8.3.5 for information on AEs related to laboratory measurements.

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 C.

The investigator and any qualified 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 reported to the sponsor or designee within 24 hours, as indicated in Appendix C. 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 (yes or no)
- Action taken with regard to IP
- 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 causal relationship between investigational product and each AE, 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 investigational product?*.

For SAEs, causal relationship should also be assessed for other medication and study

procedures. 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 C 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 protocol-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 investigational product, or are considered to be clinically relevant as judged by the investigator (which may include but 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, anaemia 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 ≥ 3 × ULN together with TBL ≥ 2 × 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 Progression

Not applicable.

8.3.8 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of UC (eg, haemorrhagic diarrhea or defecation urgency). Events which 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 investigational product.

8.3.9 Reporting of SAEs

All SAEs have to be reported, whether or not considered causally related to the investigational product, 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 one 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 staff how to proceed.

For further guidance on the definition of a SAE, see Appendix C of the CSP.

The reference document for definition of expectedness is the IB.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study participant has received any study intervention**.**

8.3.10.1 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 investigational product 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 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available. The pregnancy report (PREGREP) module in the eCRF is used to report the pregnancy, and the paper-based pregnancy outcome report (PREGOUT) module is used to report the outcome of the pregnancy.

8.3.10.2 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.

8.3.11 AEs of Special Interest

8.3.11.1 CCI

CCI

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

8.3.11.2 Malignancies

Emerging data from clinical studies 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.

Non-clinical 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 TEAE assessments. In addition, participants will be advised of the potential risk of malignancy during the informed consenting process. If a malignancy is diagnosed during the study, investigators must obtain and report biopsy results and other relevant biomarkers and/or genetic test results.

8.3.11.3 Hypersensitivity Reactions (Including Anaphylaxis)

Unlike infusion-related reactions, 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. Appropriate drugs, such as epinephrine, antihistamines, CSs, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and/or emergency procedures must be in place, and study personnel must be trained to recognize and treat anaphylaxis according to local guidelines.

8.3.11.4 Infections

The use of immunomodulatory drugs, including biological 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. Non-clinical 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 until resolution of the infection. Any clinically significant active or chronic infection must be discussed with the Study Physician/designee prior to baseline as per Exclusion Criterion 1.01.

Occurrence of infections will be monitored during studies by routine laboratory testing, physical examination, and TEAE assessments.

8.3.11.4.1 Non-opportunistic Infections

A serious non-opportunistic infection is any non-opportunistic infection that meets the SAE criteria in Appendix C. 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. Non-serious non-opportunistic infections will not be reported as AESIs.

8.3.11.4.2 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.

8.3.12 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 8.3.9) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix C 7.

8.4 Overdose

For this study, a brazikumab overdose is any CCI per administration, greater than CCI and any CCI, per administration, greater than CCI in Group B.

- 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 one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.9) 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 D.

- 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 anonymised by pooling. Additional analyses may be conducted on the anonymised, 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 pre-dose for measurement of serum brazikumab concentrations as specified in the SoA in Section 1.3.
- A serum brazikumab concentration sample will be collected at the Early Termination Visit for participants that prematurely discontinue from the study.
- Instructions for the collection and handling of biological samples are provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples may be collected at additional time points 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.
- Serum samples will be used to analyze the PK of brazikumab. Samples collected for analyses of brazikumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration 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.

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 ADAs against brazikumab (binding antibodies and NAbs) will be collected according to the SoA and will remain blinded. Instructions for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the sites.

Blood samples for ADAs and NAbs will be analyzed 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, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.5.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated 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 biomarkers according to the SoA in Section 1.3. All samples should be collected pre-dose 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 inflammatory bowel disease, immunological function, and the pharmacology of brazikumab. The intended purpose is to evaluate the association of these biomarkers 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.

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 biomarker analyses are exploratory and may be described in a separate report.

For storage, re-use and destruction of biomarker samples see Section 8.5.

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

The treatment sequences in this OLE study will be presented as Brazikumab/Brazikumab for participants who received brazikumab study intervention in the double-blind, lead-in study, and Placebo/Brazikumab for participants who received placebo study intervention in the double-blind, lead-in study. Any further details will be specified in the SAP.

All safety analyses for this study will be summarized descriptively by the visit and the treatment sequences and overall, unless stated otherwise. The baseline as defined in the double-blind, lead-in study will be used as the baseline for all data analyses in this study. Continuous variables will be summarized by the number of participants and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants. Visit time window for safety parameters and detailed statistical analyses for this study will be defined in the SAP.

9.1 Statistical Hypotheses

Not applicable.

9.2 Sample Size Determination

This study is an extension study and the sample size is determined by the number of participants in the lead-in studies who are eligible and choose to participate in this study. No separate sample size calculation was performed. Up to a maximum of CCI participants may enter the study, based on the expected number of participants in the lead-in Study D5272C00001.

9.3 Populations for Analyses

Table 11 defines the populations for analyses in this study.

Table 11 Populations for Analysis

Population/analysis set	Description
Screened Analysis Set	All participants who are screened for the study
Full Analysis Set	All participants who are assigned to an CCI CCI in this study
Safety	All participants who receive 1 or more administration of study CCI in this extension study

CCI

9.4 Statistical Analyses

The SAP will be finalized at the earliest possible timepoint after the first participant enrolls under Amendment 2. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and exploratory endpoints.

9.4.1 Efficacy Analyses

Modified Mayo scores (see Section 8.1.2) will be summarized descriptively using the Full Analysis Set population.

The efficacy analyses include, but are not limited to, the following endpoints:

- mMS
- PGA
- NRS
- IBDQ
- SF-36v2
- EQ-5D-5L
- GHI
- RHI

9.4.2 Safety Analyses

Safety analyses will be performed using the Safety Population and will be fully defined in the SAP. The safety parameters will include AEs, clinical laboratory parameters, vital signs, and ECG parameters. If the (screening) visit for this study is the last visit from the lead-in study, the safety value at screening will not be included in the PCS evaluation as it had been evaluated in the lead-in studies, but it will be included in the change-from-baseline summary

analysis.

9.4.2.1 AEs

Adverse events are defined in Appendix C.

The number and percentage of participants with treatment-related AEs during the study will be tabulated by system organ class and preferred term.

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

Summary tables will be provided for participants with treatment-emergent SAEs and participants with AEs leading to discontinuation if these occurred in 5% or more participants. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

In addition, AESIs as defined in Section 8.3.11 will also be summarized.

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

9.4.2.2 Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in conventional and international system [SI] units) at baseline, postbaseline, and changes from baseline at each postbaseline timepoint will be presented 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. 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.

9.4.2.3 Vital Signs

Descriptive statistics for vital signs (supine systolic and diastolic BP, pulse rate, weight, respiration rate, and temperature) at baseline, postbaseline, and changes from baseline at each postbaseline timepoint will be presented.

Vital signs values will be considered to be 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 signs values will be tabulated. 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.

9.4.2.4 ECGs

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

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. 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 Biomarker Analysis

Exploratory biomarker analyses may be defined and presented outside of the SAP and CSR.

9.5 Interim Analyses

No interim analysis is planned for this study.

9.6 Data Monitoring Committee

Not applicable in this study.

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 CIOMS International Ethical Guidelines
  - Applicable ICH/ISO 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 approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and EU regulation 536/2014 for clinical studies (if applicable), and EU Medical Device Regulation 2017/745 for clinical device research (if applicable).
- 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 contract research organization but the accountability remains with AstraZeneca.

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 a SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - EU 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 a 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.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

A 2 Financial Disclosure

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

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 representatives 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

- Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that 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.
- 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.
- 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.

A 5 Dissemination of Clinical Study Data

All data generated in this study are the property of the sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

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 study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs 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 physically or electronically signing the CRF.

- 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.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- 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, as stated in the clinical trial agreement. 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.
- 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, Contract Research Organizations).

A 7 Source Documents

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

A 8 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 or 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 contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants 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 9 Publication Policy

- AstraZeneca as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and AstraZeneca personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with AstraZeneca.

- 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.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. In this case, a coordinating investigator will be designated by mutual agreement.
- 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.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A 10 Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

Appendix B Sample CS Tapering

CS Tapering for Prednisone/Budesonide in mg/day

	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19
CCI									

CS = corticosteroid(s); MMX = Multi-Matrix System

Note: The rate of CS tapering will be at the investigator's discretion and may depend on the participant's medical history and clinical, laboratory, and endoscopic findings.

Examples of Approximate Equivalent Doses of Oral Prednisone

Oral prednisone equivalents	Equivalent dose
CCI	

Appendix C AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

C 1 Definition of AEs

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 unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example 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 non-serious 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.

C 2 Definition of AESIs

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's study intervention 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 AESIs have been identified for the study intervention in this protocol:

- Infusion-related reactions and injection-site reactions
- Malignancies
- Hypersensitivity reactions (including anaphylaxis)
- Infections

Non-serious AESIs are to be recorded in EDC within 72 hours, and serious AESIs are to be reported to the sponsor via EDC within 24 hours.

For PHL cases, report as soon as possible (within 24 hours of learning of the PHL case). The eCRF pages associated with PHL cases must be completed within 3 calendar days (see Appendix E).

C 3 Definition of SAEs

A 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 in-participant 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 jeopardise 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 **Serious AEs**. 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 **non-serious 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 non-serious; 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 a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). 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 anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

C 4 AE and SAE Recording

- When an AE or 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 or SAE information in the eCRF within 3 days.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. 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 the sponsor or designee.
- 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.

C 5 Intensity Rating Scale

- Mild (awareness of sign or symptom, but easily tolerated)
  - A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate (discomfort sufficient to cause interference with normal activities)
  - A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe (incapacitating, with inability to perform normal activities)
  - A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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 C 3. 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 a SAE unless it meets the criteria shown in Appendix C 3. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix C 3.

C 6 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?
- De-challenge 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 aetiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- 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.

C 7 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 the 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, for example, 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 fridge 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.

Appendix D Handling of Human Biological Samples

D 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.

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.

D 2 International Airline Transportation Association 6.2 Guidance Document

LABELING 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. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- *are to be packed in accordance with UN 3373 and IATA 650

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 E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of HL

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 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; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, 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 IMP. 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
Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law
AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP 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 TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of PHL 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:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

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 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 Section 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 PHL 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 PHL 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 PHL; 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 IMP, 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, discuss and agree 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 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 the 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 TBL) 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 PHL 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 was initially detected, the Sponsor Study Physician/designee contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to 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 TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a 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 PHL 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 TBL elevations other than the IMP:

  - 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:

- Provides any further update to the previously entered SAE of PHL, (report term now *Hy's Law case*) ensuring causality assessment is related to IMP 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.

E 6 Laboratory Tests

HL 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 & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin
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 7 References

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

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FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing

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Appendix F PRO Questionnaires, Descriptions, and Instructions

F 1 Evening Diary

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

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

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

F 2 Site Visit Instruments

Note: The questionnaires presented below are is an approximation of the planned final documents. The order of some questions may change.

F 2.1 Inflammatory Bowel Disease Questionnaire (Sample Version)

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

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

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.

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.

F 2.2 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 G 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 Table 1. 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, as long as there have not been greater than 56 days from the last dose administration in the lead-in study and the first dose in this OLE study. The investigator should confirm this with the 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 re-screen 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 identification 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 patient's 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. If applicable, assessments may be performed according to the revised SoA in the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis.

Refer to the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for step-by-step guidance.

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 medication, etc. to be collected according to study requirements to be reported and documented. If applicable, safety procedures and blood sample collection may be performed according to the revised SoA in the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis.

Refer to the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for step-by-step guidance.

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 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.

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.

Refer to the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for step-by-step guidance.

Appendix H Abbreviations

Abbreviation	Definition
ADA	antidrug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0\text{-}28days}$	area under the concentration-time curve from 0 to 28 days
BP	blood pressure
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum serum drug concentration
CRF	case report form
CS	corticosteroid
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced livery injury
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D-5L	European Quality of Life-5 Dimensions
EU	European Union
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GHI	Geboes Histological Index
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hy's Law
HRQoL	health related quality of life
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form

Abbreviation	Definition
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IgG2	immunoglobulin G2
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ISO	International Organization for Standardization
CCI	CCI
mAb	monoclonal antibody
mMS	modified Mayo score
NAb	neutralizing antibody
NRS	Numerical Rating Scale
NSAID	non-steroidal anti-inflammatory drug
OLE	open-label extension
PCR	polymerase chain reaction
PCS	potentially clinically significant
CCI	CCI
PGA	Physician's Global Assessment
PHL	potential Hy's Law
PK	pharmacokinetic
pMS	partial Mayo score
PRO	patient-reported outcome
RHI	Robarts Histopathology Index
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
CCI	CCI
SoA	Schedule of Activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SF-36v2	36-Item Health Survey Version 2
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor alpha

Abbreviation	Definition
TPV	third-party vendor
UC	ulcerative colitis
ULN	upper limit of normal
US	United States

Appendix I Protocol Amendment History

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

Amendment 2 (March 2021)

Overall Rationale for the Amendment:

In 2020, AstraZeneca resumed full ownership of brazikumab clinical development. AstraZeneca re-evaluated the development plan and the CSP D5272C00002 (Legacy #3151-202-008) was consequently reviewed and amended. 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.

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

Section # and name	Description of change	Brief rationale
Throughout	Further aligned the protocol with 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	Updated references to paper reporting (eg, CRF) to electronic methods (eg, eCRF).	Aligned with new reporting systems now in place.
Throughout	Removed references to vedolizumab.	Vedolizumab treatment was removed from D5272C00001 lead-in study and is no longer relevant.
Throughout	Rescue therapy and rescue medication terms standardized to rescue treatment.	Revised for consistency and clarity.
Throughout	Replaced the term infusion reaction with infusion-related reaction.	To align with MedDRA terminology.
Throughout	Replaced Study Physician with Sponsor Study Physician/designee.	To allow flexibility in the sponsor contact person.
Throughout	References in the text to study visit numbers (eg, Visit 1) were replaced by week numbers (eg, Week 0)	To improve clarity regarding the timing of study activities.
Throughout (see especially Section 4.1 and Section 6.1)	Removed Group A (120 mg dose level); renamed Group C to Group B and renamed Group B to Group A. Expanded Group A enrollment	The 120 mg dose level was removed as the sponsor has previously shown that treatment with CCI study in participants with Crohn's disease was associated with clinical improvement and was well tolerated. It is expected that CCI also be well

Section # and name	Description of change	Brief rationale
	criteria to all participants completing the lead-in study.	tolerated in patients with ulcerative colitis whether they were on placebo, CCI brazikumab in the lead-in study. The sponsor does not have data with CCI brazikumab to date.
Throughout	Changed the induction dose level from CCI .	As a result of the sponsor change, the development program has been re-evaluated. Based on re-evaluation of data, limited benefit of CCI This change aligns with the lead-in study.
Throughout	Aligned the induction visit schedule (Group B) with the Group A visit schedule, ie, visits on Week 0, 2, 6, … Week 50 are now to be conducted on Week 0, 4, 8, … Week 52	The study has been aligned with the design of other studies in the brazikumab program: Studies D5271C00001 and D5271C00002 (blinded induction/maintenance study and an open-label extension study, respectively) of brazikumab in participants with severely active Crohn's disease. Both studies feature induction dose regimens of Week 0, 4, and 8.
Throughout	Removed references to previous, differing dose schedules for Group A/B versus Group C.	Revised to reflect new alignment of dosing schedules for all participants.
Throughout	References to specific assessment timepoints replaced by a reference to the SoA.	Revised for clarity and to align with the lead-in study.
Throughout	Replaced references to visit numbers (eg Visit 1) with references to week numbers (eg, Week 0).	Revised for alignment with the lead-in study D5272C00001.
Title page	Added the study acronym Expedition OLE.	To conform to the AstraZeneca template.
Title page	Added international coordinating investigator.	To conform to 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.
Synopsis	Removed estimate of number of study sites.	Aligned with current AstraZeneca protocol template and other CD and UC protocols.
SoA	Table 1-1 (formerly for Group A and B) and Table 1-2 (formerly for	Tables combined to improve clarity and ease of use.

Section # and name	Description of change	Brief rationale
	Group C) combined into a single SoA table for all participants.	
SoA	Title of Table 1 shortened to Schedule of Activities.	Reference to treatment groups no longer required as all participants will use the same table.
SoA	Reorganized assessments under new header categories (eg, Safety Assessments).	Revised for clarity and ease of use.
SoA	Removed visit window of -28 to -1 days from the screening column header.	The timing of screening assessments is presented elsewhere in the protocol.
SoA	Changed Baseline visit to W0.	To improve clarity and avoid confusion with baseline values from the Screening Period.
SoA	Detailed footnotes removed when redundant with text in later sections, or moved into appropriate sections in the full protocol; or added into a new Notes column in the SoA.	Revised for clarity and to reduce redundancy.
SoA	Added column referencing the section relevant to each assessment.	Revised for clarity and to reduce redundancy.
SoA	Removed note on unscheduled collections for determination of brazikumab serum concentration.	There is no longer any requirement for unscheduled samples as there will be no dose escalation in the maintenance phase of the study, since the 120 mg arm has been removed.
SoA	Duplicate row for CRP testing removed.	CRP testing was already listed with serum hematology and chemistry.
SoA	Added colonoscopy to Week 52 visit and Early Termination Visit.	To assess endoscopic change in inflammation over the course of the study and to align with study design in the open-label extension study of Crohn's Disease (Study D5271C00002).
SoA	Added Week 52 mMS assessment.	The addition of the Week 52 colonoscopy enables mMS assessment.
SoA	Changed pMS assessment at the Early Termination Visit to mMS.	The addition of colonoscopy at the Early Termination Visit enables mMS assessment.
SoA	Replaced pMS assessments at screening, Week 24, and Week 52 with PGAs and added PGAs at Week 12 and Week 36	Partial Mayo Scores to be replaced by expanded Physician's Global Assessments to augment exploratory efficacy data.
SoA	HbA1c assessment removed.	Hemoglobin A1c value does not impact study eligibility and may be evaluated by local laboratory at the investigator's discretion. Revised to align with other brazikumab protocols.

Section # and name	Description of change	Brief rationale
SoA	Assessments grouped by category (eg, safety assessments).	Revised for clarity.
SoA	Vedolizumab-related assessments removed.	Vedolizumab treatment was removed from D5272C00001 lead-in study and references to vedolizumab-related assessments are no longer relevant.
SoA	Added physical examination at Week 0.	Correction.
SoA	Removed language specifying that C. difficile testing results can be pending upon screening and dosing.	Revised to align with D5271C00002 study and was no longer needed.
SoA	Hepatitis B virus DNA test removed.	Hepatitis B virus DNA testing to require PCR testing only when necessary, as specified in Inclusion Criterion 1.08
SoA	Virology Tests renamed to Hepatitis B and C and HIV screening and these tests removed from the Early Termination Visit and Safety Follow-up Period.	Revised for clarity and because virology tests are not needed at end of study or during follow-up.
SoA	TB test revised to QFT-TB test and or negative removed from requirement for QFT-TB testing.	Revised for clarity and consistency.
SoA	Removed TB testing (in cases of indeterminate results) from Week 12, Week 36, and Week 52 visits and shifted assessment at screening to Week 0.	Revised to align with Study D5271C00002 and to align with clarification of TB testing procedures.
SoA	Added fecal lactoferrin and exploratory biomarker assessments at Weeks 0, 12, 24, and 52, and the Early Termination Visit.	Additional biomarker assessments were added to continue assessments initiated in D5272C0001 lead-in study to evaluate biomarkers with efficacy variables to understand correlation with response.
SoA	Changed Injection-site assessment to Assessment of injection-site reactions.	Corrected to align with retitled AESI in Section 8.3.11.1
SoA	Specified that pregnancy test is urine pregnancy except at screening and removed reference to FSH collection; clarified testing for women of childbearing potential only.	Revised for accuracy.

Section # and name	Description of change	Brief rationale
SoA	Week 4 window for Group B changed from +2 days to be ±7 days.	This visit was previously at Week 2 and is now aligned with other Week 4 visits. In addition, the study has been aligned with the design of Study D5271C00002, an open-label extension study of brazikumab in participants with severely active Crohn's disease.
SoA	Replaced X in Study Intervention row with either CCI as appropriate.	Revised for clarity.
SoA	Removed the following note from the Study Intervention row: Withhold dose in case of any pending laboratory tests or other assessments.	Moved information to Section 6
SoA	Added urinalysis assessments at Week 12, Week 24, and Week 36	Revised to align urinalysis assessment with serum chemistry and hematology assessments.
SoA	Added requirement that the first dose should be administered within 8 weeks of the last dose from the lead-in study.	Alignment with the open-label extension Study D5271C00002.
SoA	Removed rows on study intervention administration from Table 2	Rows not required as no study intervention is administered during follow-up.
SoA	Removed Week 52 TB testing if QFT-TB indeterminate.	All patients already receive QFT-TB testing at this visit, not just those receiving indeterminate.
SoA	Removed Week 52 Hepatitis B and C and HIV test.	Required for the lead-in study but not for this OLE study.
SoA	Added table of PRO scheduled assessments.	Added to clarify PRO assessment visits.
Section 2	Added ulcerative colitis to the approved indications for ustekinumab.	Revised with current information.
Section 2.2	Non-clinical and clinical safety information added.	Revised to provide additional background information consistent with the D5272C0001 lead-in study.
Section 2.3	Revised statement concerning identified important risks.	Clarified the safety profile of brazikumab and aligned with text in the UC lead-in study.
Section 3	Reclassified secondary endpoint as exploratory and changed endpoint from pMS assessments to mMS assessments.	The efficacy endpoint is exploratory given the unblinded nature of this study, and the addition of the Week 52 endoscopy allows for assessment of mMS rather than pMS.

Section # and name	Description of change	Brief rationale
Section 4.1	Updated study design description, number of treatment arms and doses.	To align with study design changes.
Section 4.1	Description of participants simplified to previously enrolled in the lead-in study.	Revised for clarity and alignment with other open-label extension studies.
Section 4.1	Number of sites removed.	Alignment with AstraZeneca template.
Section 4.1 and Synopsis	Removed instructions on enrolling participants >180 days after the final dose from the lead-in study.	As the current protocol is already enrolling patients, these instructions are no longer applicable.
Section 4.1.1 and Appendix H	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 5.1, Inclusion Criterion 1.01 and 1.02	Inclusion criteria 1.01 and 1.02 merged into a single criterion (1.01); removed requirement that only participants unblinded from the lead-in study D5272C00001 are eligible.	Revised for clarity, given the simplification of study arms in this amendment, and to align with the open-label extension Study D5271C00002.
Section 5.1, Inclusion Criterion 1.03	Revised language on TB prophylaxis, QFT-TB testing, and new diagnosis of latent TB.	Revised to prevent the inclusion of newly diagnosed latent TB participants in the study. Aligns with TB criteria across brazikumab protocols.
Section 5.1, Inclusion Criterion 1.04	Removed criterion, which contained language allowing 180-day screening window in case this protocol was not available to participants.	No longer applicable to new participants since the protocol is currently available.
Section 5.1, Inclusion Criteria 2.01, 2.02, and 2.03	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 # and name	Description of change	Brief rationale
Section 5.1, Inclusion Criteria 2.01	Added requirement that cessation or continuation of contraception at least 18 weeks after last dose of study drug to be discussed with a responsible physician.	Added to respond to the Medicines and Healthcare products Regulatory Agency grounds for non-acceptance issued for the Allergan protocol. Aligns across the brazikumab program.
Section 5.1, Inclusion Criterion 5.01	Added a new criterion, specifying age range for eligible participants.	Aligned with existing criterion in D5272C00001 lead-in study.
Section 5.2, Exclusion Criterion 1.01	Text simplified for clarity and examples removed.	Aligned with brazikumab protocols and to improve clarity.
Section 5.2, Exclusion Criterion 1.05	Added new exclusion criterion for participants with a history of cancer.	Further defines study entry criteria and details exceptions for skin cancers and in situ cancer of the cervix.
Section 5.2, Exclusion Criterion 1.07	Moved existing exclusion criterion defining hepatitis B and C infections from Exclusion Criterion 4.01 (Diagnostic Assessments) to this section (Medical Conditions).	Revised for clarity.
Section 5.2, Exclusion Criterion 1.08	Moved existing exclusion criterion defining HIV infections from Exclusion Criterion 4.01 (Diagnostic Assessments) to this section (Medical Conditions).	Revised for clarity.
Section 5.2, Exclusion Criterion 1.09	Added an exclusion criterion on QTcF interval prolongations.	Revised to increase patient safety by taking into account QT variation with bundle branch block. Aligns with other AstraZeneca brazikumab protocols.
Section 5.2, Exclusion Criterion 1.010	Moved existing exclusion criterion defining kidney disease from Exclusion Criterion 4.01 (Diagnostic Assessments) to this section (Medical Conditions).	Revised for clarity.
Section 5.2, Exclusion Criterion 2.02	Removed	No longer relevant as participants entering from the D5272C00001 lead-in study will have already met this criterion.
Section 5.2, Exclusion Criterion 2.04	Changed references to baseline (Visit 2) to Week 0.	To improve clarity and avoid confusion with baseline values from the Screening Period.
Section 5.2, Exclusion Criterion 3.02	Revised criteria for participants who discontinued from the lead-in study but who had demonstrated initial clinical response.	Revised to align with new treatment guidelines in the D5272C00001 lead-in study.

Section # and name	Description of change	Brief rationale
Section 5.2, Exclusion Criterion 4.01	Added criteria for positive C. difficile stool testing, specifying that PCR testing is exclusionary in case of indeterminate results.	Revised to provide guidance in case of indeterminate results (antigen positive and toxin negative).
Section 5.2, Exclusion Criterion 4.01	Added note that pathological evidence of conjugated [direct] hyperbilirubinemia per investigator and/or sponsor discretion is exclusionary.	Added to increase patient safety and to align with the UK amendment.
Section 5.2, Exclusion Criterion 5.01	Changed the term nursing to breast feeding.	Revised for clarity.
Section 5.2, Exclusion Criterion 5.02	Clarified participant affiliations with AstraZeneca that disallow participation.	Aligned with AstraZeneca standardized processes.
Section 5.3.2	Revised guidance on use of nicotine-containing products during study intervention administration.	Revised for clarity and to align with AstraZeneca standard processes.
Section 5.3.2	Added information on recording the use of nicotine replacement therapy.	To align with standard AstraZeneca template wording and align with other brazikumab protocols.
Section 5.4	Provided information on recording screen failures in the eCRF.	Revised for clarity and alignment with AstraZeneca standard processes.
Section 5.4	Specified that participants may be retested once during screening if an initial laboratory parameter is exclusionary.	Revised for clarity and alignment with AstraZeneca standard processes.
Section 6	Relocated footnote from SoA about withholding doses in the case of pending laboratory tests.	Revised for clarity.
Section 6	Removed description of change in formulation of drug product, going from the lead-in study to this study.	The same drug product formulation is now in use in both lead-in and open-label extension studies.
Section 6	Removed requirement for reporting dosing delays > 56 days to the sponsor and for consulting with sponsor on resumption or discontinuation of dosing.	Align studies in the brazikumab program and align with guidance for rescheduled/delayed dosing.
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 # and name	Description of change	Brief rationale
Section 6.1	Added text clarifying that Group A will enroll those completing the lead-in study and Group B will enroll those with worsening disease or lack of response.	Revised for clarity to align with changes made to groups, including removal of one group from the protocol.
Section 6.1.3	Added details on brazikumab CCI concentrate and CCI [redacted].	Revised to provide update on current formulations in use.
Section 6.1.3	Added text clarifying the monitoring period required for the first 2 visits of subcutaneous dosing in each study group.	Revised to clarify that Group B participants require monitoring upon switching to subcutaneous dosing at the Week 12 and Week 16 visits.
Section 6.1.4	Added section for study intervention administration rescheduling.	To provide guidance for missed and/or delayed doses.
Section 6.1.5	Removed details of drug concentration from study supplies.	Revised for accuracy and flexibility and to align with current supplies.
Section 6.2	Added additional details on brazikumab preparation CCI [redacted] and moved details on subcutaneous dosing preparation and administration from Section 6.1.1.2.	Provides additional guidance and clarification to study sites and aligns with other brazikumab protocols.
Section 6.2	Added requirement to verify temperature conditions during transit of study intervention.	Alignment with AstraZeneca standard practices and protocol template.
Section 6.2	Clarified that brazikumab is not to be frozen and that it should remain in avoid prolonged light exposure.	Revised for clarity.
Section 6.2	Specifies responsibility for study intervention accountability, reconciliation, and record maintenance.	Alignment with AstraZeneca standard practices and protocol template.
Section 6.4	Expanded requirements related to preparing and dispensing doses and for maintaining study intervention records.	For clarity and to reiterate contemporaneous recording within eCRF.
Section 6.5	Adds requirement that participants abstain from drugs for a certain time period before study start and specified who will administer study intervention and record it.	Alignment with AstraZeneca standard practices and protocol template.

Section # and name	Description of change	Brief rationale
Section 6.5.1	Renamed to Permitted Concomitant Treatments.	Alignment with AstraZeneca protocol template.
Section 6.5.1	Removed reference to use of antibiotics in ulcerative colitis.	Revised to align more accurately with standard of care.
Section 6.5.1	Revised to allow use of probiotics and antidiarrheals, even if not being taken at screening.	Probiotics and antidiarrheals are commonly used by IBD patients in their care. This patient-centric change will not impact the exploratory efficacy assessment in this study.
Section 6.5.1	Added details on which oral corticosteroids are allowed and changed topical (rectal) am nosalicylic acid or steroids to 5-aminosalicylates.	Revised for clarity and to benefit the investigator and site personnel and to align with other brazikumab protocols.
Section 6.5.1	Clarified that permitted concomitant medications from the lead-in study should be continued at stable doses with some exceptions, rather than stating they may be tapered and discontinued at investigator's discretion.	Revised as observational efficacy data only is to be collected and to allow the investigator to decide on tapering these medications for the patient's benefit.
Section 6.5.1	Removed instruction that participants taking oral 5-aminosalicylate treatments should be continued at stable doses.	Text no longer needed given revision of guidance for all permitted treatments.
Section 6.5.2	Revised CS taper instructions and added table for corticosteroid tapering guidelines.	Revised to align and conform steroid tapering during maintenance. Steroid tapering aligns broadly with clinical guidelines.
Section 6.5.2	Added guidance about returning to previous corticosteroid dose if clinically indicated and clarified that such a return would not constitute rescue treatment.	Revised for clarity and alignment with lead-in study.
Section 6.5.3	Added 5-aminosalicylates and oral steroid doses above Day 1 dose to the list of rescue treatments that do not require stopping study intervention.	Added to clarify that the new use of these treatments for UC is considered rescue treatment as this treatment was not previously included in this section.
Section 6.5.3	Added statement that rescue treatment constitutes treatment failure and that rescue treatment may suggest study discontinuation for lack of efficacy.	Alignment with AstraZeneca standard practices and protocol template.

Section # and name	Description of change	Brief rationale
Section 6.5.3 and Section 7.1	Removed requirement to discontinue study intervention for participants who do not achieve a clinical response by Week 24	Alignment with Study D5271C00001 and Study D5271C00002.
Section 6.5.4	Added fecal microbial transplantation to the list of prohibited interventions.	This treatment could affect PROs and other efficacy assessments.
Section 7	Statement on notifying sponsor of participant discontinuation revised.	Revised for clarity.
Section 7.1	Added reasons for study discontinuation, including certain surgeries, infections, and vaccinations.	Alignment with criteria in lead-in study.
Section 7.1	Added guidance on participants who may permanently discontinue study intervention.	Alignment with AstraZeneca standard practices.
Section 7.1	Clarified aspects of abnormal liver function required for discontinuation and removed requirement for consultation with sponsor.	Provided additional details on testing and identifying potential Hy's Law cases according to AstraZeneca standard procedures.
Section 7.1	Removed legacy subsection on temporary discontinuation.	Temporary discontinuation is no longer relevant.
Section 7.1	Added guidance around participants who discontinue study intervention and do not complete all follow-up visits.	Alignment with AstraZeneca standard practices and protocol template.
Section 7.1	Added language that permits telephone follow-up visits in the case of discontinuation of study intervention.	To give the participant options for follow-up and protect participant safety.
Section 7.1	Added text clarifying that patients who discontinue study intervention are not to remain in the study.	Patients in this open-label extension study will not be kept in the study after discontinuing study intervention.
Section 7.2	Revised language regarding participant withdrawal from the study.	To align with AstraZeneca template.
Section 7.2	Revised language on use of untested samples after discontinuation in regards to patient consent.	To clarify how patient requests about untested samples after discontinuation align with the original informed consent and local regulation.

Section # and name	Description of change	Brief rationale
Section 8	Added requirement that investigator maintain screening log.	Alignment with AstraZeneca standard practices and protocol template.
Section 8	Added information on data recording and blood volume collection.	Added to provide operational details and for participant safety.
Section 8.1.1	Removed statement that endoscopies beyond screening will not be performed.	With addition of the Week 52 endoscopy, this statement is no longer accurate.
Section 8.1.2	Added footnote from SoA about the use of paper diaries.	Revised for clarity.
Section 8.1.4	Revised text describing the PRO Evening Diary.	Revised for clarification.
Section 8.1.5	New sections added to describe PRO Site Visits.	Study design changes.
Section 8.1.6	Added colon mucosal biopsies at each endoscopy.	To highlight that biopsies will be used for biomarker analysis and molecular characterization of local inflammation.
Section 8.1	Added subsections 8.1.7 and 8.1.8 providing guidance on assessing changes over time in the Geboes Histological Index and the Robarts Histopathology Index.	Endoscopies added to Week 52 and the Early Termination Visit. Biopsies will be taken at the time of each endoscopy and subsequent histological analysis performed to enable determination of long-term mucosal healing.
Section 8.2.4	Table 10 (Protocol-required laboratory safety assessments) moved to this section from the appendix	Revised for clarity and ease of use.
Section 8.2.4	Table 10 - Other Tests section revised to align with SoA footnotes	Revised for accuracy.
Section 8.2.4	Revised Table 10 to include footnotes on collecting FSH from the SoA.	Revised for clarity.
Section 8.3 (including subsections)	Revised AE/SAE language and reorganized subsections.	To align with AstraZeneca template and SOPs and across brazikumab protocols.
Section 8.3	Added requirement that the Principal Investigator is responsible for ensuring staff are familiar with the content of this section.	Alignment with AstraZeneca standard practices and protocol template.
Section 8.3	Section 8.3.8 Medical Device Incidents (Including Malfunctions) removed.	References to some regulatory requirements surrounding devices removed as this is not a device study.

Section # and name	Description of change	Brief rationale
Section 8.3.1	Clarified that certain medical occurrences should be recorded in the Medical History section of the eCRF rather than the Adverse Events section.	Alignment with AstraZeneca standard practices and protocol template.
Section 8.3.2	Removed requirement to specifically require post-mortem findings upon autopsy and aligned text with template.	Alignment with AstraZeneca standard practices and protocol template.
Section 8.3.2	Aligned language with protocol template and clarified that SAEs with a suspected causal relationship to study intervention occurring after the end of study shall be reported to the sponsor.	Alignment with AstraZeneca standard practices and protocol template.
Section 8.3.2	Removed language about introducing bias into detection of adverse events.	Alignment with AstraZeneca standard practices and protocol template.
Section 8.3.2	Removed direction to extensively follow adverse events of special interest.	Alignment with AstraZeneca standard practices lead-in study procedures.
Section 8.3.2	Two new adverse event variables added: Maximum intensity and AE caused participant's withdrawal from study (yes or no).	Alignment with AstraZeneca standard practices and protocol template.
Section 8.3.4	New section Adverse Events Based on Signs and Symptoms added.	Provides additional instructions on AEs reported spontaneously by a participant or care provider.
Section 8.3.5	New section Adverse Events Based on Examinations and Tests added.	Provides additional information on how to report AEs resulting from mandated laboratory tests and vital signs.
Section 8.3.6	Shortened to brief description of Hy's Law cases with reference to details in Appendix E	AstraZeneca standard template text was added to align with AstraZeneca template and SOPs, including new information in the appendix. The new content is consistent with the prior text.
Appendix D2	Timeline for completing the eCRF for potential Hy's Law cases shortened from 7 calendar days to 3 calendar days.	Alignment with AZ standard practices and protocol template.
Section 8.4	Removed detailed guidance on actions to take in the event of an overdose.	Alignment with other studies in the brazikumab program.

Section # and name	Description of change	Brief rationale
Section 8.3.7	New section (Disease Progression) added and marked Not applicable.	Alignment with AstraZeneca template.
Section 8.3.8	New section Disease Under Study added; old Section 8.3.6 (Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events) removed.	Clarifies that, in some cases, symptoms that are unequivocally due to UC should not be reported as AEs; the previous Section 8.3.6 was a placeholder with a reference to the Appendices.
Section 8.3.9	Incorporates information on reporting SAEs from Appendix 3; adds instructions from AstraZeneca template on emailing CRF modules; identifies the IB as the reference document for expectedness.	Aligns protocol content with the AstraZeneca template and clarifies reporting of SAEs.
Section 8.3.10	Two new subsections added (Maternal Exposure and Paternal Exposure) and redundant legacy text removed.	Adds guidance from the AstraZeneca template on reporting pregnancies and fathering children or donating sperm during the study and aligned the lead-in study.
Section 8.3.11	Potential Hy's Law cases removed as an AESI and discussed separately in Section 8.3.6	Section 8.3.6 Hy's Law aligns with AZ Protocol Template. No need to duplicate as an AESI because it is not a specific risk for brazikumab.
Section 8.3.11	Revised the AESI Infusion Reactions to Infusion-Related Reaction and Injection-Site Reaction; reordered AESI subsections.	Replaced the lowest-level term with preferred terms for accuracy and to align with other brazikumab protocols.
Section 8.3.12	Revised to include reporting requirements for medication errors associated with AEs; moved definition of overdose into Section 8.4; removed definition of underdose; added reference to Appendix C, which contains expanded information on medication errors	Expanded guidance on reporting medication errors and further alignment with standard AstraZeneca standard procedures in the AstraZeneca template.
Section 8.4	Removed and Underdose from section title and removed definition of underdose.	Alignment with AstraZeneca protocol template and other brazikumab protocols.
Section 8.4	Removed definition of underdose.	Alignment with AstraZeneca protocol template.
Section 8.4	Changed definition of overdose to match current dose levels for Group A and Group B.	Harmonizing definitions of overdoses with new induction dose level and removal of CCI dose.

Section # and name	Description of change	Brief rationale
Section 8.4	Added timeframes for reporting overdoses; added designee as contact for reporting overdoses.	Alignment with AstraZeneca protocol template.
Section 8.5	Added new section (Human Biological Samples), incorporating previous sections 8.5 (Pharmacokinetics) and 8.6 (Pharmacodynamics), which are now 8.5.1 and 8.5.2, respectively.	Alignment with AstraZeneca protocol template.
Section 8.5	Added guidance on disposal or retention of PK and ADA samples.	Alignment with AstraZeneca protocol template.
Section 8.5.1	Clarified the conditions under which PK samples may be collected at additional timepoints.	Alignment with AstraZeneca protocol template.
Section 8.5.1	Clarified the conditions under which PK samples may be collected at additional timepoints.	Alignment with AstraZeneca protocol template.
Section 8.5	Added new Section 8.5.1.1 (Determination of Drug Concentration).	Alignment with AstraZeneca protocol template, providing further details on test sites conducting analyses and on the reporting of incurred sample reproducibility analysis.
Section 8.5.2	Renumbering of former Section 8.2.5 (Immunogenicity Assessments).	Alignment with AstraZeneca protocol template.
Section 8.5.2	Provided further details on test sites conducting analyses and characterization of ADA response.	Alignment with AstraZeneca protocol template and AstraZeneca standard practices.
Section 8.6	Replaced Section 8.8 (Biomarkers and Other Assessments) with new Section 8.6 (Human Biological Sample Biomarkers), providing information on additional biomarkers to be evaluated, the purpose in doing so, and future uses of such biomarker data.	Additional exploratory biomarkers will be assessed to enhance understanding of ulcerative colitis and to study the mechanism of action of brazikumab.
Section 8.6.1	Added descriptions of a new set of mandatory samples for biomarker analysis.	Additional exploratory biomarkers to will be assessed to enhance understanding of ulcerative colitis and to study the mechanism of action of brazikumab, including but not limited to identifying biomarkers that predict and change in response to reinduction as compared to induction as well as biological changes in patients that lose response to brazikumab.

Section # and name	Description of change	Brief rationale
Section 8.7	Previous Section 8.7 (Genetics) renamed to Optional Genomics Initiative Sample.	Alignment with AstraZeneca protocol template.
Section 9.2	Estimate of participants revised from 300 to 180	Updated based on updated forecasts of enrollment in the D5272C00001 lead-in study.
Section 9.2	Added definition of enrolled.	Alignment with AstraZeneca protocol template.
Section 9.4	Added details on the SAP and when it will be finalized.	Provides further guidance consistent with the AstraZeneca protocol template.
Section 9.4	Removed reference to use of vedolizumab in the lead-in study.	Align with design changes in the D5272C00001 lead-in study.
Section 9.4.1	Efficacy analysis changed to summary of mMS instead of pMS.	Updated to align with change in exploratory objective.
Section 9.4.3	Added new section Biomarker Analysis to specify where biomarker analyses may be presented.	Provide clarity on biomarker reporting.
Section 9.6	Added new section (Data Monitoring Committee) and marked not applicable.	Alignment with AstraZeneca protocol template.
Appendix A	Added info previously in Section 8.3.4 Regulatory Reporting Requirements for SAEs.	Placed AE reporting requirements together with other information on regulatory, ethical, and study oversight considerations.
Appendix B	Clarified information on tuberculosis testing.	Revised to provide updated wording consistent with AstraZeneca standard practices and to align with open-label extension study D5271C00002.
Appendix C	Updated table with sample corticosteroid tapering schedule.	Revised to include sample prednisone/budesonide MMX tapering regimens in Weeks 11 to 19, to align with in Table 7 in Section 6.5.2 and to match lead-in study D5272C00001.
Appendix D	Removed text describing Other Situations used to define serious adverse events.	Alignment with AstraZeneca protocol template.
Appendix D	Aligned legacy text with template text throughout, wherever content was essentially identical.	Alignment with AstraZeneca protocol template.
Appendix D	Replaced legacy section Assessment of Causality with protocol template section A Guide to Interpreting the Causality Question.	Alignment with AstraZeneca protocol template.

Section # and name	Description of change	Brief rationale
Appendix D	Added section on Medication Errors and clarified that accidental overdoses will be recorded as overdoses.	Alignment with AstraZeneca protocol template and standard practices.
Appendix E	Added new appendix (Handling of Human Biological Samples) that provides details on chain of custody, withdrawal of consent, and transporting human biological samples.	Provides information consistent with current AstraZeneca standard procedures and legal requirements.
Appendix F	Updated Appendix 9 with AstraZeneca template text.	Revised to provide updated wording consistent with AstraZeneca standard practices, as the content was otherwise similar.
Appendix F	Removed timeframe in which potential Hy's Law cases must be reported.	Hy's Law and potential Hy's Law cases are to be handled and reported as an AE or SAE, according to the outcome of the review and assessment and in line with standard safety reporting practices and AstraZeneca protocol template.
Appendix G	Added an appendix with sample PROs (evening diary, IBDQ, SF-36v2, sample EQ-5D-5L)	Added to clarify PRO assessments
Appendices	Reordered appendices.	To order the appendices according to the AstraZeneca template; additional appendices were added after the template-ordered appendices.
Appendices	Removed Appendix 5 – Standard Discontinuation Criteria.	Reduced redundancy with existing text in the main body of the protocol and/or new next provided by the AstraZeneca template.
Appendices	Removed Appendix 6 – Study Tabular Summary.	This legacy appendix provided information on posting to regulatory registries that is no longer needed/relevant.
Appendices	Removed Appendix 7 – Contraceptive Guidance and Collection of Pregnancy Information.	Reduced redundancy with existing text in the main body of the protocol and/or new next provided by the AstraZeneca template.
Appendices	Removed Appendix 8 – Medical Device Incidents.	Not relevant to current study, as the pre-filled syringe is a combination product rather than a device.
Appendices	Removed Appendix 11 – Study Schedule Supplement.	Reduced redundancy with existing text in the SoA.

Amendment 1 (August 2020)

Overall Rationale for the Amendment:

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	Sponsor name changed to AstraZeneca and study number changed to AstraZeneca study number.	The sponsor of the study is changing to AstraZeneca and an AstraZeneca study code will be used moving forward.
Throughout	Changed Medical Safety Physician to Study Physician.	This change is being made to align with AstraZeneca terminology.
Title Page	Sponsor Name and Legal Registered Address changed to AstraZeneca.	The sponsor name and address were changed to AstraZeneca AB.
Title Page	Allergan emergency Telephone number removed.	AstraZeneca contact information will be provided directly to investigators.
Title Page	Allergan SAE Reporting Fax Number/email removed.	AstraZeneca will provide safety reporting information directly to investigators.
Title Page	Sponsor signatory was removed.	The Allergan sponsor signatory was removed.
Section 6.4, Table 5, Study Interventions	Provider name changed from Allergan to AstraZeneca.	With the sponsor change, AstraZeneca will be providing study interventions.
Section 6.4.3, Medical Devices	Allergan was changed to AstraZeneca.	AstraZeneca will supply the test articles for the study.
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 8.3.9.1 Potential Hy's Law Cases	The Allergan-specific AE reporting information was removed.	AstraZeneca will provide safety reporting information directly to investigators.
Appendix C 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.
Appendix F: Actions Required in Cases of Increases in Liver Biochemistry and	The Allergan-specific AE reporting information was removed.	AstraZeneca will provide safety reporting information directly to investigators.

Section # and name	Description of change	Brief rationale
Evaluation of Hy's Law		

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