Clinical Study Protocol

Study Intervention	Brazikumab
Study Code	D5271C00002 (Legacy #3150-303-008)
Version	Amendment 4 v5.0
Date	04 April 2022

An Open-label, Long-term Extension Study of Brazikumab in Participants With Moderately to Severely Active Crohn's Disease (INTREPID OLE)

Sponsor Name:
AstraZeneca AB

Legal Registered Address:
151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s)
IND: 111,773
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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D5271C00002 (Legacy #3150-303-008)

Amendment Number: 4

Study Intervention: Brazikumab

Study Phase: 3

Short Title: Open-label Extension Study of Brazikumab in Crohn's Disease

Acronym: INTREPID OLE

Sponsor Study Physician/designee and Contact Information will be provided separately

PPD
PPD
Feinstein IBD Clinical Center
17 East 102nd St, 5th Floor
New York, NY 10029

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

AstraZeneca Protocol D5271C00002 (Legacy #3150-303-008)

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

Amendment 4 (04-April-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 primary endpoint to include physical exams.	Correction to ensure physical exam was included as an endpoint for the primary safety objective.
Section 1.1 Synopsis, Section 1.2 Schema, Section 4.1 Overall Design, Section 6 Study Intervention	Revised text to clarify that participants with suboptimal response at Week 52 of lead-in study will roll over to CCI CCI	Clarification to enable non-responders at Week 52 of the lead-in study to potentially benefit from re-induction with CCI regimen.
Section 1.1 Synopsis, Section 9.3 Populations for Analyses, Section 9.4.2 Efficacy	Changed name of ITT Population to FAS.	To be consistent with AZ procedures and protocols.
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, Section 5.2 Exclusion Criterion #7, #8, #16, Section 8.2.4 Clinical Safety Laboratory Assessments, Table 12	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, Table 2, Section 5.1 Inclusion Criterion #2, Section 8.2.4 Clinical Safety Laboratory Assessments, Table 12, Previous Appendix E 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	Updated physical exam description.	Revisions were made for clarity to distinguish general physical exams for safety from those for exploratory efficacy assessments.

Section # and name	Description of change	Brief rationale
Section 1.3 SoA Table 1, Table 2, Section 5.2 Exclusion Criterion #16g, Section 8.2.4 Clinical Safety Laboratory Assessments, Table 12	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	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, PAXgene RNA) from Week 0 to Screening. Samples will only be collected from participants if not collected at the lead-in study end-of-study visit.	Biomarker assessments from the last visit in the lead-in study will be used as baseline.
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 and Table 3	Removed exploratory efficacy assessments (CDAI and PROs) at Weeks 24 and 36 and indicated Week 12 only for participants who have CCI CCI .	Decreased exploratory assessments to reduce site and participant burden.
Section 1.3 SoA Table 1, Table 3, Section 8.1.2 Crohn's Disease Activity Index, Section 8.1.3 Patient-Reported Outcomes-Evening Diary	Clarified that PRO paper diary will be collected for 7 days before visit or prior to bowel prep if endoscopy is planned for the visit.	To provide clear guidance for PRO data collection for sites and maintain data 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 # and name	Description of change	Brief rationale
Section 1.3 SoA Table 1, Section 8 Study Assessments and Procedures	Added text to footnote 'b' to indicate that a repeat ileocolonoscopy is not required for participants that discontinued from the lead-in study between Weeks 12 to 16.	The Week 12 ileocolonoscopy 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 2	Added follow-up visit window.	Added flexibility to visit window for site and participant benefit.
Section 1.3 SoA Table 2	Removed duplicate FCP row.	Revisions were made for clarity.
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	Removed biomarker sampling (exploratory biomarkers, stool for lactoferrin and FCP, and PAXgene RNA) at follow-up visit 2.	Decreased exploratory assessments to reduce site and participant burden.
Section 1.3 SoA, Table 3	Indicated evening diary to be collected at ET.	Revisions were made to maintain data integrity by aligning ET PRO data collection at Week 52 visit.
Section 2.3 Benefit/Risk Assessment	The important potential risks of brazikumab were modified to incorporate the correct terminology of 'severe hypersensitivity'.	Corrections were made to align the potential risks with terminology used in the Brazikumab IB.
Section 3 Objectives and Endpoints, Table 4	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 3 Objectives and Endpoints, Table 4	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 # and name	Description of change	Brief rationale
Section 5.1 Inclusion Criterion #1b	Removed language regarding worsening of disease.	Removed for clarity as rescue criteria are clearly defined in the lead-in study CSP and include worsening of disease.
Section 6.1 Study Interventions Administered	Revised the language describing the IP.	Modified to clearly describe the IP formulation.
Section 6.1.2 Subcutaneous Administration, Figure 2, Section 6.2 Preparation/Handling/ Storage/Accountability	Additional injection sites 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 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 prefilled syringe in the inner carton during temperature equilibration.	Further investigation has determined that an equilibration time of at least 40 minutes at room temperature is required for CCI CCI
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	A sentence was added to explain that treatment assignment from the lead-in study not be unblinded, and this OLE study is not randomized.	Explanation that while this study is open-label, it is still critical that the lead-in study is not unblinded. Blinded endoscopy review will not be performed.
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 8.1.1.2 Biopsy	Revised the language to state that histological indices for biopsies will be detailed in a separate, exploratory analysis plan.	Correction made to describe the approach for histological analysis.
Section 8.1.2 Crohn's Disease Activity Index	Amended the rating and range of the total general well-being score.	Correction of error in previous protocol version.
Section 8.1.3 Patient-Reported Outcomes-Evening Diary	Urgency and blood in stool 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 # and name	Description of change	Brief rationale
Section 8.2.4 Clinical Safety Laboratory Assessments, Table 12	Removed coagulation group assessment from the hematology panel for the clinical laboratory assessments.	Coagulopathy is adequately assessed by the remaining Hy's Law kit.
Section 8.2.4 Clinical Safety Laboratory Assessments, Table 12	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 8.3.8 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 8.3.9.1 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 8.8 Medical Resource Utilization and Health Economics	Removed Medical Resource Utilization and Health Economics data from the assessments.	These parameters were included in error and are not to be collected in this study.
Section 9.3 Populations for Analyses	Added Screened Analysis Set.	To facilitate reporting of disposition.
Appendix F 1 and 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; FAS = Full Analysis Set; FCP = fecal calprotectin; HIV = human immunodeficiency virus; IB = Investigator's Brochure; IP = investigational product; ITT = intent-to-treat; CCI OLE = open-label extension; PD = pharmacodynamic(s); 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.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-label, Long-term Extension Study of Brazikumab in Participants with Moderately to Severely Active Crohn's Disease (INTREPID OLE)

Short Title: Open-label Extension Study of Brazikumab in Crohn's Disease

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 CD in Study D5271C00001 (Legacy #3150-301-008).

The purpose of Study D5271C00002 (Legacy #3150-303-008) is to collect long-term safety data from participants in Study D5271C00001 (Legacy #3150-301-008) who receive open-label brazikumab in Study D5271C00002 (Legacy #3150-303-008).

Objectives and Endpoints

The objectives and endpoints are presented below:

Objectives	Endpoints
Primary	
• To assess the safety of long-term treatment with brazikumab in CD participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from Study D5271C00001 (Legacy #3150-301-008) at or after Week 12 due to lack of efficacy.	• AEs • Clinical laboratory values • Vital signs • Physical exams • ECGs

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

Overall Design

This is a global, multicenter, open-label extension study of brazikumab limited to participants previously enrolled in Study D5271C00001 (Legacy #3150-301-008) (hereinafter referred to as the *lead-in study*). Participants in the lead-in study are eligible to enroll in Study D5271C00002 (Legacy #3150-303-008) 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 judgement of the investigator, would disqualify them from participating. Participants will be eligible for inclusion into this study if they have completed the lead-in study, or have completed 12 weeks

of treatment, but were subsequently discontinued due to lack of efficacy. Eligible participants do not need to complete the 18-week safety follow-up period of the lead-in study, if they roll-over into this study after they complete the Week 52 visit of the lead-in study.

Disclosure Statement:

This is a parallel group treatment study with 2 arms that is open-label.

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 and choose to participate in this study. No separate sample size calculation was performed. Up to a maximum of 240 participants may enter this study, based on the expected number of participants in the lead-in study.

Intervention Groups and Duration:

The 240 mg SC dose of brazikumab will be administered every 4 weeks to all who completed requirements through Week 52 and met CDAI response (CDAI score of < 150 points or CDAI reduction from Baseline of ≥ 100 points) without ongoing rescue treatment at Week 52 in the lead-in study. Participants who met criteria for early termination due to lack of efficacy (rescue treatment criteria) or who did not meet CDAI response at Week 52 in the lead-in study are considered inadequate/non responders, and will receive CCI dosing with CCI CCI followed by maintenance dosing of brazikumab CCI .

There will be an 18-week post-last dose safety follow-up period during which there will be no intervention administered for participants in the safety follow-up.

Study Duration:

The study will consist of a 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:

Not applicable.

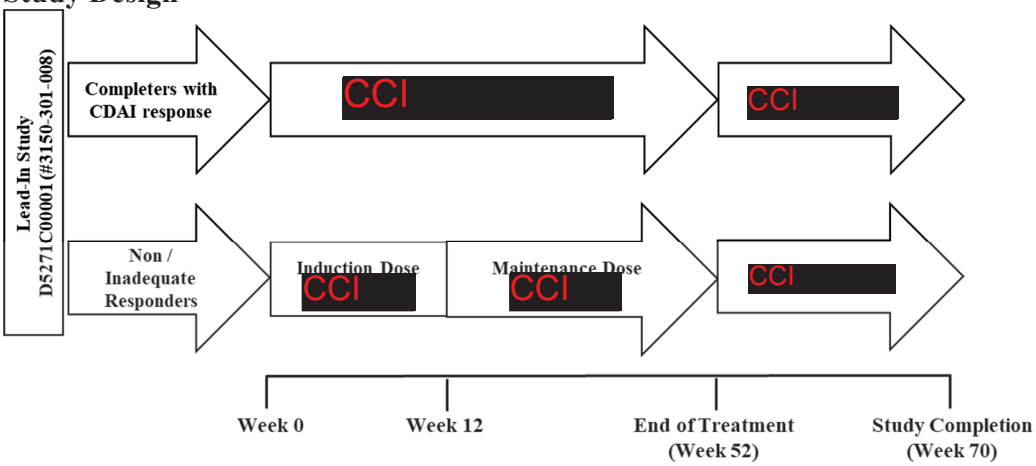
Statistical Methods

All safety and efficacy analyses for this study will be summarized descriptively by the visit and the treatment sequences and overall, unless stated otherwise. For participants who were previously enrolled in the lead-in study, the baseline from the lead-in study will be used for the analyses. 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.

The FAS population will comprise all participants who are assigned to an CCI brazikumab study intervention in the study. The Safety Population will comprise all participants who receive CCI administration of study intervention in this extension study. The efficacy analyses will be based on the FAS population using the observed-cases approach. The safety analysis will be performed using the Safety Population and will include AEs, clinical laboratory parameters, vital signs, and ECG parameters.

1.2 Schema

Figure 1 Study Design



The safety follow-up periods are based on the last investigational dose at Week 52 (Visit 14). Participants discontinued at any time during the study will be required to proceed to the untreated safety follow-up period.
CDAI = Crohn's Disease Activity Index; CCI

1.3 Schedule of Activities

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

Table 1 Schedule of Activities

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

Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UNS[a]**	**Notes**	**Details in CSP Section or Appendix**
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Study day[d]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**			
Visit window (days)			± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7			
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.5
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2.2
Safety assessments																		
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.3
Physical exam	X	X			X			X			X				X	X	Including abdominal exam, EIM assessment for CDAI score, fistula exam (as applicable) at W0, W12[e], W52	8.2.1
12-lead ECG	X														X	X		8.2.3
Assessment of injection-site reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.3.10.1

Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UNS[a]**	**Notes**	**Details in CSP Section or Appendix**
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Study day[d]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**			
Visit window (days)			± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7			
Laboratory assessments																		
Serum chemistry, hematology, and CRP	X				X			X			X				X	X		8.2.4
Stool for fecal calprotectin, fecal lactoferrin, and exploratory biomarkers	X				X[e]										X	X	All stool tests should be collected prior to start of bowel prep for visits where ileo-colonoscopy is needed	8.6
Urinalysis	X														X	X		8.2.4
Urine pregnancy test performed locally (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		5

Visit number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	UNS[a]	Notes	Details in CSP Section or Appendix
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Study day[d]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**			
Visit window (days)			± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7			
Biomarkers sampling																		
Predose PK blood sample		X			X[e]			X							X		Note the exact time and date for sampling	8.5.1
Serum for ADA (pre-dose)		X						X							X			6.1
Blood for exploratory biomarkers	X				X[e]										X			8.6.1
PAXgene RNA	X				X										X		Do not collect if whole blood transfusion within 120 days	8.6.1

Visit number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	UNS[a]	Notes	Details in CSP Section or Appendix
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Study day[d]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**			
Visit window (days)			± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7			
Efficacy assessments																		
Ileo-colonoscopy including terminal ileum and colon mucosal biopsies	X														X	X	Daily PRO data collected 7 days prior to bowel prep will be used to calculate CDAI	8.1.1.1
SES-CD assessment	X														X	X	SES-CD will be assessed by a central reader	8.1.1.1
CDAI		X			X[e]										X	X	Week 0 CDAI to be calculated using the screening hematocrit	8.1.2

Visit number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	UNS[a]	Notes	Details in CSP Section or Appendix
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Study day[d]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**			
Visit window (days)			± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7			
Provide PRO paper diary	X			X[e]										X		X	Provide the paper diary to the participant and instruct them to collect the data 1 week prior to the next visit or 1 week prior to bowel prep if endoscopy is planned for that visit; W0 paper diary to be provided at the last visit in lead-in Study D5271C00001 (Legacy #3150-301-008)	

Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**UNS[a]**	**Notes**	**Details in CSP Section or Appendix**
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Study day[d]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**			
Visit window (days)			± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7			
PRO assessments (paper)		X			X[e]										X	X	Evening diary will be collected every evening for 1 week prior to the indicated scheduled visits or 1 week prior to bowel prep if endoscopy is planned for that visit	Table 3 and 8.1.3
Site visit PROs		X			X[e]										X	X	Will be completed at site visit	

Visit number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	UNS[a]	Notes	Details in CSP Section or Appendix
Visit name	**Scr[b]**	**W0[c]**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**			
Study day[d]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**			
Visit window (days)			± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7			
Study intervention administration	CCI																First dose should be administered no earlier than 14 days and no later than 56 days from last dose in Study D5271C00001 (Legacy #3150-301-008)	4.1 and 6

[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 D5271C00001 (Legacy #3150-301-008) 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 ileocolonoscopy and CDAI. A repeat ileocolonoscopy is not required for participants who discontinue from the lead-in study after Week 12 and prior to Week 16.

[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 D5271C00001 (Legacy #3150-301-008).

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

[e] Collect Week 12 samples and data from participants who have CCI only.

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

ADA = anti-drug antibody; AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; CSP = clinical study protocol; ECG = electrocardiogram; EIM = extraintestinal manifestation; ICF = informed consent form; CCI IWRS = interactive web-response system; PK = pharmacokinetic; PRO = patient-reported outcome; RNA = ribonucleic acid; SAE = serious adverse event; CCI Scr = screening; SES-CD = Simple Endoscopic Score for Crohn's Disease; UNS = unscheduled visit; W = week; WOCBP = women of childbearing potential.

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

Study period	**Open-label**	**18-week follow-up[a]**	
Visit name	**Early Termination Visit**	**Follow-up 1 (Week 60)**	**Follow-up 2 (Week 70)**
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)**
AE/SAE assessment	X	X	X
Concomitant medications	X	X	X
Physical examination, vital signs, and weight[b]	X	X	X
ECG	X		
Serum chemistry, hematology, CRP, and urinalysis	X	X	X
Urine pregnancy test	X	X	X
PK blood sample	X	X	X
Serum brazikumab, ADA immunogenicity	X	X	X
Blood for exploratory biomarker analysis	X		
PAXgene RNA	X		
Stool for calprotectin, lactoferrin, and exploratory biomarkers	X		
Ileocolonoscopy including terminal ileum and colon mucosal biopsies	X		
SES-CD assessment	X		
CDAI and PROs	X		
Assessment of injection-site reactions	X		

[a] Study intervention will not be administered during the 18-week safety follow-up period.
[b] Including abdominal exam, EIM assessments for CDAI score, fistula exam (as applicable) to be performed only at ET.

ADA = anti-drug antibody; AE = adverse event; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; ECG = electrocardiogram; EIM = extraintestinal manifestation; ET = Early Termination Visit; PK = pharmacokinetic; PRO = patient-reported outcome; RNA = ribonucleic acid; SAE = serious adverse event; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Table 3 Schedule of Activities – PRO Assessments

PRO assessment	Frequency of administration	Notes
Evening Diary[a] (CDAI, PRO items, 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 or bowel prep if endoscopy is planned for the visit. The night before the site visit or bowel prep 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 participants who have CCI

CDAI = Crohn's Disease Activity Index; ET = Early Termination Visit; EQ-5D-5L = European Quality of Life-5 Dimensions; IBDQ = Inflammatory Bowel Disease Questionnaire; CCI NRS = Numerical Rating Scale; PRO = patient-reported outcome; SF-36v2 = 36-item Health Survey Version 2.

2 INTRODUCTION

This study is an open-label continued access study for participants with CD who have been enrolled in Study D5271C00001 (Legacy #3150-301-008). The nature of CD and the rationale for studying brazikumab in this disorder has been discussed previously in the protocol for Study D5271C00001 (Legacy #3150-301-008) and in the current Brazikumab IB (Brazikumab/MEDI2070).

Crohn's disease is a chronic transmural inflammatory disease that most commonly affects the distal ileum and colon and may occur in any part of the gastrointestinal tract (Crohn's and Colitis Foundation of America, Burger et al, 2011, Rutgeerts et al, 2003). Patients with CD have uncontrolled inflammation that causes direct damage to the intestinal mucosa. This inflammation is believed to result either from persistence of inflammatory stimulus, due to impaired gut barrier function, or from a dysregulated inflammatory response. Crohn's disease occurs most commonly between 15 to 30 and 60 to 80 years of age; although, persons of any age may be affected. Commonly used medical therapies include aminosalicylates (eg, sulfasalazine and mesalamine), systemic CS, immunosuppressive agents (eg, azathioprine and methotrexate), antibacterial agents, and biologic agents (eg, adalimumab [Humira®, Abbvie, Inc, North Chicago, IL], infliximab [Remicade®, Janssen Biotech, Inc, USA], certolizumab [Cimzia®, UCB, Inc, Smyrna, GA], vedolizumab [Entyvio®, Takeda Pharmaceuticals America Inc, Deerfield, IL], and natalizumab [Tysabri®, Biogen Idec Inc, Cambridge, MA]). Despite treatment with these agents, the residual morbidity, and the complications of CD (eg, intestinal obstruction and/or perforation, fistula formation, malnutrition) represent a burden of disease sufficient to warrant new therapies.

Brazikumab is a human immunoglobulin that selectively binds to human IL-23 with high affinity and prevents IL-23 from interacting with the IL-23 receptor. The roles of IL-23 are believed to be important for the recruitment and activation of a range of inflammatory cells involved in IBD (CD and UC). In preclinical models and studies in participants, anti-IL-12/23p40 antibodies (eg, ustekinumab and briakinumab) have been shown to induce clinical responses in a variety of inflammatory diseases. Phase 2 data in participants with CD have demonstrated clinical efficacy of brazikumab comparable with that of antibodies targeting IL-12/23, 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 clinical symptoms associated with CD; specifically, targeting IL-23 by brazikumab may offer a better benefit-risk profile compared with the IL-12/23 antibodies.

Targeting CD with brazikumab is supported by robust genetic and nonclinical data and by the demonstrated clinical efficacy of anti-IL-12/23p40 antibodies (ustekinumab and briakinumab) and anti-IL-23p19 antibodies in CD (Mannon et al, 2004, Sandborn et al, 2012, Feagan et al,

2016, Feagan et al, 2017) and UC (Sandborn et al, 2020). Mice deficient in IL-23p19 are protected against experimental colitis, while mice deficient in IL 12p35 are not (Hue et al, 2006, Yen et al, 2006). Preclinical studies in several different animal models of IBD have demonstrated strong efficacy with IL-23-specific antagonism (Kullberg et al, 2006, Uhlig et al, 2006, Ahern et al, 2008, IB Section 4.1).

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 CD in Study D5271C00001 (Legacy #3150-301-008).

The purpose of Study D5271C00002 (Legacy #3150-303-008) is to permit participants in D5271C00001 (Legacy #3150-301-008) to receive open-label brazikumab in Study D5271C00002 (Legacy #3150-303-008). This will permit long-term observation of safety in these participants and further characterize the efficacy of brazikumab. There are no formal hypotheses to be tested. Safety 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 IFNγ, and down regulation of IL-10 (Bettelli et al, 2007).

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

In the clinic, anti-IL-12/23p40 antibodies (eg, ustekinumab and briakinumab) and anti-IL-23p19 antibodies have been shown to induce clinical responses in CD (Sandborn et al, 2012, Mannon et al, 2004, Feagan et al, 2017), UC (Sandborn et al, 2020), and psoriasis

(Phase 2 and Phase 3 studies; Gordon et al, 2012, Kimball et al, 2012, Langley et al, 2012, Gottlieb et al, 2011, Reich et al, 2011, Strober et al, 2011, Leonardi et al, 2008, Papp et al, 2008). Phase 1 and Phase 2 clinical studies with anti-IL-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 Brazikumab IB (Brazikumab/MEDI2070) for details.

Brazikumab is a human, Chinese hamster ovary cell-derived, IgG2 monoclonal antibody 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 single 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 300 mg/kg 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 at 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 300 mg/kg developed binding ADAs in the recovery period. No NABs were detected in animals that tested positive for binding ADAs, and binding ADAs did not decrease brazikumab exposure. The no observed adverse effect level following CCI brazikumab was CCI the maximum dose tested, corresponding to a C_{max} of CCI and an AUC of CCI

Four clinical studies with brazikumab have been completed: Phase 1a Study 20080767, Phase 1b Study 20090519, Phase 2a Study D5170C00001, and Phase 1 Study 3150-101-008.

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

brazikumab, also showed evidence of clinical efficacy as demonstrated by improvements in the Psoriasis Area Severity Index score.

The Phase 1b Study, Study 20090519, was a randomized, double-blind, placebo-controlled, ascending multiple-dose study to evaluate safety, tolerability, PK, and pharmacodynamic of brazikumab in healthy participants (Part A) and these same parameters, plus efficacy, in participants with mild to severe CD (Part B). A total of 40 participants were randomized and received at least one dose of study intervention (brazikumab or placebo) in Part A and an additional 8 participants with CD were randomized into Part B of the study and received study intervention (brazikumab or placebo). No TESAEs or deaths were reported, and no participants withdrew from the study because of a TEAE.

Study D5170C00001 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 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 every 4 weeks; 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 1 CCI brazikumab in the open-label period; 93 participants (89.4%) completed their Week 24 Visit; and 57 participants (54.8%) completed the 100-week open-label period.

The primary efficacy endpoint of Study D5170C00001, CDAI response at Week 8 (defined by either a CDAI score of < 150 or a reduction from baseline of at least 100 points) was met. The proportion of participants that achieved a CDAI response at Week 8 was statistically significantly higher in the brazikumab group than in the placebo group (49.2% 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.

Post hoc analysis of Study D5170C00001 revealed a statistically significant treatment by-baseline interaction (p = 0.04) for the IL-22 serum interaction term in the logistic regression

model used in the analysis of clinical response at Week 8, which suggested that the treatment effect at Week 8 differed by-baseline IL-22 serum concentration (Sands et al, 2017). In addition, it was observed that the group of participants receiving brazikumab had a substantial reduction in IL-22 serum concentration (81% reduction at Week 8 compared with baseline), in contrast to the slight increase observed for the group of participants receiving placebo (6% increase, data on file). The median IL-22 serum concentration at baseline for the entire study population was CCI In the analyses of CDAI clinical response and CDAI remission stratified by the median baseline IL-22 serum concentration for the population (ie, <15.6 pg/mL and ≥ 15.6 pg/mL), it was observed that among participants with baseline IL-22 serum concentrations of ≥ 15.6 pg/mL, the brazikumab-treated participants had an increased likelihood of clinical response and clinical remission at Week 8. In the subgroup of participants meeting this threshold, the placebo-adjusted CDAI clinical response rate was 41.6% (p = 0.0009 for brazikumab versus placebo) and the placebo-adjusted CDAI clinical remission rate was 29.2% (p = 0.0116 for brazikumab versus placebo). In contrast, among participants with baseline IL-22 serum concentrations of < 15.6 pg/mL, brazikumab-treated participants had CDAI clinical response and remission rates similar to participants receiving placebo; the placebo-adjusted rates were 3.0 and -3.9, respectively (p = 0.8026 and p = 0.6681, respectively), for brazikumab compared with placebo.

The safety data from Study D5170C00001 for CCI and CCI CCI showed an acceptable safety profile that is consistent with previous studies and supports clinical development. AEs reported in this study were generally mild or moderate in intensity. There were no deaths reported.

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

In Study D5271C00001 (Legacy #3150-301-008), the brazikumab and brazikumab placebo CCI will be administered in a CCI

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. Presently available treatments for IBD act to reduce inflammation by different actions including inhibition of cyclooxygenase and prostaglandin production and inflammatory cytokines (eg, aminosalicylates, steroids), immunomodulatory effects, inhibition α4β7 integrin (eg, vedolizumab), or blockade of TNFα (eg, infliximab). There are limited options for patients who fail biological treatment with the aforementioned therapies and continue to have evidence of active IBD. Brazikumab is being developed to meet this unmet need.

Interleukin-23 blockade represents a novel mechanism to inhibit the inflammation and clinical symptoms associated with autoimmune diseases such as CD, UC, and psoriasis. Therapeutic agents have previously targeted the IL-12/23p40 subunit, including the monoclonal antibodies ustekinumab and briakinumab. Because the IL-12/23p40 subunit is common to IL-12 and IL-23, these agents inhibit the actions of both cytokines. In contrast, brazikumab is a monoclonal antibody that specifically targets the IL-23p19 subunit preventing IL-23 from interacting with the IL-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 have failed or are intolerant to anti-TNFα therapy) the primary endpoint of the study, CDAI response at Week 8 (defined by either a CDAI score of < 150 or a CDAI score reduction from baseline of at least 100 points), was met. In the modified intent-to-treat Population, the proportion of participants that achieved a CDAI response at Week 8 was statistically significantly higher in the brazikumab group than in the placebo group. Brazikumab, at doses of CCI 4 weeks apart or CCI was well tolerated and showed an acceptable short- and long-term safety profile. During the entire study period, 21/111 (18.9%) of participants experienced a Grade 3 TEAE and there were no Grade 4 (life-threatening) or Grade 5 (fatal) TEAEs. Crohn's disease was the most frequently reported SAE. No malignancies were reported and no MACE occurred. Clinically significant infections were mostly urinary tract infection, vulvovaginal mycotic infection, sinusitis, bronchitis, and upper respiratory tract infection. No clinically significant trends were observed in the clinical laboratory evaluations, vital sign measurements, ECGs, or physical findings.

The safety profile of brazikumab, as determined at this stage of clinical development does not include any important identified risks. 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
- Infusion-related reactions and injection-site reactions
- Severe hypersensitivity (including anaphylaxis)
- 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.

2.3.1 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with brazikumab are justified by the anticipated benefits that may be afforded to participants with CD.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints of the study are shown in Table 4.

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety of long-term treatment with brazikumab in participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from the study at or after Week 12 due to lack of efficacy.	• AEs • Clinical laboratory values • Vital signs • Physical exams • ECGs
Exploratory	
• To assess efficacy of long-term treatment with brazikumab in participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from the study at or after Week 12 due to lack of efficacy.	• SES-CD • CDAI • 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 participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from the study at or after Week 12 due to lack of efficacy, 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; CDAI = Crohn's Disease Activity Index; ECG = electrocardiogram; PK = pharmacokinetic(s); PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease.

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 D5271C00001 (Legacy #3150-301-008) (hereinafter referred to as the "lead-in study"). Participants in the lead-in study are eligible to enroll in Study D5271C00002 (Legacy #3150-303-008) 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. Participants will be eligible for inclusion into this study if they have completed the lead-in study, or have completed 12 weeks of treatment in the lead-in study, but were subsequently discontinued due to lack of efficacy. 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 Week 52 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 endoscopic and clinical remission to no response or worsening of their signs and symptoms of CD. Participants who roll over to this open-label extension study (Study D5271C00002 [Legacy #3150-303-008]) within 28 days of completing their final visit (Week 52 or Early Termination Visit) assessments in the lead-in study may use the assessments from the final visit of the lead-in study as screening assessments for this study.

A study schematic is presented in Section 1.2.

Intervention and Study Duration

Intervention:

CCI of brazikumab will be administered every 4 weeks to all who completed requirements through Week 52 and met CDAI response without ongoing rescue treatment at Week 52 in the lead-in study. Participants who met criteria for early termination due to lack of efficacy (rescue treatment criteria) or who did not meet CDAI response at Week 52 in the lead-in study are considered inadequate/non-responders, and will receive CCI dosing with CCI of brazikumab at Week 0, Week 4, and Week 8 followed by maintenance dosing of brazikumab CCI

There will be an 18-week post-last dose safety follow-up period during which there will be no intervention administered for participants in 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 at the participant's next contact with the study site).
- 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 or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home IP 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.

4.2 Scientific Rationale for Study Design

The sponsor proposes to conduct an open-label study to obtain safety and efficacy experience

with long-term administration of brazikumab and to provide an opportunity, for participants who agree, to continue treatment with brazikumab for up to 1 year (52 weeks).

4.3 Justification for Dose

The no adverse effect level of CCI for brazikumab was established in cynomolgus monkeys in 3 studies in which brazikumab was CCI CCI 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 of CCI brazikumab in a CCI has been 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. This CCI CCI brazikumab represents approximately comparable brazikumab exposure ($AUC_{0\text{-}28}$ days) to a third CCI dose administered by CCI The administered CCI CCI 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, CCI brazikumab infused over a CCI and CCI period was well tolerated. The CCI brazikumab study interventions in this study will be administered in a CCI

Table 5 presents the margins of exposure calculated for the doses proposed in this study, based on C_{max} and AUC 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

CCI

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; CCI

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 participated in Study D5271C00001 (Legacy #3150-301-008). The inclusion and exclusion criteria are meant to create a population of participants that is well characterized as having CD with symptoms that require 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

1 Male or female participants with successful completion or early termination due to lack of efficacy from Study D5271C00001 (Legacy #3150-301-008).

Meets 1 of the following criteria for successful completion or early termination due to lack of efficacy from Study D5271C00001 (Legacy #3150-301-008):

(a) A participant is considered to have completed the D5271C00001 (Legacy #3150-301-008) study if they have received scheduled study interventions, completed scheduled visits, and completed Week 52 assessments.

(b) A participant in Study D5271C00001 (Legacy #3150-301-008) who discontinued from the study due to lack of efficacy after a minimum of 12 weeks of double-blind treatment and met criteria for the use of rescue treatment (Table 6) in the lead-in protocol.

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

Table 6 Rescue Criteria from Study D5271C00001 (Legacy #3150-301-008)

Week of Assessment	Criteria for use of rescue treatment
Week 12-16	• No improvement in CDAI by at least 70 points from Baseline CDAI for 2 consecutive visits starting at Week 12 AND • No improvement in the SES-CD score by at least 1 point from Baseline relative to Week 12 endoscopy
After Week 16 (disease worsening after induction)	• CDAI has increased by at least 70 points from Week 12 CDAI for 2 consecutive visits AND • No improvement in the SES-CD score by at least 25% from Baseline Note: Must obtain 2 CDAI scores prior to proceeding with endoscopy after Week 16

CDAI = Crohn's Disease Activity Index; SES-CD = Simple Endoscopic Score for Crohn's Disease.

2 Criterion deleted as part of Amendment 4.

3 Each participant must have had the ileocolonoscopic procedure at the final visit (Week 52, Week 12, or early termination after Week 12 [endoscopy used for assessment of rescue criteria may be utilized for Early Termination Visit]) of the lead-in Study D5271C00001 (Legacy #3150-301-008).

Reproduction

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

4 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 least18 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

5 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.

6 Nonsterilized males who are sexually active with a female partner of childbearing potential should use condoms during treatment and until the end of relevant systemic exposure in the male participant, plus a further 18 weeks. For a female partner of childbearing potential, contraception recommendations should also be considered (as described in Inclusion Criterion 4).

Informed Consent

7 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

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

9 Legally authorized representative consent has been obtained (if applicable).

10 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 [European Union sites]).

Other

11 Demonstration of adequate compliance with the study procedures in Study D5271C00001 (Legacy #3150 301-008) in the opinion of the investigator and/or sponsor.

12 Willingness and ability to attend all study visits, comply with the study procedures, read and write in order to complete questionnaires, and be able to complete the study.

5.2 Exclusion Criteria

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

Medical Conditions

1 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 8.3). Any unresolved AE related to an infection will require further discussion with the Study Physician/designee prior to enrollment.

2 Current diagnosis of ischemic colitis, colonic mucosal dysplasia, or primary sclerosing cholangitis. Bile acid malabsorption and other conditions that may potentially confound assessments must be treated prior to baseline (Week 0).

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

4 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, ECG (including QTc prolongation), or clinically significant renal, hepatic, cardiopulmonary disease, or any demyelinating condition.

5 History of cancer with the following exceptions:

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

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

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

6 Participant meets criteria for discontinuation of study intervention during prior lead-in study (excluding lack of efficacy).

7 Criterion deleted as part of Amendment 4.

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

9 Prolonged QTcF interval (QTc >450 msec or QTC >480 for participants with bundle branch block; determined by 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.

10 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 MDRD equation, as applicable, by the central laboratory at screening are excluded.

Prior/Concomitant Therapy

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

12 Participant received a Bacille Calmette-Guérin vaccination within 12 months of Week 0 (Visit 1) or any other live vaccine < 4 weeks prior to Week 0 (Visit 1) or is planning to receive any such vaccine over the course of the study.

13 Participant received a prohibited medication during participation in the lead-in study or during screening for this study (see Section 6.5.4).

Prior/Concurrent Clinical Study Experience

14 Participant is planning to receive an investigational drug (other than study intervention) or investigational device at any time during Study D5271C00002 (Legacy #3150-303-008) with the exception of "registry" or "cohort" trials, which may include periodic biological sampling and/or participant questionnaires but in which no other unlicensed IP is administered.

15 Participants with a known hypersensitivity to brazikumab or any of the excipients of the product.

Diagnostic Assessments

16 Abnormal laboratory results at screening (screening window may be extended to obtain screening test results after discussion with the Study Physician/designee):

(a) Liver tests: either AST, ALT, or ALP > 2.0 × ULN or TBL > 1.5 × ULN (except for subjects with Gilbert Syndrome, pathological evidence of conjugated [direct] hyperbilirubinemia per investigator and/or sponsor discretion is exclusionary)

(b) Neutrophil count < $1 \times 10^3/\mu L$ (or < $1.0 \times 10^9/L$)

(c) Hemoglobin < 8 g/dL

(d) Platelet count < $100 \times 10^3/\mu L$ (or < $100 \times 10^9/L$)

(e) Criterion deleted as part of Amendment 4.

(f) Criterion deleted as part of Amendment 4.

(g) Criterion deleted as part of Amendment 4.

(h) Participant has any other abnormal laboratory results at screening, which, in the opinion of the investigator, will prevent the participant from completing the study or will interfere with the interpretation of the study results.

Other Exclusions

17 Females who are pregnant, nursing, or planning a pregnancy during the study OR females who are of childbearing potential and do not agree to use a highly effective method of contraception consistently and correctly

18 Participant is directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, study coordinator, other study staff member, or employee of AstraZeneca, 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.

19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

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

21 Previous participation 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 4, 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 Due to the influence of such lifestyle factors on the severity of CD symptoms, participants should keep their habits broadly constant throughout the study. Use of nicotine replacement therapy should be recorded as concomitant medication.

2 Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted during study intervention administration CCI

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

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but subsequently do not receive open-label study intervention. Participants entering from the lead-in study who are defined as screen failures and discontinued under this protocol must participate in the 18-week safety follow-up period for the lead-in study.

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 indicating screen failure as reason for ending the study, demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened, except for participants who are awaiting resolution of an AE or those who cannot reach the site due to the COVID-19 pandemic (see Appendix G) who may be rescreened once.

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 once every 4 weeks to all participants enrolled. Administration is to be CCI CCI dosing and CCI

IV Induction Dosing

Intravenous induction dosing CCI brazikumab at CCI will be administered to participants who met criteria for early termination due to lack of efficacy (rescue treatment criteria) or who did not meet CDAI response at Week 52 in Study D5271C00001 and therefore, considered inadequate/non-responders.

Maintenance Dosing

Participants who completed requirements through Week 52 and met CDAI response without ongoing rescue treatment at Week 52 of the lead-in study will receive CCI CCI

6.1 Study Interventions Administered

Participants will receive all study intervention administrations at the investigational site. Table 7 presents details regarding study interventions and administration.

Table 7 Study Interventions

Study intervention name	**Brazikumab** CCI	**Brazikumab** CCI
Dosage form	CCI	
Route of administration		
Dose (mg)		
Dosing instructions		
Packaging and labeling	CCI Each CCI will be labeled as required per country requirement.	CCI . Each CCI will be labeled as required per country requirement.
Provider	AstraZeneca	AstraZeneca

[a] For CCI, contents of CCI will be added to an CCI bag of CCI to a CCI of CCI then administered by CCI CCI CCI

Brazikumab for CCI

Brazikumab for CCI administration will be supplied as a CCI CCI brazikumab, CCI CCI The CCI volume is CCI

Brazikumab for CCI is a sterile, CCI

Brazikumab for CCI

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

Brazikumab for CCI is a sterile, CCI

All Formulations

CCI

6.1.1 CCI

If criteria for induction dosing are met, participants will receive brazikumab CCI CCI An experienced and qualified staff member will place the CCI The total volume administered will be recorded in the eCRF.

Vital signs (BP, temperature, pulse rate, and respiration rate) will be obtained before CCI intervention administration at all treatment visits. In addition, participants will be monitored for changes in vital signs and/or new symptoms approximately every 15 minutes during CCI administration, immediately after completion of infusion, CCI 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, CCI CCI for the CCI The CCI CCI the discretion of the investigator.

Infusion-related reactions have been reported with the administration of CCI CCI. 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 8.3.7).

6.1.2 CCI Administration

Brazikumab will be administered to all participants by CCI at the visits specified in Table 1 (Section 1.3). Each CCI dose will be administered by an experienced and qualified staff member. Each CCI will be no more than CCI in volume CCI Each open-label brazikumab intervention will be administered via CCI CCI Injections will be over CCI for all CCI and at a distance of CCI.

It is advised that the site of study intervention injection be rotated such that the participant receives study intervention at a different anatomical site at each treatment visit. CCI CCI (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. CCI the reason for this must be documented in the source.

CCI CCI

CCI

Vital signs (BP, temperature, pulse rate, and respiration rate) will be obtained before and immediately after 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 Visits 1 and 2, 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 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.

6.1.3 Study Intervention Administration Rescheduling

Every effort should be taken to keep study intervention administration within the scheduled window. If a participant presents with a condition that contraindicates dosing, IP will be withheld and administered as soon as possible after the contraindicating condition resolves.

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

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

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

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

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

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

If a participant misses more than 1 dose of study intervention during the treatment period, it is

recommended that a conversation between the investigator and Sponsor Study Physician/designee takes place to review the participant's adherence to treatment and decide on the participant's further disposition.

6.1.4 Study Supplies

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

1 Brazikumab CCI for CCI of deliverable volume at a concentration of CCI brazikumab.
2 Brazikumab CCI for CCI consisting of CCI of deliverable volume at a concentration of CCI brazikumab.

Additional instructions for brazikumab use are provided in the Pharmacy Manual. All defects in study intervention (including malfunction, use error, and inadequate labeling) shall be reported by the investigator as described in the Pharmacy Manual.

6.2 Preparation/Handling/Storage/Accountability

1 Brazikumab must be CCI and CCI Brazikumab must be CCI CCI . The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention.
3 All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4 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).
5 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 accounted for by the site. Where local destruction is not possible, then return to supplying depot can be arranged.

Brazikumab Preparation for CCI

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

administered [redacted]

[redacted] will be administered [redacted]

Brazikumab [redacted]

Brazikumab infusions are to be administered through an [redacted] set with a [redacted] filter; acceptable configurations include [redacted]

The brazikumab [redacted] however, if there are interruptions, the total allowed time must [redacted]

[redacted]

The [redacted] according to local practices to ensure the [redacted] is administered. [redacted]

If either preparation time or [redacted] time exceeds the time limits a new dose must be prepared from new [redacted] Brazikumab [redacted], and any unused portion must be discarded.

Brazikumab for [redacted]

[redacted] are required for [redacted]. The dose of brazikumab for [redacted] must be administered at room temperature within 6 hours after removal of [redacted]

Brazikumab [redacted]

For [redacted] the person administering the dose will wipe the skin surface of the injection site with alcohol and allow the skin to air dry. The skin will be pinched to isolate the [redacted] from the [redacted] Avoiding the belly button, ribs, hip bones, scars, or moles, the needle will be inserted at a [redacted] approximately halfway into the [redacted] Brazikumab will be [redacted] into the [redacted] using gentle pressure. The area is not to be massaged after injection. [redacted] 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

Precautions will be taken so that activities conducted during the open-label Study

D5271C00002 (Legacy #3150-303-008) do not unblind treatment allocation in Study D5271C00001 (Legacy #3150-301-008). 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. **Concomitant Therapy**

Any medication or vaccine (including over-the-counter, prescription medicines, vitamins, herbal supplements, and/or 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.

6.5.1 Permitted Interventions

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 antibiotics, 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 CD are permitted during the study:

- Oral antibiotics for CD
- Probiotics (eg, Culturelle® and *Saccharomyces boulardii*)
- Antidiarrheals (eg, loperamide and diphenoxylate with atropine) for control of chronic diarrhea, as needed
- Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)
- 5-ASA
- CS therapy (oral prednisone and oral budesonide)

Permitted concomitant medications used for the treatment of CD 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 CD 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 8.

Table 8 Permitted Concomitant Treatments

Treatment	Details
Oral antibiotics for CD (except for the treatment of acute illness)	Permitted only if being taken at Screening for the treatment for CD. If participant is taken off an oral antibiotic for CD treatment, the antibiotic is not to be restarted for the purpose of treating CD during the treatment period. Antibiotics used for the treatment of acute illness are permitted as needed and are to be recorded in association with an AE.
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 and recorded as part of the CDAI score (as applicable).
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.

AE = adverse event; CD = Crohn's disease; CDAI = Crohn's disease activity index; 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 9. Additional details are provided in Appendix E.

Table 9 Corticosteroid Tapering Guidelines

Initial corticosteroid dose	Dose reduction
CCI (or equivalent)	CCI
CCI (or equivalent)	
CCI	
Oral beclomethasone CCI	
CCI	

General tapering guidelines:

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

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 CD symptoms (except for antidiarrheal medications) will be considered rescue treatment. Other IPs are not permitted to be used as rescue treatment. An increase in CCI that does not exceed the Week 0 dose level for participants undergoing CS tapering within the guidelines in Section 6.5.2 is not considered rescue treatment.

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

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

Administration of rescue treatment constitutes treatment failure. Rescue treatments are not to be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety. If rescue treatment is needed, investigators should consider study discontinuation for lack of efficacy. The use of specific rescue treatment (eg, prohibited interventions) in the lead-in study will be exclusionary for this study (Study D5271C00002/ Legacy #3150-303-008) 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)
- Calcineurin inhibitors (eg, cyclosporine and tacrolimus)
- Mycophenolate mofetil
- Sirolimus (rapamycin)
- Thalidomide
- Live attenuated vaccine
- Intra-abdominal surgery
- Fecal microbial transplantation
- 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 safety follow-up period.

6.6 Dose Modification

There is no provision for brazikumab dose reduction or increase. There will be a recommended CCI [redacted] 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.

See Section 6.1.3 for details on dose delays.

6.7 Intervention After the End of the Study

No 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.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the CRF.

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

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

7.1 Discontinuation of Study Intervention

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

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

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

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

Discontinuation of study intervention for abnormal liver function is to be considered by the investigator when a participant meets 1 of the conditions outlined below, or if the investigator believes that it is in best interest of the participant.

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 D 2), 1 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 AEs up to 18 weeks post-last dose 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 > 500 msec or of > 60 msec over baseline 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.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original ICF. 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.

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.

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 or not 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 should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, 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.
- All assessments made at the final visit of Study D5271C00001 (Legacy #3150-301-008) 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 ileocolonoscopy and CDAI. A repeat ileocolonoscopy is not required for participants who discontinue from the lead-in study after Week 12 and prior to Week 16.
- Week 0 dose administration must occur no earlier than 14 days and no later than 56 days from the last dose administration in Study D5271C00001 (Legacy #3150-301-008).
- Paper PRO collection must be initiated 7 days prior to Week 0.
- 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

The SES-CD, CDAI, and PROs will be used for efficacy assessments.

8.1.1 Ileocolonoscopy

An ileocolonoscopy will be performed at screening and at the end of the study (Week 52 [Visit 14]) or at an Early Termination or Unscheduled Visit. In all cases, video recordings are to be performed for the duration of the ileocolonoscopy procedure, including collection of biopsy specimens. Technical instructions for making the video recording will be provided separately (these instructions will include how to capture the depth of insertion and how to mark bowel segments during the recording).

Ileocolonoscopic procedures will be recorded using a video capture kit as supplied by the central reading facility. All video recordings will be labeled with segment names by the local reader vendor to produce a complete ileocolonoscopy video visualized up to the terminal ileum. A complete endoscopic video may not include the terminal ileum if it cannot be visualized. The video clips will be read centrally for mucosal lesions and endoscopic severity based on the SES-CD score by independent gastroenterologists experienced in IBD. The worst affected area of each segment is to be assessed for the SES-CD score calculation.

The risks for endoscopy procedures may include perforation, bleeding after collection of biopsy samples, and complications related to sedation when administered. Individual risks and benefits of the endoscopy procedure should be further discussed with participants and consent for the procedure should be obtained per local guidelines.

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 CD.

To ensure quality data and standardization, the same endoscopist for a participant is to be used at each study site throughout the study whenever possible.

If the participant cannot complete a full ileocolonoscopy due to technical failure in obtaining evaluable video recording for SES-CD scoring and/or biopsy or participant-related reason (other than non-compliance), a potential repeat of the procedure can be scheduled. The ileocolonoscopy can be repeated within a reasonable timeframe from the originally scheduled time, under the discretion of the investigator after consultation with the Study Physician/designee.

8.1.1.1 Simple Endoscopic Score for Crohn's Disease

The SES-CD is a validated endoscopic activity score used to assess the status and change of mucosal lesions in participants with CD (Daperno et al, 2004). The SES-CD for each of the 5 segments will be assessed during ileocolonoscopy. The score assesses 4 variables in up to 5 segments to yield its result (Table 10).

The 5 segments assessed are:

- Rectum, defined as that portion distal to the rectosigmoid junction
- Left colon including the sigmoid colon
- Transverse colon defined as the segment between the hepatic and the splenic flexures
- Right colon including the ileocecal valve, cecum, and ascending colon to the hepatic flexure
- Ileum

Table 10 Simple Endoscopic Score for Crohn's Disease Values

Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers	Large ulcers	Very large ulcers
Ulcerated surface	None	< 10%	10-30%	> 30%
Affected surface	Unaffected segment	< 50%	50-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

8.1.1.2 Biopsy

Mucosal biopsies will be collected for each study ileocolonoscopic procedure performed. At least 4 biopsies per segment (total of 5 segments) are to be obtained, focusing on the areas of greatest inflammation or areas of ulceration within each segment. If no inflammation or ulceration is present, then random biopsies of the segment are to be obtained. The biopsies will be used to support assessments of changes in inflammation or BMs over time. Histological indices that will be used for evaluation of the biopsies will be detailed in a separate, exploratory analysis plan.

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

8.1.2 Crohn's Disease Activity Index

The CDAI is a composite index with weighted domains that quantifies the global disease severity in a single numerical score in a range from 0-600. The CDAI measures the severity of active disease using symptom scores that are monitored over the previous week and includes participant-reported symptoms, physician-assessed signs, and laboratory markers (Best et al, 1976, Sands and Ooi, 2005). The CDAI is calculated by summing weighted scores for subjective items (number of liquid or very soft stools, AP, and general well-being) recorded by a diary during a 1-week period, and objective items (associated symptoms, taking antidiarrheal such as loperamide/opiates, abdominal mass, hematocrit, daily morning temperature, and body weight). The CDAI scores range from 0 to 600, with higher scores indicating greater disease activity. Subjects with scores of < 150, 150 to 219, and 220 to 450 represent remission, mild disease, and moderate to severe disease, respectively; whereas subjects with scores of > 450 have very severe disease (Buxton et al, 2007).

The components of the CDAI score (Table 11) are collected as follows:

- Abdominal mass, EIM: physical examination (Section 8.2.1)

- Antidiarrheal medications (Section 6.5.1)
- Hematocrit: laboratory assessment (Section 8.2.4)
- Weight (calculated as percent change from standard; Best et al, 1976) assessed with vital signs (Section 8.2.2)
- Temperature: paper diary (Section 8.1.3)
- Patient-reported components (LSF [Appendix F 1], AP, and general well-being): paper Diary (Section 8.1.3). Daily PRO data collected 7 days prior to the scheduled visit or prior to bowel prep if endoscopy is planned for that visit, will be used to calculate CDAI.

Participants will be provided a paper diary at the visit prior to the reporting visit described in the SoA (Section 1.3). The daily diary will contain the following participant-reported components of the CDAI: temperature, LSF, AP, and general well-being. These 4 assessments will be recorded by the participant for the 7 days prior to the scheduled visit or prior to bowel prep if endoscopy is planned for the visit for which CDAI will be assessed. The study participant will be prompted 7 days prior to the scheduled visit or bowel prep to begin recording temperature, LSF, AP, and general well-being.

Table 11 Items Included in CDAI and Their Weights

Item	Weight	Total
Total number of liquid or very soft stools over past week	×2	X_1
Total abdominal pain score (rating: 0-3) over past week (range: 0-21)	×5	X_2
Total general well-being score (rating: 0-4) over past week (range: 0-28)	×7	X_3
Sum of presence of following clinical signs over past week: 1. Arthritis/arthralgia (1 = yes, 0 = no) 2. Iritis/uveitis (1 = yes, 0 = no) 3. Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis (1 = yes, 0 = no) 4. Anal fissure, fistula or abscess (1 = yes, 0 = no) 5. Other fistula (1 = yes, 0 = no) 6. Fever >37.8 ºC during past week (1 = yes, 0 = no)	×20	X_4
Antidiarrheal use (eg, diphenoxylate hydrochloride) (0 = none, 1 = yes)	×30	X_5
Abdominal mass (none = 0, equivocal = 2, present = 5)	×10	X_6
Deviation of hematocrit levels (minimum value = 0) 47 - hematocrit (males) 42 - hematocrit (females)	×6	X_7 (if value < 0, enter 0)
Weight ratio 100 × (1-[Current body weight / standard weight]) Minimum = -10 for overweight subject Maximum = 10 for underweight subject	×1	X_8 (if value < -10, enter -10, if value > 10, enter 10)
CDAI score		Sum total of all weighted scores

CDAI = Crohn's Disease Activity Index.

8.1.3 Patient-reported Outcomes - Evening Diary

The Evening Diary will be collected 1 week before each visit where CDAI is calculated, and if endoscopy is planned for the visit, the 1 week prior to bowel prep. The Evening Diary will include the CDAI items of AP, LSF, well-being, and temperature. The diary will also include items to capture urgency and blood in stool, as well as NRS symptom items including AP, fatigue, tiredness, weakness, lack of energy, and joint pain. The NRS measures the severity of symptoms in the past 24 hours using an 11-point scale (0 to 10). 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 (or prior to bowel prep, if endoscopy is scheduled for that visit), with the last daily diary of the 7-day period completed the evening prior to the study visit or bowel prep. Participants will bring the diaries to the site at the appropriate visit. Participants will be prompted as to when to begin recording these assessments.

8.1.4 Patient-reported Outcomes – Site Visits

The HRQoL measures IBDQ, SF-36v2, and EQ-5D-5L, will be administered via paper at select site visits.

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.

8.2 Safety Assessments

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

8.2.1 Physical Examinations

Physical examination will be performed at timepoints as specified in the SoA (Section 1.3).

- A complete physical examination will include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears,

eyes, nose, and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities), and neurological systems.

- Abdominal mass and EIM will be assessed during the physical examination and will be used to calculate CDAI.
- Any new findings or aggravated existing abnormalities, judged as clinically significant by the investigator, will be reported as an AE as described in Section 8.3.5.
- For participants who present with a fistula (eg, perianal fistula), a fistula exam should include the following assessments: number of openings, location of openings, and whether the openings drain with gentle compression.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Section 1.3).

- Pulse rate, respiratory rate, temperature, and BP will be assessed.
- Blood pressure and pulse measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 BP measurement and will be recorded on the eCRF.
- Weight will be recorded in kilograms as part of CDAI.
- Procedure for monitoring vital signs before, during, and CCI [redacted] CCI [redacted] are further detailed in Sections 6.1.1 and 6.1.2.

8.2.3 Electrocardiograms

- Single 12-lead ECGs will be obtained as outlined in the SoA (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

- See Table 12 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The 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.
  - All protocol-required laboratory assessments, as defined in Table 12, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results will be recorded in the eCRF.

The clinical chemistry, hematology, and urinalysis will be performed by the central laboratory.

The following laboratory variables will be measured.

Table 12 Protocol-required Safety Laboratory Assessments

Laboratory assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV MCH %Reticulocytes	WBC count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a]	BUN C-reactive protein Creatinine eGFR Glucose (nonfasting) Magnesium Uric acid	Potassium Sodium Calcium Chloride	AST ALT Alkaline phosphatase Albumin	Total and direct bilirubin Total protein Bicarbonate Phosphate
Fecal Tests	Fecal calprotectin	Fecal lactoferrin		

Laboratory assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (reflexively as needed)
Other Screening Tests	• FSH (as needed in women of non-childbearing potential only)[b] • Urine hCG is to be performed locally at each visit prior to administering study intervention and as outlined in the SoA. • 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 D.
[b] FSH does not need to be repeated at Week 52 if it was in the post-menopausal range at screening. If not, and the female participant becomes amenorrhoeic during the course of the study, FSH should be assessed at Week 52.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; 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.

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAE from the signing of the ICF and until 18 weeks after the last dose of study intervention will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IP that

occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

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

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

AE Variables

The following variables will be collected for each AE:

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

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

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

8.3.3 Causality Collection

The investigator should assess causal relationship between IP 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 IP?'

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 B to the CSP.

8.3.4 AEs Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider, reported in response to the open question from the study-site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 AEs Based on Examinations and Tests

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

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the IP, or are considered to be clinically relevant as judged by the investigator (which may include but 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 D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.7 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of CD (eg, AP and diarrhea). 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 IP.

8.3.8 Reporting of SAEs

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

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 calendar 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 B of the CSP.

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

8.3.9 Pregnancy

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

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

8.3.9.1 Maternal Exposure

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

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

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

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

The same timelines apply when outcome information is available. The 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.

8.3.9.2 Paternal Exposure

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

Pregnancy of the participant’s partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal

birth, or congenital anomaly), occurring from the date of the first dose until 18 weeks following the last dose should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3.10 AEs of Special Interest

8.3.10.1 CCI

CCI

CCI

8.3.10.2 Malignancies

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

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

Participants in this study will be monitored for the development of any malignancies by routine laboratory physical examination and 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 BMs and/or genetic test results.

8.3.10.3 Hypersensitivity Reactions (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.

8.3.10.4 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. Nonclinical studies have suggested that IL-23 may play a role in host defense against certain extracellular and intracellular pathogens. Participants administered brazikumab may be at risk of developing, or have difficulty overcoming, certain types of infections.

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

8.3.10.4.1 Non-opportunistic Infections

A serious non-opportunistic infection is any non-opportunistic infection that meets the SAE criteria in Appendix B 3. Any relevant culture results and diagnostic and/or therapeutic procedure results for a participant with a serious non-opportunistic infection must be provided as an SAE update. Nonserious non-opportunistic infections will not be reported as AESIs.

8.3.10.4.2 Opportunistic Infections

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

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

8.3.11 Medication Error

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

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

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

8.4 Overdose

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

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

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

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

8.5 Human Biological Samples

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

- Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.
  - Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or 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 for measurement of serum brazikumab concentrations prior to study intervention administration as specified in the SoA (Section 1.3). The exact time and date of the samples should be noted.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, for example, 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.

8.5.1.1 Determination of Drug Concentration

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

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 BMs according to the SoA in Section 1.3. All samples should be collected predose and will be analyzed centrally at contracted third-party labs.

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

8.7 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

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 study who are eligible and choose to participate in this study. No separate sample size calculation was performed. Up to a maximum of 240 participants may enter this study, based on the expected number of participants in the lead-in study.

9.3 Populations for Analyses

The following populations are defined in Table 13:

Table 13 Populations for Analysis

Population/analysis set	Description
Screened Analysis Set	All participants who are screened for the study.
FAS	All participants who are assigned to an CCI brazikumab study intervention in the study.
Safety	All participants who receive ≥ 1 administration of study intervention in this extension study.

FAS = Full Analysis Set; CCI

9.4 Statistical Analyses

The SAP will be finalized prior to the lead-in study data base lock and it 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 General Considerations

The treatment sequences in this open-label extension 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. In addition, brazikumab patients in this extension study will be further classified and separated by those that needed induction and those that received maintenance dose directly. All safety and efficacy analyses for this study will be summarized descriptively by the visit and the treatment sequences and overall, unless stated otherwise. 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 will be defined in the SAP.

9.4.2 Efficacy

The efficacy analyses will be based on the FAS population using the observed-cases approach. Descriptive statistics for each efficacy endpoint, PK, and ADA will be presented overall. Pharmacokinetic data may be pooled and analyzed with data from other studies, and reported outside of the CSR.

Efficacy endpoints are exploratory in this extension study.

9.4.2.1 Exploratory Endpoints

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

- Endoscopic response
  - Minimum of 50% decrease from baseline in SES-CD total score
- Endoscopic remission
  - Enhanced endoscopic remission with definition as SES-CD score of 0-2
  - SES-CD total score of 0-2 OR
  - SES-CD total score of ≤ 4 and at least 2-point reduction from baseline with no subscore > 1
- CDAI response
  - CDAI score < 150 or reduction from baseline CDAI score of ≥ 100 points
- CDAI remission
  - CDAI score < 150
- PRO remission
  - Average daily LSF subscore of ≤ 3 as assessed on the CDAI LSF item AND
  - Average daily AP subscore of ≤ 1 as assessed on the CDAI AP item
- CS-free (for the last 12 weeks before the assessment at Week 52) endoscopic response at Week 52
- CS-free endoscopic remission at Week 52
- CS-free CDAI response at Week 52
- CS-free CDAI remission at Week 52
- CS-free PRO remission at Week 52

9.4.3 Safety

The safety analysis will be performed using the Safety Population and will be fully defined in

the SAP. The safety parameters will include AEs, clinical laboratory parameters, vital signs, and ECG parameters. If Visit 1 for this study is the last visit from the lead-in study, the safety value at Visit 1 will not be included in the PCS evaluation as it had been evaluated in the lead-in study, but it will be included in the change-from-baseline summary analysis.

Safety endpoints are primary in this extension study.

9.4.3.1 AEs

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of study intervention in this study.

An AE that occurs more than 18 weeks after the last dose of study intervention in this study will not be counted as a TEAE.

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

The number and percentage of participants with TEAEs during the study will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants with treatment-related TEAEs 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 TESAEs and participants with TEAEs 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 8.3.7 will also be summarized.

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

9.4.3.2 Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in conventional and 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.

9.4.3.3 Vital Signs

Descriptive statistics for vital signs (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.

9.4.3.4 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.

9.4.4 Exploratory BM Analyses

Exploratory BM 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.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a 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 SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

- An investigator who receives an investigator safety report describing 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.

A 2 Financial Disclosure

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

A 3 Informed Consent Process

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

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

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

A 4 Data Protection

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

A 5 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the 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 eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH, GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 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 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 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 CRO(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 participant and should assure appropriate participant therapy and/or follow-up.

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

A 9 Publication Policy

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

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

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

B 2 Definition of SAEs

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

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

Life-threatening

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

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal 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 anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity Rating Scale

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

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

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

B 3 Definition of AESIs

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

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

- Infusion-related reactions and injection-site reactions
- Malignancies
- Hypersensitivity reactions (anaphylaxis)
- Infections
  - Serious non-opportunistic infections
  - Opportunistic infections

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

B 4 A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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

B 5 Medication Error

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

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

Medication error includes situations where an error.

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

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

- Drug name confusion

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

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

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

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

B 6 AE and SAE Recording

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

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

The investigator:

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

AstraZeneca ensures the organization(s) holding the samples is/are informed about the

withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

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. Examples of Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are to be packed in accordance with UN 3373 and IATA 650 and assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

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

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

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

D 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 (eg, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

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

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

D 2 Definitions

Potential Hy's Law
Potential Hy's Law is defined as AST 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
Hy's Law is defined as 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.

D 3 Identification of Potential Hy's Law Cases

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

- 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 the AstraZeneca representative).

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

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

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

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

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria Not Met

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

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

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

D 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria of *Important Medical Event* and causality assessment *yes/related* according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Sponsor Study Physician/designee contacts the investigator, to provide guidance, discuss and agree on an approach for the study participant's 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. Complete follow-up SAE Form as required
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Sponsor Study Physician/designee

[#]**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.

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

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

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

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

Where there is an agreed alternative explanation for the ALT, AST, or 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 as detailed below:

- 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 for the ALT or AST and TBL elevations other than the IP:

- Update the 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.

D 6 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

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

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

ANA = antinuclear antibody; Anti-LKM = Anti-Liver/Kidney Microsomal Ab; 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.

D 7 References

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

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

clinical evaluation.' Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix E Sample Corticosteroid Tapering

Corticosteroid 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									

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

CCI Equivalents	Equivalent Dose
CCI	

Appendix F Patient-reported Outcomes 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.

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.

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

F 2.2 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 2.3 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 assessment and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions, and other measures implemented to ensure patient's safety. In case of doubts please contact the AstraZeneca Sponsor Study Physician/designee. If patient testing is performed as a result of the public health crisis, results may be documented for this study.

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 Section 8. 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 designated Sponsor Study Physician/designee.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrollment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Table 1 of CSP the participant will need to be

rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a participant in addition to that detailed in Section 5.4. The procedures detailed in Table 1 must be undertaken to confirm eligibility using the same identification number for the participant.

Home or Remote Visit to Replace On-site Visit (Where Applicable)

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

Telemedicine Visit to Replace On-site Visit (Where Applicable)

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

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

At-home or Remote Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified site HCP, provided this is acceptable within local regulation/guidance. The option of at-home or remote location IP 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 IP administration during other study disruptions (eg, site closures due to natural disaster).

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

A qualified HCP from the study site or TPV service may administer the IP 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 IP administration will be provided.

Additional information related to the visit can be obtained via a telemedicine or home visit. Refer to the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for step-by-step guidance including drug accountability and reconciliation requirements.

Data Capture During Telemedicine or Home/Remote Visits

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

Appendix H Abbreviations

Abbreviation or special term	Explanation
5-ASA	5-aminosalicylates
ADA	anti-drug antibody
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AP	abdominal pain
AST	aspartate aminotransferase/transaminase
AUC	area under the serum concentration time-curve
AUC_{0-28}	area under the curve from time 0 to 28 days
BM	biomarker
BP	blood pressure
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CFR	Code of Federal Regulations
C_{max}	maximum serum concentration
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organisation
CRP	C-reactive protein
CS	corticosteroids
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIM	extraintestinal manifestation
EQ-5D-5L	5-level European Quality of Life - 5 Dimensions
FAS	Full Analysis Set
FCP	fecal calprotectin

Abbreviation or special term	Explanation
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HCP	Health Care Professional
HIPAA	Health Insurance Portability and Accountability Act
HL	Hy's Law
HIV	human immunodeficiency virus
HRQoL	health related quality of life
IATA	International Airline Transportation Associations
IB	investigator's brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
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
CCI	CCI
LSF	loose stool frequency
MACE	major adverse cardiac events
MDRD	modification of diet in renal disease
NABs	neutralizing antibodies
NRS	Numerical Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
PCR	polymerase chain reaction
PCS	potentially clinically significant
PFS	pre-filled syringe

Abbreviation or special term	Explanation
PHL	potential Hy's law
PI	principal investigator
PK	pharmacokinetic(s)
PRO	patient reported outcome
QTc	corrected QT interval
RBC	red blood cell
RNA	ribonucleic acid
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
CCI	CCI
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36v2	Short-Form 36 Health Survey Version 2
SoA	schedule of activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNFα	tumor necrosis factor-alpha
TPV	third-party vendor
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
VAS	visual analog scale
W	week
w/v	weight/volume

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 3 (March 2021)

Overall Rationale for the Amendment:

In 2020, AstraZeneca resumed full ownership of brazikumab clinical development. AstraZeneca has re-evaluated the development plan and the CSP D5271C00002 (Legacy #3150-303-008) has consequently been reviewed and amended.

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

Section # and name	Description of change	Brief rationale
Throughout	The protocol was transferred to the AstraZeneca protocol template.	The sponsor of the study has changed to AstraZeneca. The protocol was transferred to the AstraZeneca template to align the study with AstraZeneca processes and approved language.
Throughout	Removed reference to Study D5170C00002 (previously terminated Ph2b study).	Participants from this terminated study were not enrolled in this protocol and therefore would no longer be applicable for this amendment.
Throughout	Changed optional induction dosing to mandatory induction dosing for nonresponder/inadequate responders.	Maintain consistency in study population that receives induction dosing.
Synopsis	Revised to align with changes to the protocol and the AstraZeneca 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.
SoA	Added screening visit.	To make it clear what assessments are for eligibility requirements and separate these from the baseline visit (Week 0). For most participants, these assessments will be the same as their last visit in the lead-in study.
SoA	Added footnote regarding visit schedule calculation.	Revised for clarity.
SoA	Removed serum adalimumab immunogenicity test.	Removed Humira arm in Stage 1 of the lead-in study.
SoA	Moved assessments that are used for screening/eligibility from baseline (Week 0) to screening column.	A screening visit was added to the protocol to separate assessment needed for eligibility and to ensure all screening

Section # and name	Description of change	Brief rationale
		assessments are performed prior to the Week 0 visit.
SoA	FSH should be carried forward from screening visit from lead-in study.	Menopausal status based on entry into lead-in study should not change and may be carried forward to reduce participant burden.
SoA	Removed HbA1c.	Not included in lead-in study and does not impact eligibility into OLE study.
SoA	Added FCP sampling at Week 12	Evaluate effect of reinduction on FCP as inflammatory marker.
SoA	Added PAXgene RNA sampling	Revised to allow for RNA biomarker (IL-23 signature) analysis at late clinical endpoint.
SoA, Table 2	Added blood sample for exploratory biomarker analysis; PAXgene RNA; and stool for calprotectin, lactoferrin and exploratory biomarkers at ET and Week 70 follow-up.	Biomarker assessment at ET is needed to compare changes in clinical efficacy to changes in BM profiles to enhance better understanding of brazikumab's mechanism of action.
SoA, Table 2	Removed hepatitis B virus DNA test	Hepatitis B eligibility criteria modified to include PCR testing as applicable, and therefore, DNA testing removed.
SoA	Added PRO table	Added for clarity.
Section 2.2	Text was revised to update information from the recently completed Study 3150-101-008	Updated to include most recent data.
Section 2.3	Benefit/risk text from the Germany-specific protocol amendment was added in place of the prior cross-reference to the IB.	Text was added to provide more information on the benefits and potential risks of brazikumab administration, in alignment with the AstraZeneca template and SOPs and the Germany-specific amendment.
Section 4.1	Revised text regarding responders/completers and non-responders	Text revised to reflect Humira arm removal in the lead-in study. More granular description of participants subgroups eligibility for OLE study added for clarity.
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

Section # and name	Description of change	Brief rationale
		to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.
Section 4.3	Revised section on justification for dose	Edited for clarity.
5.1 Inclusion Criterion 1(b)	Revised criterion to include rescue criteria. Added text regarding participants who demonstrate evidence of endoscopic improvement.	Clarification of eligibility in the context of rescue criteria.
5.1 Inclusion Criterion #2(c), Appendix D	Excluded participants with newly-identified latent TB.	Revised in consideration for participant safety in countries with high burden of TB.
5.1Inclusion Criteria #4-6	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.
5.2 Exclusion Criterion #5(a)	Removed the exception for participants with a history of basal or squamous cell carcinoma > 3 months if the participant has no prior history of, or current, thiopurine use.	Revised for clarity and safety.
5.2 Exclusion Criterion #9	Defined a prolonged QTcF interval	Added for clarification.
5.2 Exclusion Criterion #16(a)	Aligned Gilbert syndrome wording with UK amendment	Provided alignment between the global and the UK protocol amendments.
Section 5.3	Added restrictions regarding contraception and donation of blood	Added to align with standard AstraZeneca template wording.
Section 5.3.2	Added text as clarification that use of nicotine replacement therapy should be recorded as a concomitant medication.	Clarification for recording nicotine replacement therapy as concomitant treatment to support appropriate collection and review of applicable data.
Section 5.4	Added text regarding screen failures and rescreening.	Added for clarification.
Sections 6 and 6.1	Revised study intervention table and text.	Aligned with study design change from the main body of the protocol.
Section 6.1.1	Revised description of [redacted] administration.	Aligned with study design changes and operational changes.
Section 6.1.3	Added section on Study Intervention Administration Re-Scheduling.	Section added to clarify guidance for rescheduling study drug administration if required.

Section # and name	Description of change	Brief rationale
Section 6.1.4	Revised description of study supplies.	Revised for clarity and to align with available supplies.
Section 6.2	Revised text regarding study intervention handling.	Revised to align with AstraZeneca template and to provide clarification of existing text.
Section 6.5	Text added to describe study intervention compliance.	Revised to align with AstraZeneca template.
Section 6.5.1	Specified information to be collected on concomitant medications.	Added for clarification.
Section 6.5.2 and Appendix F	Revised corticosteroid study guidelines text; included an example steroid tapering schedule table	Revised to align and conform steroid tapering during maintenance. Steroid tapering aligns broadly with clinical guidelines.
Section 6.5.3	5-aminosalicylates and oral steroid doses above initial randomization (Day 1) dose added to the new initiation of medications or interventions specified as rescue treatment.	Added for clarity.
Section 6.5.4	Added fecal microbial transplantation to list of prohibited interventions during the study.	Avoid confounding safety or efficacy assessments.
Section 7.1	Revised criteria for participant discontinuation.	Revised to align with lead-in study protocol.
Legacy Section 7.1.1	Removed Temporary Discontinuation section.	Revised for consistency of discontinuation criteria with lead-in study. Relevant text moved to Section 6.1.3.
Section 7.2	Added template text regarding participant withdrawal.	Additional text from the AstraZeneca template provides details on participant follow-up after discontinuation and guidance regarding the use of participant samples.
Section 8	Added information on data recording and blood volume collection.	Added to provide operational details and for participant safety.
Section 8.1.2 Crohn's Disease Activity Index	Provided details on the calculation of the CDAI.	Added for clarification.
Section 8.1.3	Revised text describing the PRO Evening Diary.	Revised for clarification.
Section 8.1.4	New sections added to describe PRO Site Visits.	Study design changes.

Section # and name	Description of change	Brief rationale
Section 8.2.1 Physical Examinations	Provided a list of assessments that constitute a full physical examination; added the requirement to assess abdominal mass, EIM, and fistula exam (as applicable).	To provide clarity for the investigator and to support the assessment of CDAI.
Section 8.2.2 Vital Signs	Revised text for vital signs; added text on recording weight.	For clarification and for study design changes.
Section 8.2.4	Revised the description of clinical laboratory assessments.	Revised to align with AstraZeneca template.
Sections 8.3 and 8.3.1	New text added to describe collection of AEs and SAEs.	Added to align with AstraZeneca template.
Sections 8.3.2	Removed prior Section 8.3.2 Method of Detecting AEs and SAEs. Replaced prior text regarding follow-up of AEs and SAEs with standard AstraZeneca template text.	Prior section 8.3.2 text is not needed per AstraZeneca template and SOPs New text regarding follow-up of AEs and SAEs is consistent with prior information and includes more details. Provides alignment with AstraZeneca template and SOPs.
Section 8.3.3	New section on assessment of AE causality.	Revised to align with AstraZeneca template and SOPs; consistent with text that was in the prior Appendix 10.4.
Section 8.3.4	New section added to inform the sites of how to handle AEs based on signs and symptoms.	New information; added to align with AstraZeneca template and SOPs.
Section 8.3.5	New section added to inform the sites of how to handle AEs that were identified through examinations and tests.	New information; added to align with AstraZeneca template and SOPs.
Section 8.3.6 and Appendix D	Text on Hy's Law replaces prior Section 8.3.9.1 and Appendix 9.	AstraZeneca standard template text was added to align with AstraZeneca template and SOPs. The new content is consistent with the prior text.
Section 8.3.7	New section was added to inform the sites how to handle AEs due to the disease under study.	New information; added to align with AstraZeneca template and SOPs.
Section 8.3.8	Text was added to inform the sites how to report SAEs; this information was previously provided in Appendix 10.3.	Added to align with AstraZeneca template and SOPs; content is similar to the information that was removed from Appendix 10.3.

Section # and name	Description of change	Brief rationale
Section 8.3.9	Replaced previous Section 8.3.5 with standard AstraZeneca template text on the handling of pregnancies Removed the requirement to report elective abortions without complications as AEs or SAEs.	Added to align with AstraZeneca template and SOPs; except as noted, the content is similar to the information that was removed from previous Section 8.3.5.
Legacy Section 8.3.9	Section on Medical Device Incidents was removed.	The medical devices section was removed as irrelevant because the prefilled syringes are not medical devices but are combination products.
Section 8.3.10	Removed the AESI of Hy's Law in Section 8.3.10. Hy's Law is now included in Section 8.3.6.	Section 8.3.6 Hy's Law aligns with AstraZeneca Protocol Template. No need to duplicate as an AESI because it is not a specific risk for brazikumab.
Section 8.4	New text replaces prior Section 8.4 with AstraZeneca standard template text on overdose. Added details on overdose of [redacted] brazikumab. Removed standard Allergan text on the handling of overdose and replaced with standard AstraZeneca text.	Details on overdose of [redacted] brazikumab were added to provide more information to the sites. Remaining changes were for alignment with AstraZeneca template and SOPs.
Section 8.5	Text was added to describe standard AstraZeneca process regarding the handling of biological samples.	Added to align with AstraZeneca template and SOPs.
Section 8.5.1	Revised PK collection details; added template text.	Study design change and alignment with AstraZeneca template.
Section 8.5.1.1	New section added to provide details on the determination of drug concentrations.	Added to align with AstraZeneca template.
Section 8.5.2	Template text was added to existing text.	Added to align with AstraZeneca template.
Sections 8.6 and 8.6.1	Added text to support new samples (stool samples and biopsies).	Study design change, additional BM assessment to enhance understanding of MOA and to provide rationale for IL-22 as BM for IL-23-driven inflammation in gut for CDx regulatory approval.
Section 8.8	Text added to support new medical resource utilization and health economics assessments.	Revised to align with lead-in study design change, and for clarification.

Section # and name	Description of change	Brief rationale
Section 9.4.1	Deleted all references to Humira. Added details regarding analyses of patients (induction versus maintenance directly).	Revised to align with lead-in study design change, and for clarification.
Section 9.4.2 and 9.4.2.1	Clarified that efficacy endpoints are exploratory.	Section structure alignment with AstraZeneca study protocol and clarification of efficacy endpoints categorisation.
Section 9.4.2.1	Added bullet for analyses of endoscopic remission.	Added definition of endoscopic remission / alignment with lead-in study protocol.
Section 9.4.3	Clarified that safety endpoints are primary endpoints for this study.	Section structure alignment with AstraZeneca study protocol and clarification of safety endpoints categorisation.
Section 9.4.4	Added section to state that exploratory biomarker analyses may be defined and presented outside of SAP and CSR.	Section structure alignment with AstraZeneca study protocol and clarification of safety endpoints categorisation
Appendix A	Replaced legacy Appendix 10.1.1.	Alignment with AstraZeneca template.
Appendix B	Replaced legacy Appendix 10.3.	Alignment with AstraZeneca template.
Appendix C	New appendix.	Alignment with AstraZeneca template.
Appendix G	Updated PRO Appendix 10.11.	Revised to align with prior sections of the protocol.
Appendix G2.1	IBDQ sample version replaced with approved version.	Alignment with AstraZeneca licensed version.
Appendix D	Replaced legacy Appendix 10.9.	Alignment with AstraZeneca template.
Legacy 10.8	Removed legacy Appendix 8 Medical Device Incidents.	Study design change.
Appendix I and Appendix K	Updated the list of abbreviations and list of references.	Revised to align with prior sections of the protocol.

Amendment 2: (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, the study number, and SAE reporting information.

Section # and name	Description of change	Brief rationale
Throughout	Change sponsor to AstraZeneca and change study number to AstraZeneca study number	The sponsor of the study is changing to AstraZeneca and an AstraZeneca study code will be used moving forward
Throughout	Removed study 3150-302-008 from the text	Study 3150-302-008 will not be initiated.
Throughout	Changed study number of lead-in study 3150-301-008 to D5271C00001 (Legacy #3150-301-008)	The sponsor of the lead in study is changing to AstraZeneca and an AstraZeneca study code will be used moving forward
Throughout	Change Medical Safety Physician (MSP) to study physician.	This changed is being made to align with AstraZeneca terminology.
Title Page	Change in Sponsor Name and Legal Registered Address	The Sponsor name and address were changed to AstraZeneca AB
Title Page	Emergency Telephone number removed	The Allergan emergency number was removed from the title page. This will be provided directly to investigators
Title Page	SAE Reporting Fax Number/email removed	The Allergan SAE reporting Fax number/email were removed. Safety reporting information will be provided directly to investigators.
Title Page	Sponsor signatory was removed	The Allergan sponsor signatory was removed
Section 6.3, Study Intervention(s) Administered	AstraZeneca will be providing study interventions.	With the sponsor change, AstraZeneca will be providing study interventions.
Section 6.3.3, Study Supplies	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 8.3.8.1 Potential Hy's Law Cases	The Allergan specific AE reporting information was removed.	AstraZeneca will provide safety reporting information directly to investigators.
Section 10.3, Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The Allergan specific AE reporting information was removed. AstraZeneca protocol language was added.	AstraZeneca language was added due to change in Sponsor. AstraZeneca will provide safety reporting information directly to investigators.

Section # and name	Description of change	Brief rationale
Section 10.9, Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments	The Allergan specific AE reporting information was removed.	AstraZeneca will provide safety reporting information directly to investigators.

Amendment 1: (June 2019)

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

Overall Rationale for the Amendment

This protocol amendment includes updates to correct editorial errors, make clarifications to the protocol, and make updates to laboratory testing procedures, including the addition of adalimumab serum ADA sampling and hepatitis B virus DNA testing.

Formatting and grammatical edits are not listed below.

Section # and name	Description of change	Brief rationale
Title page	Added EudraCT #	No longer TBD
Header throughout	Updated to correct protocol number	Correction to protocol
1.1 Synopsis	Added exploratory efficacy to objectives and endpoints table	Clarification to protocol
1.1 Synopsis	Added that participants do not need to complete the 18-week follow-up period of the lead-in study	Clarification to protocol
1.1 Synopsis	Updated language for sample size calculation	Clarification to protocol
1.1 Synopsis	Added that information on non-responder qualification is found in Section 6.1	Clarification to protocol
1.2 Schema	Updated figure to add “optional” for induction dose	Clarification to protocol
1.2 Schema	Removed sentence about continuing the study until brazikumab is commercially available or study discontinued	Updated to align with planned studies for the program
1.3 Schedule of Activities	Added HbA1c at Week 24	Update to the protocol
1.3 Schedule of Activities	Added line and footnote n for hepatitis B virus DNA testing for participants with positive hepatitis B core antibody	Updated procedure for participant safety

Section # and name	Description of change	Brief rationale
1.3 Schedule of Activities	Removed “pre-dose” for adalimumab	Correction to the protocol
1.3 Schedule of Activities	Added adalimumab serum ADA immunogenicity testing and updated footnote i	Updated procedures for efficacy assessment
1.3 Schedule of Activities	Footnote k modified to add reference to Appendix 11	Appendix 11 added with PRO diary information
Table 1-2	Added QFT-TB and hepatitis B virus DNA testing to early termination visit and added footnote b	As above and correction to protocol
2.2 Background	Corrected dose for 3150-101-008 protocol from CCI	Correction to protocol
2.2 Background	Update to results of 3150-101-008	Updated based on new information from study
3 Objectives and Endpoints	Added exploratory efficacy to objectives and endpoints table	Clarification to protocol
4.1 Overall Design	Added that participants do not need to complete the 18-week follow-up period of the lead-in study and that the final visit is at Week 52 for Study 3150-301-008	Clarification to protocol
4.1 Overall Design	Added that information on non-responder qualification is found in Section 6.1	Clarification to protocol
5.1 Inclusion Criteria	Criterion 1.01 updated to correct study number for roll-over study	Correction to protocol
5.1 Inclusion Criteria	Updated criterion 3.02 to align with SoA and Appendix 7	Correction to protocol
5.2 Exclusion Criteria	Added other conditions that may potentially confound assessments to criterion 1.02	Clarification to protocol
5.2 Exclusion Criteria	Updated criterion 1.04 to add sponsors opinion	Clarification to protocol
5.2 Exclusion Criteria	Added criterion 1.05, cancer exclusions	To align with other studies in the program
5.2 Exclusion Criteria	Added additional exclusions with respect to hepatitis B to criterion 4.01	Updated based on new hepatitis B virus DNA laboratory testing added to protocol
6 Study Intervention	Added subheadings 6.1 and 6.2 to clarify IV induction versus maintenance dosing	Clarification to the protocol

Section # and name	Description of change	Brief rationale
CCI	Clarified dose is CCI brazikumab and that CCI dosing is at the discretion of the investigator	Clarification to the protocol
CCI	Set minimum time for monitoring to CCI and CCI and added an option for emergency procedures to be in place to treat anaphylaxis	To align with other studies in the program and clarification to the protocol
6.4 Preparation/ Handling/ Storage/ Accountability	Added that additional guidance is found in the Pharmacy Manual	To align with other studies in the program
6.7.1 Permitted Interventions	Added more detail to CS therapy and tapering; added that oral 5-aminosalicylate treatments should be continued at stable doses as tolerated; added use of NSAIDS is discouraged	To align with other studies in the program
6.7.4 Prohibited Interventions During the Study	Added an exception for live attenuated vaccine and directed to see Section 7.1.1. Added that use of alternative and complementary treatments must be discussed and that Chinese herbal therapies are prohibited	Clarification to the protocol and to align with other studies in the program
7 Discontinuation	Moved this sentence from 7.3, "That discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.	Clarification to the protocol
8.1.1 Ileocolonoscopy	Added that video will be taken for duration of the procedure and that central reader should also notify the investigator of any findings	Clarification to the protocol and to align with other studies in the program
8.1.1.1 Simple Endoscopic Score for Crohn's Disease	Added, "SES-CD for each of the 5 segments will be assessed during ileocolonoscopy"	To align with other studies in the program
8.1.3 Patient Reported Outcomes-Evening Diary	Added evening diary to the header, added abdominal pain to list of NRS items, reworded to make it clear the diary is to be completed in the evening	Correction and clarification to the protocol
8.2.1 Physical Examinations	Added neurological systems would be assessed	Alignment with other studies in the program
8.2.4 Clinical Safety Laboratory Assessments	Removed laboratory manual as redundant in sentence	Correction to the protocol
8.2.5 Immunogenicity Assessments	Added adalimumab and that sample collection will remain blinded	Added to explore the effect of adalimumab ADA on efficacy and a clarification to the protocol

Section # and name	Description of change	Brief rationale
8.3.3 Follow-up of AEs and SAEs	Added "if autopsy is performed"	To align with other studies in the program
8.3 Adverse Events	Added subsections 8.3.6 and 8.3.7	To align with other studies in the program
8.3.8.4 Hypersensitivity Reactions	Added examples of appropriate drugs and that emergency procedures are to be in place for anaphylaxis treatment	Clarification to the protocol
8.4 Treatment of Overdose	Added that MSP information is in Study Contact Information tab and that it is at least 18 weeks for brazikumab to be eliminated from the body	To align with other studies in the program
9 Statistical Considerations	Added that participants who were previously enrolled in the lead-in studies of 3150-301-008 and 3150-302-008, the baseline from the lead-in studies will be used for the analyses. For participants who were previously enrolled in Study D5170C00002, the last assessment before the first dose of the study intervention in this study will be used as the baseline for the analyses.	Clarification to the protocol
9.2 Sample Size Determination	Updated the description of how the sample size was calculated	Clarification to the protocol
9.3 Populations for Analyses	Updated wording for the populations	Clarification to the protocol
9.4.1.1 Efficacy Endpoints	Added more detail to the endpoints	Clarification to the protocol and to align with other studies in the program
9.4.1.2 Analyses for Efficacy Endpoints	Added that will also be presented by biomarker group and updated header	Clarification to the protocol
9.4.2 Safety Analyses	Added if Visit 1 for this study is the last visit from the lead-in study, the safety value at Visit 1 will not be included in the PCS evaluation, but will be included in the change-from-baseline summary analysis.	Clarification to the protocol
9.4.2.1 Adverse Events	Removed reference related to study intervention	Correction to the protocol
9.4.2.2 Clinical Laboratory Assessments	Changed Visit 1 to baseline	Clarification to the protocol
10.1.3 Informed Consent Process	Added option for legally authorized representative	To align with other studies in the program
Table 10-1	Updated wording for microscopic examination of urinalysis	To align with other studies in the program

Section # and name	Description of change	Brief rationale
10.3 Appendix 3	Deleted redundant sentence	Correction to the protocol
10.4 Appendix 4	Added FCP to abbreviations	Correction to the protocol
10.11 Appendix 11	This appendix was added and includes an example of the evening diary and the Bristol stool formation scale	To provide additional clarification on what is tested as part of PRO, and to better define liquid or soft stools.
10.12.1 Baseline	Added virology-related and ADA immunogenicity	As above
10.12.2 Open-label Treatment Period	Added HbA1C at Week 24 and hepatitis B virus DNA	As above
10.12.3 Early Termination	Added hepatitis B virus DNA and QFT-TB	As above

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