Clinical Study Protocol	
Study Intervention	Brazikumab
Study Code	D5271C00001 (Legacy #3150-301-008)
Version	Amendment 5 v6.0
Date	07Dec2021

Redacted for Public Disclosure

A 52-Week, Multicenter, Randomized, Double-blind, Placebo and Active-Controlled, Operationally Seamless Phase 2b/3, Parallel-group Study to Assess the Efficacy and Safety of Brazikumab in Participants With Moderately to Severely Active Crohn's Disease (INTREPID Lead-In)

Sponsor Name: AstraZeneca AB

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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: D5271C00001 (Legacy #3150-301-008)

Amendment Number: 5

Study Intervention: Brazikumab, Humira®, placebo
Study Phase: 2b/3

Short Title: 52-Week Phase 2b/3 Crohn's Disease Study

Acronym: INTREPID Lead-in

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

AstraZeneca Protocol D5271C00001 (Legacy # 3150-301-008)

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	December 2021
Amendment 4	February 2021
Amendment 3	August 2020
Amendment 2	November 2018
Amendment 1	November 2018
Original Protocol	September 2018

Amendment 5 [07-December-2021]

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

Overall Rationale for the Amendment

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

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

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

Section # and Name	Description of Change	Brief Rationale
Throughout	Corrected typographical errors.	Corrections were made to improve accuracy.
Throughout	Removed the study number of the open-label extension brazikumab study.	The open-label study number was removed to avoid needing additional updates to the D5271C00001 study protocol if future changes occur on the open-label study number.
Section 1.3 SoA, Table 1	Clarified the days that define Screening Visit 1.	Revisions were made for clarity.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 SoA, Table 1 Section 8.1.3.1 PRO Assessments	Clarified the minimum time interval between Screening Visit 1 and Screening Visit 2.	Clarification was made to minimize misunderstanding of the screening time interval for collection of PRO data.
Section 1.3 SoA, Table 2	Removed timepoints for QFT-TB testing during the treatment period.	Investigators will take a risk-based approach to repeat QFT-TB testing through the study based upon participant presentation (eg, cough, shortness of breath, or persistent fever).
Section 1.3 SoA, Table 2	Removed timepoints for Hepatitis B and C and HIV screening during the treatment period.	Investigators will take a risk-based approach to repeat Hepatitis B and C and HIV screening through the study based upon participant presentation.
Section 1.3 SoA, Table 2	Merged PK sampling information from 3 rows to 2 rows, and included more notes.	Revisions were made for clarity.
Section 1.3 SoA, Table 2	Removed timepoints for testing of stool for C. difficile during the treatment period.	Investigators will take a risk-based approach to repeat C. difficile testing throughout the study based upon participant presentation (eg, increased stool frequency or abdominal pain).
Section 2.3 Benefit/Risk Assessment	The important potential risks of brazikumab were updated to include injection-site reactions and severe hypersensitivity.	Updates were made to align potential risks with language in the brazikumab IB to ensure continuity.
Section 3 Objectives and Endpoints, Table 5	Added an additional (exploratory) objective needed to cover any/all biomarker analyses to be completed, even if not planned for inclusion in the clinical study report.	Biomarker sampling is mandatory per the SoA and ICF, and planned sample analysis is well defined (Section 8.6). This addition is to ensure intended use is appropriately reflected in the study objectives.
Section 3 Objectives and Endpoints, Table 5	A footnote will be added explaining that additional exploratory efficacy endpoints may be described, with corresponding statistical analyses, in the SAP.	Addition made so that the study team may identify more exploratory variables to analyze.
Section 4.1 Overall Design	Moved text describing number of patients to be randomized to Stage 1.	The text was in a section that was describing Stage 2 of the study, and was moved for clarity.
Section 5.1 Inclusion Criterion #6	Revised the QFT-TB test criteria for study inclusion.	Participants with repeated indeterminate QFT-TB testing to be excluded from the study, as TB status cannot be determined, reducing risk to potential participants.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criterion #4	Added details to clarify that participants "are excluded irrespective of the time from surgery."	Details were added to improve clarity.
Section 6.1 Study Interventions Administered: Stage 1 Section 6.1.3 Study Supplies Section 6.3 Preparation/Handling/Storage /Accountability	Introduced placebo vials to be provided centrally for placebo CCI dosing.	The inclusion of placebo CCI will support study integrity by enabling blinded qualified site personnel to prepare the study intervention for both brazikumab and placebo.
Section 6.1.1 Dosing Regimen Section 6.1.1.2 CCI Administration Section 6.3 Preparation/Handling/Storage /Accountability Section 6.4 Measures to Minimize Bias: Randomization and Blinding Section 6.5 Study Intervention Compliance	Revised the language describing the involvement of the individual(s) who will be administering the IP.	Revisions were made to outline the modified requirement for blinded staff given the introduction of the placebo vial to the study.
Section 6.1.1.2 CCI Administration Section 6.3 Preparation/Handling/Storage /Accountability	Additional injection sites for CCI administration 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 injection sites.
Section 6.3 Preparation/Handling/Storage/ Accountability	Updated the volumes of CCI CCI that will be removed from the CCI and replaced with brazikumab and placebo, in preparation for the CCI CCI	With the introduction of the placebo vial and blinded pharmacist, it is necessary to use CCI brazikumab CCI and CCI placebo CCI during preparation of CCI dose to ensure blinding between dose levels, as CCI brazikumab CCI are required for CCI dose.
Section 6.3 Preparation/ Handling/Storage/ Accountability	Revised the language for the time and temperature of the CCI CCI. Included a standard clause regarding storing the CCI in the inner carton during temperature equilibration.	Further investigation has determined that an equilibration time of at least CCI .

Section # and Name	Description of Change	Brief Rationale
Section 6.4 Measures to Minimize Bias: Randomization and Blinding	A sentence was added explaining that regular transfers of the live randomization schema will be performed from the IxRS vendor to the bioanalytical lab until randomization is complete for correct identification of brazikumab patients for PK analyses.	AZ's standard process does not analyze placebo samples. Therefore, the Bioanalytical Lab will need the random live list to identify placebo samples. Details are added to improve clarity and transparency of process that affect the blind.
Section 6.6.2 Permitted Concomitant Treatments	Removed text to clarify CS tapering guidance.	Clarification that patient clinical status must be considered before enforcing CS tapering.
Section 6.6.3 Prohibited Interventions During the Study	Added details to clarify the duration to avoid prohibited therapies.	Details were added to improve clarity.
Section 6.6.4 Rescue Treatment	Correction of text associated with worsening or no improvement in CD to align with Table 11.	Revisions were made to ensure continuity and clarity.
Section 8.1.1.1 Ileocolonoscopy	Revised the language to state that video recordings will be performed with biopsies taken upon endoscopic withdrawal.	Revisions were made to align the language with the central endoscopy vendor instructions.
Section 8.1.1.3 Biopsy	Revised the language to state that histological indices for biopsies will be detailed in a separate, exploratory analysis plan.	Revisions were made to clarify the approach for histological analysis.
Section 8.1.1.4 Crohn's Disease Activity Index	Corrected an error in the rating and range of the total general well-being score.	Revisions were made to correct errors.
Section 8.1.3.5 Participant Qualitative Interview Sub-study	Added extra English-speaking countries to sub-study.	Additions were made to ensure recruitment target to sub-study will be met.
Section 8.2.4 Clinical Laboratory Assessments	Removed coagulation group assessment from the hematology panel for the clinical laboratory assessments.	Coagulation group reflex testing, prothrombin time, and international normalized ratio are covered in the AZ Hy's Law kit.
Section 8.2.4 Clinical Laboratory Assessments	To clarify that laboratory values requiring a change in participant management or considered clinically significant will be recorded in the eCRF.	Revision was made to align with the data collection methods within AZ.
Section 8.3.8 Reporting of SAEs	Revised the language of safety reporting via EDC.	Revision was made to align with current AZ standard safety reporting.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.9.1 Maternal Exposure	Revised the language of pregnancy reporting.	Revision was made to align with current AZ pregnancy reporting.
Section 9.4.1 General Considerations	Revised language on the analyses that will be performed with the study data collected prior to protocol amendment 4.	Details were added to improve clarity.
Appendix G Procedures for Tuberculosis Testing From Screening	Revised the procedures for TB testing from Screening.	Aligned with updated TB inclusion criteria but maintained risk-based monitoring of patients especially in high-risk countries/regions.

AE = adverse event; AZ = AstraZeneca; CD = Crohn's disease; CS = corticosteroid; eCRF = electronic case report form; EDC = electronic data capture; HIV = human immunodeficiency virus; IB = Investigator's Brochure; ICF = informed consent form; IP = investigational product; CCI [redacted] IxRS = Interactive Voice/Web Response System; PK = pharmacokinetic(s); PRO = patient-reported outcomes; QFT-TB = QuantiFERON-TB test; SAE = serious adverse event; SAP = Statistical Analysis Plan; SC = subcutaneous; SoA = schedule of activities; TB = tuberculosis.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A 52-Week, Multicenter, Randomized, Double-blind, Placebo and Active-controlled, Operationally Seamless Phase 2b/3, Parallel-group Study to Assess the Efficacy and Safety of Brazikumab in Participants with Moderately to Severely Active Crohn's Disease (INTREPID Lead-In)

Short Title: 52-Week Phase 2b/3 Crohn's Disease Study

Rationale:

Crohn's disease, a chronic transmural inflammatory disease of unknown etiology, most commonly affects the distal ileum and colon, but may occur in any part of the gastrointestinal tract and has the potential for systemic and extraintestinal complications. Current treatment options for patients with moderately to severely active CD is usually guided by severity of disease, location, and presence of additional clinical complications such as extraintestinal manifestations and malabsorption. The therapeutic options currently available include 'conventional treatments,' which include antibiotics, CS, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), and biologic treatments such as TNFα antagonists, integrin antagonists, and IL-12 and IL-23 antagonists.

Despite the availability of these treatments, there is still a need for novel therapies for the treatment of CD due to the evidence that not all patients will respond or maintain their response to the available treatment options. Approximately 13 to 40% of patients do not respond initially to TNFα antagonists, and approximately 23 to 46% of patients lose response over time. Treatment options for patients who are refractory to standard therapies are limited, and, despite treatment with available therapies, morbidity and CD complications often lead to surgery, thus representing a burden of disease that sufficiently warrants new therapies.

Recent studies have demonstrated that patients with IBD, specifically CD or ulcerative colitis, have increased human IL-22 expression in the colonic tissue (Andoh et al, 2005; Brand et al, 2006), and serum IL-22 concentrations in patients with CD have been found to correlate strongly with disease activity. In a Phase 2a study evaluating the efficacy and safety of brazikumab in participants with moderately to severely active CD who failed treatment with an anti-TNFα agent, post hoc analysis revealed a statistically significant treatment by Baseline serum IL-22 concentration interaction ($p = 0.04$) 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 serum IL-22 concentration (Sands et al, 2017). In addition, it was observed that the group of participants receiving brazikumab had a substantial reduction in serum IL-22 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).

Therefore, serum IL-22 concentration may have clinical relevance as a potential predictive in vitro companion diagnostic device for safe and effective use in patients with CD and could potentially enable identification of a targeted subpopulation of patients who are most likely to benefit from treatment with brazikumab over other currently available biological treatments.

The primary goal of this study is to demonstrate the efficacy and safety of brazikumab in participants with moderately to severely active CD and demonstrate the clinical utility of serum IL-22 concentrations as a predictive BM to prospectively identify participants who are most likely to benefit from treatment with brazikumab.

Brazikumab is being developed as a treatment for CD to reduce intestinal inflammation and improve signs and symptoms. This operationally seamless, Phase 2b/3 study design combines, within a single study, objectives that have traditionally been addressed in separate studies, and may substantially reduce the time that would have occurred between the studies had they been conducted separately. The operationally seamless design allows for a confirmatory study to proceed after the Phase 2b study, but the data from the 2 studies are kept distinct. Stage 1 of this study represents the Phase 2b study, and Stage 2 of this study represents the confirmatory Phase 3 study. The sponsor will commence Stage 2 after all participants are randomized into Stage 1, have completed the Week 12 Induction Period, and the data from the Stage 1 primary analysis have been fully evaluated. The sponsor will amend the Stage 2 part of the protocol prior to initiating this stage of the study.

This study will be conducted in 2 distinct stages and will assess:

- The efficacy and safety of brazikumab, the evaluation and establishment of a clinical cutoff for serum IL-22 concentration as a potentially predictive in vitro companion diagnostic device, and brazikumab exposure response (Stage 1) AND
- The efficacy and safety of brazikumab compared to Humira in participants who are BM+ (Stage 2)

Objectives and Endpoints

The primary and secondary objectives, endpoints, and estimands for Stage 1 are presented below:

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
Primary				
To compare the efficacy of brazikumab with that of placebo to achieve CDAI remission at Week 12	• CDAI remission at Week 12: – CDAI score < 150	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 12: – discontinue treatment prematurely for any reason – take rescue treatment or meet the rescue criteria – use prohibited treatment	Percentage of participants achieving the endpoint
Secondary				
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic response, CDAI response, and clinical remission at Week 12	• **Key Secondary**: Endoscopic response at Week 12: – Minimum of 50% decrease from Baseline in SES-CD total score • Clinical remission at Week 12: – 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 • CDAI response at Week 12: – CDAI score of < 150 points or CDAI reduction from Baseline of ≥ 100 points	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 12: – discontinue treatment prematurely for any reason – take rescue treatment or meet the rescue criteria – use prohibited treatment	Same as primary

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
To compare the efficacy of brazikumab with that of placebo to achieve sustained CDAI remission, CDAI response, endoscopic response, and clinical remission at both Week 12 and Week 52	• CDAI remission at both Week 12 and Week 52 • CDAI response at both Week 12 and Week 52 • Endoscopic response at both Week 12 and Week 52 • Clinical remission at both Week 12 and Week 52	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 52: – discontinue treatment prematurely for any reason – take rescue treatment or meet the rescue criteria – use prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo in achieving CDAI remission, CDAI response, endoscopic response, SES-CD total score of 0-2, endoscopic remission, and clinical remission at Week 52	• Endoscopic remission at Week 52 – 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 • Clinical remission at Week 52 • CDAI response at Week 52 • CDAI remission at Week 52 • Endoscopic response at Week 52 • SES-CD total score of 0-2 at Week 52	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events Week 12: – discontinues treatment prematurely for any reason – take rescue treatment or meet the rescue criteria – use prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic response at Week 12 and endoscopic remission at Week 52	• Endoscopic response at Week 12 and endoscopic remission at Week 52	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 52: – discontinue treatment prematurely for any reason – take rescue treatment or meet the rescue criteria – use prohibited treatment	Same as primary

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
To evaluate the PK and immunogenicity of brazikumab in participants with CD	• Population PK model of serum concentrations of brazikumab and analysis for serum anti-brazikumab antibodies	Participants with moderately to severely active CD		
To characterize the exposure-response relationships of brazikumab	• Exposure-response model linking primary endpoint to metrics of model-predicted individual brazikumab exposures	Participants with moderately to severely active CD		
To establish the serum IL-22 concentration Baseline clinical cutoff for its value in predicting the efficacy of brazikumab	• Exploration of relationship of Baseline serum IL-22 concentration with efficacy of brazikumab at Week 12, and establishment of the serum IL-22 concentration clinical cutoff to stratify participants in Stage 2 through CDAI remission and endoscopic response at Week 12.	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 12: – discontinues treatment prematurely for any reason – take rescue treatment or meet the rescue criteria – Use prohibited treatment	Differential approach method
To evaluate the safety and tolerability of brazikumab in participants with CD	• AEs, clinical laboratory values, vital signs, physical exams, ECGs	Participants with moderately to severely active CD		
All primary, secondary, and exploratory efficacy endpoints will be evaluated in the BM+ and BM- populations as well				

AE = adverse event; AP = abdominal pain; BM+ = biomarker serum IL-22 concentrations at or above a pre-established cutoff; BM- = biomarker serum IL-22 concentrations below a pre-established cutoff; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; ECG = electrocardiogram; IL-22 = interleukin-22; LSF = loose stool frequency; NRI = non-responder imputation; PK = pharmacokinetics; SES-CD = Simple Endoscopic Score for Crohn's Disease.

For additional objectives and endpoints, see Section 3 of the protocol. Objectives and endpoints for Stage 2 are presented in Appendix F 4.

Overall Design

Global, multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group, operationally seamless Phase 2b/3, 52-week study.

This protocol comprises 2 distinct 52-week study stages:

Stage 1: A Phase 2b study to evaluate the dose-response relationship to select CCI brazikumab doses for continued development and to determine the serum IL-22 concentration cutoff for use in stratification of BM+ and BM- participants (serum IL-22 concentrations at/above or below a pre-established cutoff) in Stage 2. Participants in Stage 1 are not eligible for enrollment in Stage 2.

Stage 2: A Phase 3 study to evaluate the safety and efficacy of brazikumab compared with Humira® in participants who are BM+, and to validate the clinical utility of serum IL-22 concentrations as a predictive BM of efficacy of brazikumab in participants with CD. Stage 2 Screening will be initiated upon completion of Stage 1 primary (Week 12) analyses. Investigators, participants, and sponsor personnel will remain blinded to BM status (eg, BM+ or BM-) for the duration of the study.

Participants who complete either Stage 1 or Stage 2 or have an incomplete response to Induction treatment are eligible to enroll in an open-label extension study.

Disclosure Statement: This is a global, multicenter (up to CCI sites), randomized, double-blind, placebo- or active-controlled, parallel-group, operationally seamless, Phase 2b/3, 52-week study. Stage 1 includes 3 treatment arms, and Stage 2 includes up to 3 treatment arms.

Number of Participants:

Approximately CCI will be randomized to Stage 1 of the study.

Approximately CCI, stratified 2:1 by BM+/BM- status, will be randomized to 1 of the 3 treatment groups in Stage 2.

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

Intervention Groups and Duration:

Stage 1

- Treatment Groups:
  - Brazikumab high dose: CCI brazikumab CCI on Days 1, 29, and 57, followed by CCI brazikumab CCI on Day 85 and every 4 weeks through Week 48
  - Brazikumab low dose: CCI brazikumab CCI on Days 1, 29, and 57, followed by CCI brazikumab CCI on Day 85 and every 4 weeks through Week 48
  - Placebo: CCI placebo on Days 1, 29, and 57, followed by CCI placebo on Day 85 and every 4 weeks through Week 48

Study Duration: Following a Screening Period of up to 5 weeks, the study duration is up to 66 weeks, consisting of a 52-week Treatment Period (last dose of study intervention is at Week 48) and an 18-week post-last brazikumab/placebo dose Safety Follow-up Period. For participants who qualify and enroll into an open-label extension study of brazikumab, the Safety Follow-up Period will not be applicable.

Stage 2

Stage 2 Screening will be initiated upon completion of the Stage 1 primary (Week 12) analysis results.

- Treatment Groups:
  - Brazikumab high dose: CCI brazikumab CCI on Days 1, 29, and 57, followed by CCI brazikumab CCI on Day 85 and every 4 weeks through Week 48
  - Brazikumab low dose: CCI brazikumab CCI on Days 1, 29, and 57, followed by CCI brazikumab CCI on Day 85 and every 4 weeks through Week 48
  - Humira: CCI Humira CCI on Day 1, CCI on Day 15, and CCI beginning on Day 29 and every 2 weeks through Week 50

Study Duration: Following a 4-week Screening Period, the study duration is up to 66 weeks, consisting of a 52-week Treatment Period and an 18-week post-last brazikumab/brazikumab placebo dose Safety Follow-up Period. For participants who qualify and enroll into an open-label extension study of brazikumab, the Safety Follow-up Period will not be applicable.

Data Monitoring Committee: No

Statistical Methods

For this operationally seamless Phase 2b/3 study, Stage 1 is a dose-ranging, BM+/BM- identification, learning phase, and Stage 2 is a confirmatory phase serving as one of the Phase 3 confirmatory efficacy and safety studies.

Brazikumab and placebo CDAI remission responder rates, after a 12-week induction treatment period, are assumed to be CCI and CCI, respectively. Based on these assumptions, a sample size of 85 participants per brazikumab dose and 51 in placebo provides at least 80% power to detect a difference vs. placebo in the CDAI remission responder rate using continuity-corrected Mantel-Haenszel (Cochran) test of odds ratio=1 with 2 strata using a 2-sided 0.05 level test. This sample size will also provide at least CCI power to detect a difference in brazikumab and placebo endoscopic response responder rates, after a 12-week induction treatment period, assuming the responder rates are set to CCI and CCI, respectively.

Analysis populations for Stage 1 include the Full Analysis Set (all participants who are randomized to a Stage 1 treatment group), the Safety population (all participants who receive ≥ 1 administration of Stage 1 study intervention), and the PK population (all participants who receive at least 1 dose of study intervention and have at least 1 PK sample containing detectable brazikumab concentrations).

Key objectives for Stage 1 are to examine the efficacy and safety of brazikumab, evaluate serum IL-22 concentration as a potentially predictive BM, and evaluate the brazikumab exposure response. Stage 1 will also serve to select an appropriate serum IL-22 concentration cutoff value to define the BM+ and BM- subpopulations, and to make a go/no-go decision before proceeding to Stage 2.

The Stage 1 primary efficacy endpoint percentage of participants achieving CDAI remission at Week 12, will be analyzed using a Cochran-Mantel-Haenszel test controlling for 2 randomization stratification factors (status of prior biologic use and current CS use [yes or no] at randomization). In addition, the observed response proportions will be provided by treatment group.

To check the impact of baseline biomarkers to each primary efficacy endpoint, a logistic regression model will be performed controlling for 2 randomization stratification factors (status of prior biologic use and current CS use [yes or no] at randomization), and baseline serum IL-22 values as covariates. This sensitivity analysis is for the same primary estimand.

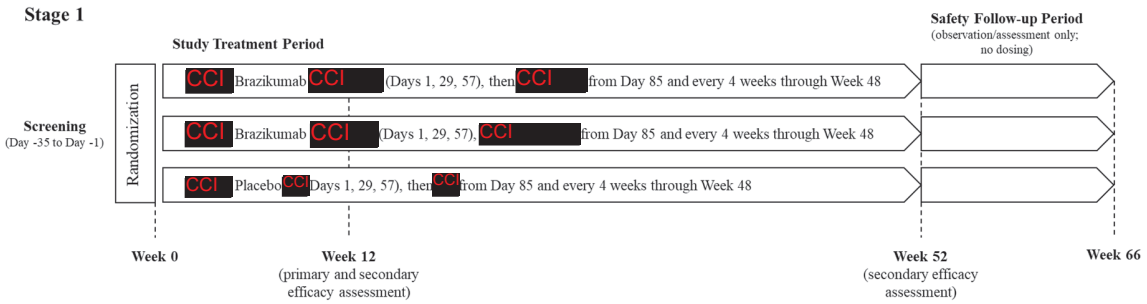
The key and all secondary binary endpoints will be analyzed in the same way as the primary endpoint. Secondary continuous endpoints will be analyzed using mixed models. Immunogenicity and brazikumab serum concentrations will be analyzed by descriptive statistics.

Stage 1 safety data will be summarized descriptively using the Safety Population. The safety parameters will include AEs, clinical laboratory, vital sign, physical exams, and ECG parameters. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of study intervention will be used as the Baseline for all analyses of that safety parameter. Continuous variables will be summarized by

the number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

1.2 Schema

Figure 1 Study Design (Stage 1)



BM+ = biomarker serum IL-22 concentrations at or above a pre-established cutoff; BM- = biomarker serum IL-22 concentrations below a pre-established cutoff; CCI [redacted]

1.3 Schedule of Activities

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

Screening is up to a 35-day period (+3 days if needed for ileocolonoscopy results); however, the CDAI cannot be completed prior to Day -14 and must be reviewed for eligibility prior to the ileocolonoscopy.

For Stage 1, separate SoAs are presented for the Screening Period (Table 1), the Treatment Period (Table 2), and Early Termination/Safety Follow-up Period (Table 3), and for the PROs (Table 4).

For Stage 2, the SoA is provided in Appendix F 2.

Table 1 Schedule of Activities – Screening (Stage 1)

	Screening up to 35 days (+3 days)				
Procedure	**Screening Visit 1**	**Screening Visit 2**	**Ileocolonoscopy**	**Notes**	**Details in CSP Section or Appendix**
Day	**-35 to -15**	**After Day -14**	**After Day -12**		
Visit	**SV1**	**SV2**	**Ileocolonoscopy**	**A minimum of 2 consecutive weeks with evaluable evening diary data (at least 4 days of evening diary data in each 7-day period) is required immediately prior to Screening Visit 2.**	
Informed consent	X				5.1 and 8.1.3.5
Inclusion and exclusion criteria	X	X			5.1 and 5.2
Demography	X				
Medical history (incudes surgical history and CD history)	X			Includes substance use	
Height	X				8.2.2
Physical exam including abdominal exam, EIM assessment for CDAI score, fistula exam (as applicable)	X	X		Physical exam at SV2 can be a focused exam to include components of CDAI score	5.1, 5.2, and 8.2.1
12-lead ECG	X				8.2.3
Vital signs, weight	X	X		Weight included in CDAI score	8.2.2
Laboratory assessments				Laboratory assessments may be retested once per investigator's discretion.	
Clinical chemistry, hematology, CRP	X				8.2.4
Hematocrit, CRP		X		Hematocrit is included in CDAI score. If SV2 hematocrit is not available (eg, hemolyzed sample), SV1 hematocrit may be used to calculate CDAI eligibility score.	8.2.4
Serum pregnancy test (WOCBP only)	X			For women not of childbearing potential, FSH if applicable	Inclusion criteria #7 and #8 and 8.2.4
Hepatitis B and C and HIV screening	X				8.2.4
Urinalysis	X				8.2.4

	Screening up to 35 days (+3 days)				
Procedure	**Screening Visit 1**	**Screening Visit 2**	**Ileocolonoscopy**	**Notes**	**Details in CSP Section or Appendix**
Day	**-35 to -15**	**After Day -14**	**After Day -12**		
Visit	**SV1**	**SV2**	**Ileocolonoscopy**	**A minimum of 2 consecutive weeks with evaluable evening diary data (at least 4 days of evening diary data in each 7-day period) is required immediately prior to Screening Visit 2.**	
QuantiFERON-TB test	X			TB worksheet is to be completed when QFT-TB testing is performed. Participants with an indeterminate QFT-TB test result are to have the test repeated during Screening.	Inclusion Criterion #6 and Appendix G
Chest x-ray (if required)	X				Inclusion Criterion #6 and Appendix G
Serum sample for IL-22		X			8.5
Stool sample for *C. difficile*	X			Must be collected prior to bowel prep for ileocolonoscopy	8.2.4
Stool sample for fecal calprotectin and fecal lactoferrin		X		Must be collected prior to bowel prep for ileocolonoscopy	8.6.1
Efficacy assessments					
Provide PRO device and instructions	X				Table 4 and 8.1.3.1
Check ePRO compliance		X		It is recommended that the site check compliance between SV1 and SV2.	Table 4, 8.1.3.1, and 8.1.3.3
Select visit date on the handheld device for the scheduled visit assessments; confirm that all PRO assessments have been completed		X			Table 4 and 8.1.3.4
Calculate PRO (LSF, AP, temperature, general well-being) and CDAI eligibility scores (investigator or designee)		X		At least 4 days of evening diary data in the 7-day period used for CDAI.	Table 4 and 8.1.1.4

	Screening up to 35 days (+3 days)				
Procedure	**Screening Visit 1**	**Screening Visit 2**	**Ileocolonoscopy**	**Notes**	**Details in CSP Section or Appendix**
Day	**-35 to -15**	**After Day -14**	**After Day -12**		
Visit	**SV1**	**SV2**	**Ileocolonoscopy**	**A minimum of 2 consecutive weeks with evaluable evening diary data (at least 4 days of evening diary data in each 7-day period) is required immediately prior to Screening Visit 2.**	
Ileocolonoscopy, including terminal ileum and colon mucosal biopsies			X	Ileocolonoscopy must be within 12 days (± 3 days) of randomization; SES-CD score is assessed by central reader	8.1.1.1
AEs/SAEs	X	X			8.3
Concomitant medication	X	X			6.6

AE = adverse event; AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CSP = clinical study protocol; ECG = electrocardiogram; EIM = extraintestinal manifestation; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; IL-22 = interleukin-22; CCI [redacted]; LSF = loose stool frequency; PRO = patient-reported outcome; QFT-TB = QuantiFERON-TB test; SAE = serious adverse event; SES-CD = Simple Endoscopic Score for Crohn's Disease; SV = Screening Visit; TB = tuberculosis; WOCBP = women of childbearing potential.

Table 2 Schedule of Activities - Treatment Period (Stage 1)

Procedure	Induction Period					Maintenance Period (weeks)										UNS[b]	ET or E/D	Notes	Details in CSP Section or Appendix
Week	W0	W2	W4	W8	W12	W16[a]	W20[a]	W24	W28[a]	W32[a]	W36	W40	W44[a]	W48[a]	W52				
Study Day[c]	1	15	29	57	85	113	141	169	197	225	253	281	309	337	365				
Visit Window (days)		±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7				
Efficacy assessments																			
Review ePRO compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	eDiary assessment at home and at site	Table 4, 8.1.3.1, and 8.1.3.3
Select visit date on the handheld device for the scheduled visit assessments; confirm that all PRO assessments have been completed					X			X				X			X		X		Table 4 and 8.1.3.4
CDAI (investigator or designee)	X	X	X	X	X			X				X			X	X	X	CDAI is a calculated score. CDAI should be assessed anytime rescue treatment is considered.	8.1.1.4
Remind participants selected for qualitative sub-study interview														X					8.1.3.5
Ileocolonoscopy, including terminal ileum and colon mucosal biopsies [d]					X										X	X	X	SES-CD assessed by central reader.	8.1.1.1

Procedure	Induction Period					Maintenance Period (weeks)										UNS[b]	ET or E/D	Notes	Details in CSP Section or Appendix
Week	W0	W2	W4	W8	W12	W16[a]	W20[a]	W24	W28[a]	W32[a]	W36	W40	W44[a]	W48[a]	W52				
Study Day[c]	1	15	29	57	85	113	141	169	197	225	253	281	309	337	365				
Visit Window (days)		±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7				
Safety assessments																			
Physical exam including abdominal exam, EIM assessment for CDAI score, fistula exam (as applicable)	X	X	X	X	X			X				X			X	X	X	Contributes to CDAI	8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2.2
Weight	X	X	X	X	X			X				X			X	X	X	Assessed as part of CDAI.	8.2.2
12-lead ECG	X				X			X				X			X		X		8.2.3
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.3
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.6
Assessment of injection-site reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.3.10.1
Healthcare resource utilization	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.8
Laboratory assessments																			
Clinical chemistry, hematology, urinalysis, CRP	X		X		X			X				X			X	X	X		8.2.4
Hematocrit, CRP		X		X														Hematocrit is assessed as part of CDAI.	8.1.1.4

Procedure	Induction Period					Maintenance Period (weeks)										UNS[b]	ET or E/D	Notes	Details in CSP Section or Appendix
Week	W0	W2	W4	W8	W12	W16[a]	W20[a]	W24	W28[a]	W32[a]	W36	W40	W44[a]	W48[a]	W52				
Study Day[c]	1	15	29	57	85	113	141	169	197	225	253	281	309	337	365				
Visit Window (days)		±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7				
Urine pregnancy test performed locally (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2.4
Biomarkers sampling																			
Predose PK blood sample	X		X	X	X	X		X				X						Note the exact time and date of sampling.	8.5.1
PK blood sample (post-dose or flexible)	X	X		X											X	X	X	Day 1: 2 samples, at 1 hour and 2-4 hours post-dose. Day 57: 1 sample at 1 hour post-dose. On days without dosing, sampling time is flexible (but has to be recorded).	8.5.1
Serum for ADA	X				X			X				X			X	X	X		8.5.2
Serum for IL-22	X	X	X	X	X			X				X			X		X	Sample to be collected before dosing.	8.6.1
CCI	X	X	X	X	X			X				X			X		X	Sample to be collected before dosing.	8.6.1

Procedure	Induction Period					Maintenance Period (weeks)										UNS[b]	ET or E/D	Notes	Details in CSP Section or Appendix
Week	W0	W2	W4	W8	W12	W16[a]	W20[a]	W24	W28[a]	W32[a]	W36	W40	W44[a]	W48[a]	W52				
Study Day[c]	1	15	29	57	85	113	141	169	197	225	253	281	309	337	365				
Visit Window (days)		±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7				
Blood for investigative biomarkers	X	X	X	X	X			X				X			X		X		8.6.1
PAXgene for whole blood RNA transcript profiling	X				X										X		X	Do not collect if whole blood transfusion within 120 days.	8.6.1
Genomics Initiative optional, exploratory genetic sample	X																	Do not collect if whole blood transfusion within 120 days.	8.7 and Appendix D
Stool for fecal calprotectin, fecal lactoferrin, and exploratory biomarkers	X				X			X				X			X	X	X	All stool tests should be collected prior to start of bowel prep for visits where ileocolonoscopy is needed.	8.6.1
Investigational product administration																			
Randomization	X																		6.4
CCI																			6.1

ADA = anti-drug antibodies; AE = adverse event; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; CSP = clinical study protocol; ECG = electrocardiogram; E/D = Early Study Intervention Discontinuation; EIM = extraintestinal manifestation; ePRO = electronic PRO assessments; ET = early termination; HIV = human immunodeficiency virus; IL-22 = interleukin-22; CCI [redacted] PK = pharmacokinetics; PRO = patient-reported outcome; QFT-TB = QuantiFERON-TB test; RNA = ribonucleic acid; SAE = serious adverse event; CCI [redacted]; SES-CD = Simple Endoscopic Score for Crohn's Disease; TB = tuberculosis; UNS = unscheduled; W = week; WOCBP = women of childbearing potential.

[a] If the participant opts for home administration, these visits can be performed remotely (home health agency and telephone/telemedicine content).

[b] Unscheduled Visit – not all assessments indicated for the Unscheduled Visit need to be performed. The assessments are to be performed at the discretion of the investigator, as clinically indicated. Assessments that are performed as part of an Unscheduled Visit may be used for evaluation of rescue criteria (eg, CDAI and ileocolonoscopy).

[c] The visit schedule will always be calculated from the Randomization Visit date.

[d] Endoscopies that qualify for rescue criteria may be used for ET as applicable. Daily PRO data collected 7 days prior to bowel prep will be used to calculate CDAI.

Table 3 Schedule of Activities - Safety Follow-up Period (Stage 1)

Procedure	18-Week Follow-up		Notes	Details in CSP Section or Appendix
Visit type	Follow-up 1	Follow-up 2		
Week	8 weeks after the last dose	18 weeks after the last dose		
Visit Window	± 7 days	± 7 days		
Safety assessments				
AEs/SAEs	X	X		8.3
Concomitant medications	X	X		6.6
Assessment of injection-site reactions	X	X		8.3.10.1
Physical examination	X	X		8.2.1
12-lead ECG	X	X		8.2.3
Vital signs, weight	X	X		8.2.2
Laboratory assessments				
Serum chemistry, hematology, C-reactive protein, urinalysis	X	X		8.2.4
Urine pregnancy test performed locally (WOCBP only)	X	X		8.2.4
Biomarkers sampling				
PK blood sample	X	X		8.5.1
Serum for ADA	X	X		8.5.2
Serum for IL-22	X	X		8.6.1
CCI [redacted]	X	X		8.6.1
Blood for investigative biomarkers	X	X		8.6.1
Stool for fecal calprotectin, fecal lactoferrin, and exploratory biomarkers	X			8.6.1

ADA = anti-drug antibodies; AE = adverse event; CSP = clinical study protocol; ECG = electrocardiogram; IL-22 = interleukin-22; CCI [redacted] PK = pharmacokinetics; SAE = serious adverse event; WOCBP = women of childbearing potential.

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

Table 4 Schedule of Activities – PRO Assessments (in clinic and at home) (Stage 1)

Instruments	Schedule
Event-Driven: Bowel Movement eDiary	Every day from SV1 through W52; real-time entry after every bowel movement
Daily PRO: Evening Diary: • CDAI items (LSF, AP, temperature, general well-being) • NRS items (AP, fatigue, tiredness, weakness, lack of energy, joint pain) • Entry of additional bowel movements not reported in real time	Every evening [a]. First assessment at home on the day of SV1 and continuing through W52
Periodic PROs: IBDQ, FACIT-Fatigue, PGI-S	At site at SV2, W12, W24, W40, W52; also complete at ET or E/D
Periodic PROs: PGI-C	At site on W12, W24, W40, W52; also complete at ET or E/D
Periodic PROs EQ-5D-5L, SF-36v2	At site at SV2, W12, W24, and W52; also complete at ET or E/D
Other assessments: Participant qualitative interview	One-on-one phone interview at Week 52. Select sites only: Participants will be introduced to the sub-study during the informed consent process using the participant communication materials. Remind consented participants of upcoming interview in Participant Qualitative Interview Sub-study.

AP = abdominal pain; CDAI = Crohn's Disease Activity Index; E/D = Early Study Intervention Discontinuation; eDiary = electronic diary; EQ-5D-5L = European Quality of Life-5 Dimensions; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; IBDQ = Inflammatory Bowel Disease Questionnaire; LSF = loose stool frequency; NRS = Numerical Rating Scale; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PRO = patient-reported outcome; SF-36v2 = 36-item Health Survey Version 2; SV = Screening Visit; W = week.

[a] Evening is defined as 18:00 to 23:59.

2 INTRODUCTION

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 (Burger and Travis, 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 the ages of 15 to 30 and 60 to 80, although persons of any age may be affected. Commonly used medical therapies include aminosalicylates, (including sulfasalazine and mesalamine), systemic CS, immunosuppressive agents (eg, azathioprine and methotrexate), antibacterial agents, and biologic agents (eg, adalimumab [Humira®, Abbvie, Inc, North Chicago, IL (Humira Package Insert)], 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 ulcerative colitis). In preclinical models and studies in patients, anti-IL-12/23 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-23 p19 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, Brazikumab, 2020).

2.1 Study Rationale

Current treatment options for patients with moderately to severely active CD are usually guided

by severity of disease, location, and presence of additional clinical complications such as extraintestinal manifestations and malabsorption. The therapeutic options currently available include 'conventional treatments,' which include antibiotics, CS, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), and biologic treatments such as TNFα antagonists, integrin antagonists, and IL 12 and IL 23 antagonists. Treatment options for patients who lose response or are refractory to standard therapies are limited.

Recent studies have demonstrated that patients with IBD, specifically CD or ulcerative colitis, have increased human IL-22 expression in the colonic tissue (Andoh et al, 2005; Brand et al, 2006), and serum IL-22 concentrations in patients with CD have been found to correlate strongly with disease activity. In a Phase 2a study evaluating the efficacy and safety of brazikumab in participants with moderately to severely active CD who failed treatment with an anti-TNFα agent, post hoc analysis revealed a statistically significant treatment by Baseline interaction for the serum IL-22 concentration ($p = 0.04$) 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 serum IL-22 concentration (Sands et al, 2017). In addition, it was observed that the group of participants receiving brazikumab had a substantial reduction in serum IL-22 concentration (81% mean reduction at Week 8 compared with Baseline), in contrast to the slight increase observed for the group of participants receiving placebo (6% mean increase) (data on file).

Therefore, serum IL-22 concentrations may have clinical relevance as a potential predictive BM for safe and effective use in patients with CD. The BM could potentially enable identification of a targeted subpopulation of patients who are most likely to experience a favorable clinical outcome with brazikumab treatment and reduce unnecessary exposure to subgroups not deriving optimal benefit.

The ultimate goal of this operationally seamless Phase 2b/3 study is to demonstrate the efficacy and safety of brazikumab in participants with moderately to severely active CD and demonstrate the clinical utility of serum IL-22 concentrations as a predictive BM to prospectively identify participants who are most likely to benefit from treatment with brazikumab.

Brazikumab is being developed as a treatment for CD to reduce intestinal inflammation and improve signs and symptoms. This operationally seamless, Phase 2b/3 study design combines, within a single protocol, objectives that have traditionally been addressed in separate studies, and is intended to substantially reduce the time that would have occurred between the studies had they been conducted separately. The operationally seamless design allows for a confirmatory study to proceed after the Phase 2b study, but the data from the 2 studies are kept distinct. Stage 1 of this study represents the Phase 2b study, and Stage 2 is a Phase 3, confirmatory, marketing registration study. The sponsor will commence Stage 2 after all participants are randomized into Stage 1 and have completed 12 weeks induction treatment and after the Stage 1

primary analysis.

2.2 Background

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

Studies in patients have demonstrated that IL-23 is upregulated in cells and target tissues of CD and ulcerative colitis while IL-12 is not (Schmidt et al, 2005). Similar observations have been reported in psoriatic skin lesions (Lee et al, 2004), dendritic cells from patients with multiple sclerosis (Vaknin-Dembinsky et al, 2006), and active lesions from patients with multiple sclerosis (Li et al, 2007). Genome wide association studies in CD and psoriasis patients showed significant association between polymorphisms in the unique IL-23 receptor component and disease (Cargill et al, 2007; Duerr et al, 2006). Furthermore, allelic variants of IL-23 receptor have shown significant correlation with the frequency of ulcerative colitis (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 Investigator's Brochure (Brazikumab, 2020) for details.

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

The nonclinical safety of brazikumab was evaluated in several studies with cynomolgus monkeys as the pharmacologically relevant species. In a safety pharmacology study, no brazikumab related effects were noted on evaluated cardiovascular, respiratory, or neurobehavioral

parameters after single CCI In studies of 2 weeks, 3 months, and 6 months duration in cynomolgus monkeys, brazikumab was generally well tolerated when administered IV or SC. 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 once weekly for 26 weeks had no toxicologically significant effects on study parameters. Approximately CCI of the brazikumab-treated animals developed binding ADA during the dosing period and CCI of animals at CCI developed binding ADA in the recovery period. No neutralizing antibodies were detected in animals that tested positive for binding ADA, and binding ADA did not decrease brazikumab exposure. The no observed adverse effect level following 26 weekly CCI of brazikumab was CCI the maximum dose tested, corresponding to a C_{max} of CCI and an AUC of CCI on Study Day 176.

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

The first study with brazikumab was Study 20080767 (conducted by Amgen), a 2-part, single dose study in healthy participants (Part A) and participants with moderate to severe psoriasis (Part B). A total of 73 participants was administered brazikumab as a single CCI dose CCI CCI or single CCI dose CCI or placebo. Overall, brazikumab demonstrated an acceptable safety profile that supported further clinical development. In participants with psoriasis, CCI and 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 PD of brazikumab in healthy participants (Part A) and these same parameters, plus efficacy, in participants with mild to severe CD (Part B). A total of 40 participants were randomized and received at least CCI of investigational product (brazikumab or placebo) in Part A and an additional 8 participants with CD were randomized into Part B of the study and received investigational product (brazikumab or placebo). No TESAEs or deaths were reported, and no participant withdrew from the study because of a TEAE.

Study CD-IA-MEDI2070-1147 was a 2-part, Phase 2a study comprising a 12-week, double-blind, placebo-controlled period followed by a 100-week, open-label period to evaluate the short-term efficacy and the short- and long-term safety of brazikumab in participants with moderate to severe active CD who have failed or are intolerant to anti-TNFα therapy. During the double-blind period of the study, participants received a fixed CCI dose 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 investigational product during the double-blind period of the study, 112 participants had completed study participation through Week 8 (primary efficacy timepoint to assess efficacy) and 104 participants had completed the double-blind period to Week 12 and entered the open-label period of the study. All 104 participants received at least CCI of CCI brazikumab in the open-label period and 93 participants (89.4%) completed their Week 24 visit and 57 participants (54.8%) completed the 100-week open-label period.

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

The median serum IL-22 concentration at Baseline for the entire study population was 15.6 pg/mL. In the analyses of CDAI clinical response and CDAI remission stratified by the median Baseline serum IL-22 concentration for the population (ie, < 15.6 pg/mL and ≥ 15.6 pg/mL), it was observed that among participants with Baseline serum IL-22 concentrations of ≥ 15.6 pg/mL, the brazikumab-treated participants had an increased likelihood of CDAI clinical response and clinical remission at Week 8. In the subgroup of participants meeting this threshold, the placebo-adjusted CDAI clinical response rate was CCI for brazikumab versus placebo) and the placebo-adjusted CDAI clinical remission rate was CCI for brazikumab versus placebo). In contrast, among participants with Baseline serum IL-22 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 CD-IA-MEDI2070-1147 CCI of brazikumab CCI and CCI (brazikumab CCI show 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 and CCI and multiple CCI of CCI followed by an CCI of CCI brazikumab or placebo were administered to 3 groups of 16 male and female study participants (8 Japanese and 8 White). A single CCI dose of brazikumab in a 30-minute infusion 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 induction doses will be administered in a CCI

2.3 Benefit/Risk Assessment

Medical therapy of IBD remains complex with the need to individualize treatment based on various clinical factors and prior treatments. The overall goal of treatment in IBD is diminishing inflammation and improving signs and symptoms of IBD. There are limited options for patients who have an intolerance or inadequate response to available biological treatment and continue to have evidence of active CD. 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, ulcerative colitis, 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 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 treatment-emergent AE and there were no Grade 4

(life-threatening) or Grade 5 (fatal) treatment-emergent AEs. Crohn's disease was the most frequently reported SAE. No malignancies were reported and no MACE occurred. Clinically significant infections were mostly urinary tract infection, vulvovaginal mycotic infection, sinusitis, bronchitis, and upper respiratory tract infection. No clinically significant trends were observed in the clinical laboratory evaluations, vital sign measurements, ECGs, or physical findings.

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

- Serious and medically significant infections
- Malignancies
- Vaccine complications
- 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 an IL-12 inhibitor, its safety profile is expected to be free of IL-12 inhibitory side effects.

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

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

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

3 OBJECTIVES AND ENDPOINTS

Table 5 Objectives and Endpoints: Stage 1

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
Primary				
To compare the efficacy of brazikumab with that of placebo to achieve CDAI remission at Week 12	• CDAI remission at Week 12: – CDAI score < 150	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 12: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Percentage of participants achieving the endpoint
Secondary				
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic response, CDAI response, and clinical remission at Week 12	• **Key Secondary**: Endoscopic response at Week 12: – Minimum of 50% decrease from Baseline in SES-CD total score • Clinical remission at Week 12: – 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 • CDAI response at Week 12: – CDAI score of < 150 points or CDAI reduction from Baseline of ≥ 100 points	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 12: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
To compare the efficacy of brazikumab with that of placebo to achieve sustained CDAI remission, CDAI response, endoscopic response, and clinical remission at both Week 12 and Week 52	• CDAI remission at both Week 12 and Week 52 • CDAI response at both Week 12 and Week 52 • Endoscopic response at both Week 12 and Week 52 • Clinical remission at both Week 12 and Week 52	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 52: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo in achieving CDAI remission, CDAI response, endoscopic response, SES-CD total score of 0-2, endoscopic remission, and clinical remission at Week 52	• Endoscopic remission at Week 52: – 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 • Clinical remission at Week 52 • CDAI response at Week 52 • CDAI remission at Week 52 • Endoscopic response at Week 52 • SES-CD total score of 0-2 at Week 52	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events week 12: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve endoscopic response at Week 12 and endoscopic remission at Week 52	• Endoscopic response at Week 12 and endoscopic remission at Week 52	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 52: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
To evaluate the PK and immunogenicity of brazikumab in participants with CD	• Population PK model of serum concentrations of brazikumab and analysis for serum anti-brazikumab antibodies	Participants with moderately to severely active CD		
To characterize the exposure-response relationships of brazikumab	• Exposure-response model linking primary endpoint to metrics of model-predicted individual brazikumab exposures	Participants with moderately to severely active CD		
To establish the serum IL-22 concentration Baseline clinical cutoff for its value in predicting the efficacy of brazikumab	• Exploration of relationship of Baseline serum IL-22 concentration with efficacy of brazikumab at Week 12, and establishment of the serum IL-22 concentration clinical cutoff to stratify participants in Stage 2 through CDAI remission and endoscopic response at Week 12.	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 12: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Differential approach method.
To evaluate the safety and tolerability of brazikumab in participants with CD	• AEs, clinical laboratory values, vital signs, physical exams, ECGs	Participants with moderately to severely active CD		

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
Additional				
To compare the efficacy of brazikumab with that of placebo to achieve CS-free (for the last 12 weeks before the assessment at Week 52) CDAI remission, CDAI response, endoscopic remission, endoscopic response, SES-CD total score of 0-2, and clinical remission at Week 52	• CS-free CDAI remission at Week 52 • CS-free CDAI response at Week 52 • CS-free endoscopic remission at Week 52 • CS-free clinical remission at Week 52 • CS-free endoscopic response at Week 52 • CS-free SES-CD total score of 0-2 at Week 52	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 52: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve CS-free CDAI remission, CDAI response, endoscopic remission, endoscopic response, SES-CD total score of 0-2, and clinical remission at Week 52 for participants taking CS at Baseline	• CS-free CDAI remission at Week 52 for participants taking CS at Baseline • CS-free CDAI response at Week 52 for participants taking CS at Baseline • CS-free endoscopic remission at Week 52 for participants taking CS at Baseline • CS-free clinical remission at Week 52 for participants taking CS at Baseline • CS-free endoscopic response at Week 52 for participants taking CS at Baseline • CS-free SES-CD total score of 0-2 at Week 52 for participants taking CS at Baseline	Participants with moderately to severely active CD who are taking CS at Baseline	NRI will be used for the following intercurrent events before Week 52: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
To compare the efficacy of brazikumab with that of placebo to achieve sustained endoscopic remission and SES-CD total score of 0-2 at both Week 12 and Week 52	• Endoscopic remission at both Week 12 and Week 52 • SES-CD total score of 0-2 at both Week 12 and Week 52	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 52: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve primary symptom remission at Week 12	• Primary symptom remission at Week 12: – For participants with Baseline LSF subscore of ≥ 5 and AP subscore < 2: Average daily LSF subscore of ≤ 3 AND no worsening of Baseline AP subscore as assessed on the CDAI OR • For participants with Baseline AP subscore of ≥ 2 and LSF subscore < 5: Average daily AP subscore of ≤ 1 AND no worsening of Baseline LSF subscore as assessed on the CDAI	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 52: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo to achieve sustained primary symptom remission at Week 12 and Week 52	• Primary symptom remission at Week 12 and Week 52	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 52: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
To compare the efficacy of brazikumab with that of placebo to achieve clinical response at Week 12	• Clinical response at Week 12, defined as minimum 25% reduction in LSF subscore or AP subscore from Baseline	Participants with moderately to severely active CD	NRI will be used for the following intercurrent events before Week 52: – discontinues treatment prematurely for any reason – takes rescue treatment or meet the rescue criteria – uses prohibited treatment	Same as primary
To compare the efficacy of brazikumab with that of placebo in changes from baseline in CDAI	• Change from Baseline at Week 12 and Week 52 in CDAI score	Participants with moderately to severely active CD	Accounted for by the mixed model (assumes missing at random).	LS mean and associated 95% CI from a mixed model for repeated measures, assuming unstructured covariance matrix (if converges – compound symmetry otherwise)
To evaluate the impact of brazikumab on the signs and symptoms of CD at Week 12 and Week 52	• Change from Baseline at Week 12 and Week 52 in signs and symptom scores (eg, LSF, AP, urgency, fatigue) derived from the BSFS, NRS, and FACIT-F	Participants with moderately to severely active CD	Accounted for by the mixed model (assumes missing at random).	LS mean and associated 95% CI from a mixed model for repeated measures, assuming unstructured covariance matrix (if converges – compound symmetry otherwise)
To evaluate the impact of brazikumab on HRQoL at Week 12 and Week 52	• Change from Baseline at Week 12 and at Week 52 in IBDQ, SF-36, and EQ-5D-5L	Participants with moderately to severely active CD	Accounted for by the mixed model (assumes missing at random).	LS mean and associated 95% CI from a mixed model for repeated measures, assuming unstructured covariance matrix (if converges – compound symmetry otherwise)

Stage 1 Objectives	Stage 1 Endpoints	Population	Intercurrent event strategy	Population level summary (analysis)
To explore changes in signs and symptoms and HRQoL using a range of measures	• Exploratory analysis of subscale scores from BSFS, IBDQ, and additional symptom NRS items	Participants with moderately to severely active CD	Accounted for by the mixed model (assumes missing at random).	LS mean and associated 95% CI from a mixed model for repeated measures. Assuming unstructured covariance matrix (if converges – compound symmetry otherwise).
To explore transcriptional, histological, protein, and microbiome biomarkers in study participants and their relationship with study intervention, disease features, clinical outcomes, and patient characteristics.	• Serum, plasma, fecal, or gut tissue proteins; whole blood or gut tissue transcriptional changes; histological and microbiome assessments.	Participants with moderately to severely active CD	Exploratory analysis plans, including intercurrent event strategy and summary statistics, to be detailed in the SAP or separate exploratory analysis plan.	

All primary, secondary, and exploratory efficacy endpoints will be evaluated in the BM+ and BM- populations as well.
Additional exploratory efficacy endpoints may be described, with corresponding statistical analyses in the SAP.
AE = adverse event; AP = abdominal pain; BM = biomarker serum IL-22 concentrations at or above a pre-established cutoff; BSFS = Bristol Stool Form Scale; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CS = corticosteroid; ECG = electrocardiogram; EQ-5D-5L = 5-level European Quality of Life - 5 Dimensions; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; IL-22 = interleukin-22; LS = least squares; LSF = loose stool frequency; NRI = non-responder imputation; NRS = Numerical Rating Scale; PK = pharmacokinetics; SAP = Statistical Analysis Plan; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF-36 = Short-Form 36 Health Survey.

Objectives and endpoints for Stage 2 are presented in Appendix F 4.

4 STUDY DESIGN

4.1 Overall Design

This study will utilize an operationally seamless Phase 2b/3 clinical trial design as an alternative to the traditional drug development program of sequential, independent clinical trials. The confirmatory, operationally seamless Phase 2b/3 clinical trial has been developed to efficiently combine the Phase 2b and Phase 3 stages of drug development (Maca et al, 2006). Furthermore, this operationally seamless Phase 2b/3 study design combines, within a single protocol, objectives that have traditionally been addressed in separate studies, and is intended to substantially reduce the time that would have occurred between the studies had they been conducted separately. This design allows for the confirmatory study (Stage 2) to proceed after Stage 1, but the data from the 2 studies are kept distinct. The sponsor will commence Stage 2 after all participants are randomized into Stage 1, have completed the Week 12 Treatment Period, and the data from the Stage 1 primary analysis have been fully evaluated. The sponsor will amend the Stage 2 part of the protocol prior to initiating this stage of the study.

This study is planned as a global, multicenter (up to 400 sites), randomized, double-blind, placebo- or active-controlled, parallel-group, operationally seamless, Phase 2b/3, 52-week study.

This protocol comprises 2 distinct stages:

- **Stage 1**: A Phase 2b study to evaluate the dose-response relationship to select IV brazikumab induction doses for continued development and to establish the serum IL-22 concentration clinical cutoff to stratify enrollment into Stage 2. Participants in Stage 1 will be stratified by prior history of biologic use and current CS use. Stage 1 objectives and endpoints at Week 12 will inform Stage 2 design features:
    - Determine BM cutoff value of serum IL-22 concentration
    - Confirm number of brazikumab treatment arms for Stage 2
    - Confirm sample size for Stage 2 (to achieve endoscopic response and clinical remission at Week 12)
    - Confirm selection of PROs for Stage 2

After Week 12, Stage 1 participants will continue with their assigned study group treatments through Week 52. Participants in Stage 1 are not eligible for enrollment in Stage 2. The study will be unblinded, and the primary analysis for the study will be conducted, after the last participant has completed the Week 12 visit. AstraZeneca personnel who are directly involved with the conduct of the study, study site personnel, as well as participants will remain blinded to the treatment assignment for individual participants until the completion of the study. Details on what roles will remain blinded and how trial integrity will be maintained will be documented separately.

Stage 2 will be amended prior to initiation, and enrollment into Stage 2 (see below) will only commence at the direction of the sponsor. In addition, the final (Week 52) analysis in Stage 1 may be used to determine if the sample size for Stage 2 needs to be adjusted. Based on the final analysis from Stage 1, a brazikumab CCI [redacted] may be dropped from Stage 2.

Participants who complete either Stage 1 or Stage 2 or have an incomplete response to Induction treatment are eligible to enroll in an open-label extension study.

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

- **Stage 2**: A Phase 3 study to evaluate the safety and efficacy of brazikumab compared with Humira in participants who are BM+ (serum IL-22 concentrations at or above a pre-established cutoff), and to validate the clinical utility of serum IL-22 concentration as a predictive BM for efficacy of brazikumab in a subset of participants with CD. Stage 2 Screening will be initiated upon completion of the Stage 1 primary analysis. The identification of a pre-specified serum IL-22 concentration cutoff in Stage 1 is essential to initiate enrollment of Stage 2. The specified serum IL-22 concentration clinical cutoff is intended to represent a point where the sponsor can reliably identify the participants who are defined as being BM+ or BM- (serum IL-22 concentrations below a pre-established cutoff) for randomization into Stage 2 of the study. To confirm the appropriateness of restricting brazikumab use to a BM+ population, the primary objective and analysis will be based on the participants who are BM+. Data from participants who are BM- will serve as a reference to compare the clinical utility of serum IL-22 concentration in BM+ participants as a predictive BM for the efficacy of brazikumab. Based on the clinical hypothesis, the treatment effect for brazikumab compared to Humira is expected to be much smaller, if any, in the BM- participants. However, including BM- participants may provide an estimate of the effect in that population and may also potentially provide an overall risk–benefit assessment for brazikumab for the overall general population. The randomization stratification ratio of BM+ or BM- participants is planned to be 2:1 for all treatment groups; this ratio will be finalized upon review of the Stage 1 primary analysis.
- Participants will also be stratified according to prior history of biologic use and current CS use.

A study schematic is presented in Section 1.2 (Stage 1) and Appendix F 1 (Stage 2).

Intervention Groups and Study Duration:

<u>Stage 1</u>

- Treatment Groups:

  - Brazikumab high dose: CCI brazikumab CCI on Days 1, 29, and 57, followed by CCI brazikumab CCI on Day 85 and every 4 weeks through Week 48
  - Brazikumab low dose: CCI brazikumab 720 mg on Days 1, 29, and 57, followed by CCI brazikumab CCI on Day 85 and every 4 weeks through Week 48
  - Placebo: CCI placebo on Days 1, 29, and 57, followed by CCI placebo on Day 85 and every 4 weeks through Week 48
- Study Duration: Following a Screening Period of up to 5 weeks, the study duration is up to 66 weeks, consisting of a 52-week Treatment Period (last dose of study intervention at Week 48) and an 18-week post-last brazikumab/placebo dose Safety Follow-up Period. For participants who qualify and enroll into an open-label extension study of brazikumab, the Safety Follow-up Period will not be applicable.

Approximately 240 participants will be randomized to Stage 1 of the study (Figure 1).

Stage 2

Stage 2 Screening will be initiated upon completion of the Stage 1 primary (Week 12) analysis.

- Treatment Groups:
  - Brazikumab high dose: CCI brazikumab CCI on Days 1, 29, and 57, followed by CCI brazikumab CCI on Day 85 and every 4 weeks through Week 48
  - Brazikumab low dose: CCI brazikumab CCI on Days 1, 29, and 57, followed by CCI brazikumab CCI on Day 85 and every 4 weeks through Week 48
  - Humira: CCI Humira CCI on Day 1, CCI on Day 15, and CCI beginning on Day 29 and every 2 weeks through Week 50
- Study Duration: Following a 4-week Screening period, the study duration is up to 66 weeks, consisting of a 52-week Treatment Period and an 18-week post-last brazikumab/brazikumab placebo dose Safety Follow-up Period. For participants who qualify and enroll into an open-label extension study of brazikumab, the Safety Follow-up Period will not be applicable.

Approximately 690 participants, stratified 2:1 by BM+/BM- status, will be randomized to 1 of the 3 treatment groups in Stage 2 (Figure 3).

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

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS CoV-2 or similar pandemic

infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

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

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

4.2 Scientific Rationale for Study Design

Several design features have been incorporated into both stages to minimize bias, including double-blind technique and random assignment of participants, helping to ensure that both known and unknown risk factors are distributed evenly between treatment groups.

Traditional study designs that assess 'induction of remission' and 'maintenance of remission' as separate studies require that a specific timepoint is established that defines when induction ends and maintenance treatment begins. Disadvantages of these separate study designs include the potential of selecting an inappropriate timepoint that may not reflect the optimal time at which the pharmacodynamic properties of the treatment occurs, highly variable response rates that encumber estimation of the sample size needed for re-randomization, treatment carryover effects, and difficulties assessing whether the underlying disease process is still active. The current study design will make it possible to evaluate long-term maintenance of remission in participants who have achieved response or remission at an earlier specified timepoint.

The current study is designed to combine both initial treatment (induction) and maintenance phases into a single study, in a 'treat-straight-through' approach. Using this design, participants are randomized to receive induction therapy with study intervention or placebo (Stage 1) or active control (Stage 2) and are then treated straight through for the remainder of the study, which includes both an assessment of endoscopic response and clinical remission at Week 12 and an assessment of sustained endoscopic response and clinical remission in participants who were in response and/or remission at both Week 12 and Week 52. The major advantage of this naturalistic design is that it allows evaluation of both induction and maintenance treatment in a single study and avoids some of the complexities noted above that are associated with a traditional re-randomization maintenance design. Also, the consolidation of the benefits of initial treatment can be evaluated with continued treatment, especially for those participants who have responded to the initial treatment but did not meet the endoscopic response or clinical remission criteria at Week 12 but could be converted to a responder/remitter with continued treatment. This naturalistic design also mimics clinical practice as patients would continue to be treated along a continuum and not have their treatment truncated into an artificially selected timepoint. Furthermore, preserving the initial randomization assignment to treatment would ensure that long-term maintenance treatment was not biased in favor of participants that achieved remission during the Induction Period because those who achieved remission with their treatment would still be on the same treatment in the maintenance phase, without any influence of withdrawal or discontinuation of the treatment. Additionally, those who responded to placebo (in Stage 1 only) during the induction phase would still be on placebo in the maintenance phase, without any influence of discontinuation of placebo.

4.3 Justification for Dose

The no adverse effect level of CCI for brazikumab was established in cynomolgus monkeys in 3 studies in which brazikumab was CCI weekly for up to 14 weeks and CCI weekly up to 6 months. At this dose, no toxicologically significant effects were observed.

In the Phase 1 Study 3150-101-008, conducted in healthy Japanese and White participants to evaluate the PK, dose proportionality, safety, and tolerability of brazikumab, a CCI 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 of CCI brazikumab represents approximately comparable brazikumab exposure (AUC_{0-28} days) to a third CCI dose administered by CCI The administered CCI and CCI as part of the induction treatment and the CCI administered CCI dose as part of the maintenance treatment in this study are therefore also expected to be well tolerated. Furthermore, in Study 3150-101-008, a CCI of CCI brazikumab infused over a CCI CCI were well tolerated. The CCI brazikumab study interventions in Study D5271C00001 (Legacy # 3150-301-008) will be administered in CCI

Table 6 presents the margins of exposure calculated for the doses proposed in this study, based on C_{max} and AUC values following CCI [redacted] in the 14-week toxicology study, the clinical Phase 1b Study 20090519, and the clinical Phase 1 Study 3150-101-008.

Table 6 Exposure Margins Supporting Planned Doses

	CCI [redacted]		CCI [redacted]		CCI [redacted]	
Margin of Exposure	$AUC_{0-28days}$	C_{max}	$AUC_{0-28days}$	C_{max}	$AUC_{0-28days}$	C_{max}
	54.2	47.4	27.1	23.7	22.2	16.2

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

The use of a placebo group in Stage 1 is necessary given the inherent variability in disease flares and the use of subjective assessments. Participants in the placebo group will undergo the same study assessments as the brazikumab-treated participants.

4.4 End of Study Definition

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

A participant is considered to have completed the study if he/she has completed all phases of either Stage 1 or Stage 2 of the study including the last scheduled procedure shown in the SoA (Section 1.3 and Appendix F 2).

5 STUDY POPULATION

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

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

Inclusion and exclusion criteria are the same for both Stage 1 and Stage 2; however, participants enrolled in Stage 1 will not be permitted to enroll in Stage 2.

5.1 Inclusion Criteria

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

Age

1 At the time of signing the ICF, the participant must be 18 to 80 years of age, inclusive.

Type of Participant and Disease Characteristics

2 A diagnosis of ileal, ileocolonic, or colonic CD with an onset of symptoms for a minimum of 3 months prior to Screening as determined by the investigator based on clinical history, exclusion of other etiologies including infectious causes, and characteristic endoscopic and/or histologic findings.

3 Moderately to severely active CD, defined by a CDAI score of 220 to 450 points AND (3a and 3b must be met):

(a) CDAI LSF and AP scores will be obtained during Screening on an eDiary. The total CDAI score will be calculated at Screening Visit 2 and will include data from the last 7 days. Within the 7 consecutive day period, participants are to have at least 4 days of evening diary entries. This calculation will be used to determine CDAI LSF and AP eligibility and allow for scheduling of the ileocolonoscopy.
The following criteria must also be met:

i. Average daily CDAI LSF score ≥ 5

OR

ii. Average daily CDAI AP score ≥ 2

(b) Evidence of active intestinal mucosal inflammation, as demonstrated on video-recorded ileocolonoscopy performed during the Screening Period prior to first dose of study intervention and scored by a blinded central reader with agreement on the following findings:

i. SES-CD score of at least 6. A narrowing that cannot be passed is exclusionary (please refer to Exclusion Criterion #9). The SES-CD score is to be calculated based on segments that can be evaluated by the endoscopist.

OR

ii. For isolated ileal disease, SES-CD score of greater than 4.

All efforts are to be made to complete the ileocolonoscopy no less than 5 business days prior to randomization to allow for the evaluation of the endoscopic subscore by the central reader.
Note: CDAI and PRO scores for eligibility must be met before endoscopy is performed.

4 Participant had an inadequate response or intolerance to intervention with conventional treatment [oral aminosalicylates, oral CS, azathioprine, methotrexate, or 6-mercaptopurine], or prior biological treatment, or demonstrated CS dependence for the treatment of CD. For

participants who have previously used biological treatment, a participant may have failed up to 3 biologics that include up to 2 different mechanisms of action. To fulfill this criterion, the participant must meet at least 1 of the following:

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

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

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

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

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

(b) Oral prednisone (or equivalent) up to 25 mg/day or equivalent, must be at a stable dose for 2 weeks prior to the Screening ileocolonoscopy and kept stable until the Week 12 assessment. Please see Section 6.6.2 for additional details for CS.

(c) Budesonide up to 9 mg/day, must be at a stable dose for 2 weeks prior to Screening ileocolonoscopy and kept stable until the Week 12 assessment. Please see Section 6.6.2 for additional details for CS.

(d) Oral antibiotics for the treatment of CD must be at a stable dose for at least 2 weeks prior to Screening ileocolonoscopy. This criterion does not apply to antibiotics used for the treatment of active infection.

(e) Immunomodulators (specifically azathioprine, 6-mercaptopurine, and methotrexate): participant must have been on treatment for a minimum of 8 weeks and must be kept at stable doses (except for cases of toxicity when the dose may be lowered) for 4 weeks prior to Randomization (Day 1).

(f) Probiotics (eg, Culturelle® and *Saccharomyces boulardii*) must be at a stable dose at Randomization (Day 1).

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

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

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

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

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

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

OR

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

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

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

Reproduction

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

7 Female participants of childbearing potential must have a negative urine pregnancy test prior to administration of study intervention and must agree to use a highly effective method of birth control (confirmed by the investigator) from randomization throughout the study duration and for at least 18 weeks after last dose of study intervention; cessation or continuation of contraception after this point is to be discussed with a responsible physician in accordance with local regulations and guidelines. Highly effective methods (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation- oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation- oral, injectable, or implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

- Sexual abstinence, ie, refraining from heterosexual intercourse (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant)
- Vasectomized sexual partner, provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success

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

- 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.

9 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 7).

Informed Consent

10 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.

11 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 period.

12 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.
NOTE: All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

5.2 Exclusion Criteria

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

1 Participant is unable or unwilling to have endoscopic procedures performed during the study.

2 History or current diagnosis of ulcerative colitis, indeterminate colitis, microscopic colitis, ischemic colitis, colonic mucosal dysplasia, primary sclerosing cholangitis, or untreated bile acid malabsorption.

3 History of toxic megacolon within 3 months prior to Randomization (Day 1).

4 Any intra-abdominal surgery, bowel resection, diversion, placement of ostomy or stoma within 3 months prior to Screening. Participants with a draining stoma, ostomy, or extensive colonic resection are excluded irrespective of the time from surgery.

5 Participant has an enterocutaneous or enterovesicular fistula. Participants with other active fistulas, including perianal fistulas, may be considered for enrollment if there is no anticipation for surgery and there is no evidence of active infection (eg, abscess).

6 Bowel perforation during the 6 months prior to Screening or evidence of obstruction within 3 months of Screening.

7 Complications of CD including short bowel syndrome, strictures/stenoses with obstruction or pre-stenotic dilation, or conditions where surgery may be anticipated within 6 months, or other conditions that may confound efficacy evaluations for the study.

8 Participant has any non-passable colonic stenosis/narrowing identified during the qualifying ileocolonoscopy (successful endoscope passage to the caecum with inability to enter the endoscope into the ileum is not covered under this exclusion criterion, and does not require exclusion).

9 Ongoing nutritional dependency for total parenteral nutrition or an elemental diet at Screening.

10 Participant has any of the following related to infections:

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

(b) Any infection requiring hospitalization or treatment with CCI [redacted] (including antiviral treatment) within 4 weeks of Screening

(c) Cytomegalovirus or Epstein-Barr virus infection that has not resolved within 8 weeks prior to Screening

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

(e) Nonserious infection requiring oral anti-infectives within 2 weeks prior to randomization must be further discussed with the Study Physician/designee. Chronic suppressive antiviral treatment for herpes simplex virus in the absence of active lesions or uncomplicated urinary tract infections are not considered exclusionary.

(f) Participant has clinical evidence of or suspected to have an abscess during Screening. Cutaneous and perianal/perirectal abscesses are not exclusionary if drained and adequately treated at least 3 weeks prior to Screening and there is no anticipation for surgery.

(g) Diagnosis of peritonitis or receiving treatment for peritonitis within 8 weeks prior to Screening

(h) Participant has any underlying condition that predisposes participant to infections

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

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

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

12 Chronic hepatitis B or C infection defined as:

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

13 Known history of primary immunodeficiency, splenectomy, or any underlying condition that predisposes the subject to infection, including HIV infection. Participants with positive results of HIV testing by the central laboratory will be excluded.

14 Prior history of or current diagnosis of a demyelinating disorder.

15 Participant has received the following treatment:

(a) Adalimumab, certolizumab pegol, infliximab, or golimumab: within 8 weeks prior to Randomization (Day 1)

(b) Vedolizumab or ustekinumab within 12 weeks prior to Randomization (Day 1)

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

(d) Fecal microbiota transplantation: within 8 weeks prior to Screening ileocolonoscopy

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

17 Participants who received cyclosporine, mycophenolate mofetil, sirolimus (rapamycin), thalidomide, tacrolimus (FK-506), or tofacitinib within 2 weeks prior to Screening Visit 1.

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

19 Participants received more than CCI or intramuscular steroids within 2 weeks prior to Screening Visit 1.

20 Participant received topical (rectal) aminosalicylic acid (eg, mesalamine) or topical (rectal) steroids within 2 weeks prior to Randomization (Day 1).

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

22 Participant has known or suspected history of chronic use of NSAIDs (defined as at least 3 times per week for more than 3 months; not applicable to daily aspirin use up to 325 mg per day) and/or opiates, drug, or alcohol abuse. Participants who use marijuana for medicinal purposes, including treatment of symptoms associated with CD and improving quality of life, will be permitted in the study. Marijuana use is to be documented as a concomitant medication. Participants who abuse marijuana (ie, interferes with aspects of the participant's life) as judged by the investigator are excluded.

23 History of cancer with the following exceptions:

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

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

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

24 Clinically significant cardiovascular conditions including recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or CCI heart failure within 6 months of Screening.

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

26 Clinically significant kidney disease including but not limited to:

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

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

27 Abnormal laboratory results at Screening:

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

(b) Neutrophil count < CCI [redacted]

(c) Hemoglobin < 8 g/dL

(d) Platelet count < CCI [redacted]

(e) Evidence of acute or chronic hepatitis B or C infection on central laboratory serology (see exclusion criterion 12)

(f) Positive central laboratory result for HIV

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

(h) 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.

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

29 Participant is currently enrolled in another investigational device or drug study, or is within 35 days or 5 half-lives, whichever is longer, since ending another investigational device or drug study, or receiving other investigational agent(s), with the exception of "registry" or "cohort" trials, which may include periodic biological sampling and/or participant questionnaires but in which no other unlicensed investigational product is administered. In the event that a participant has received an investigational agent, the elimination half-life of

which is not known, then the last dose must have been received at least 6 months prior to Randomization (Day 1).

30 Transfusion of blood, plasma, or platelets within the 30 days prior to Screening.

31 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.

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

33 Previous randomization in the present study.

Rationale for Inclusion and Exclusion Criteria

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

In the Phase 2a study (CD-IA-MEDI2070-1147), brazikumab demonstrated efficacy, without an identified safety risk, in a population of 18 to 65 years of age with moderate to severe, active CD. This study seeks to confirm and expand upon those observations, and to extend them into a population of 18 to 80 years of age. Most currently available treatments for moderately to severely active CD, including glucocorticosteroids, immunomodulators, and anti-TNFα agents are associated with significant adverse effects. The mechanism of action of brazikumab, and the results of the Phase 2a study in participants with CD, suggests that brazikumab has the potential to offer effective treatment with a reduced risk of adverse effects.

Despite the availability of current treatments, there is still a need for novel therapies for the treatment of CD due to the evidence that not all patients will respond or maintain their response to the available treatment options. As such, a considerable proportion of patients with moderately to severely active CD are unresponsive to both conventional therapy and current biological therapy, and considerable unmet medical need remains among these patients for safe and effective long-term therapy.

5.3 Lifestyle Considerations

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

1 Women of childbearing potential must use highly effective contraceptive methods from enrollment throughout the study and at least for 18 weeks after last administration of the study intervention, as stated in inclusion criterion 7, Section 5.1. Cessation or continuation of contraception after this point is to be discussed with a responsible physician in accordance with local regulations and guidelines.

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

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco

1 Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted during study intervention administration ([redacted] Use of nicotine replacement therapy should be recorded as concomitant medication.

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

5.4 Screen Failures

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

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

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

6 STUDY INTERVENTION

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

protocol.

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

6.1 Study Interventions Administered: Stage 1

In Stage 1 of this study, participants who satisfy all inclusion and exclusion criteria (Sections 5.1 and 5.2) will receive study intervention, defined as any investigational treatment or placebo intended to be administered to a study participant according to the study protocol. Table 7 presents details regarding study intervention and administration.

Table 7 Stage 1 Study Interventions

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

[a] CCI contents of CCI will be added to an CCI to a total volume of CCI then administered by CCI
CCI

Brazikumab CCI

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

Brazikumab for CCI is a CCI [redacted].

Brazikumab for CCI [redacted]

Brazikumab for CCI will be supplied as a CCI for injection in a CCI [redacted]

Brazikumab for CCI [redacted]

Placebo CCI [redacted]

Placebo CCI [redacted]. The label-claim volume is CCI [redacted]

Placebo CCI [redacted]

Placebo CCI [redacted]. The label-claim volume is CCI [redacted]

All formulations

CCI [redacted]

6.1.1 Dosing Regimen

In Stage 1, brazikumab CCI [redacted] Details regarding CCI and CCI for the CCI may be CCI [redacted]

For the double-blind Maintenance Period, all participants will receive CCI every 4 weeks per the administration schedule (Table 7). Please refer to the CCI for CCI [redacted]

All study interventions will be handled by a pharmacist (or appropriately qualified individual) and handed over to the qualified site staff who will administer the study intervention to participants according to the brazikumab investigational directions for use. Due to viscosity differences between brazikumab and placebo, the person who administers CCI study intervention must not be involved in performing assessments on patients. A study monitor will perform study

intervention accountability. In the event that the treatment allocation for a participant becomes known to the investigator or other blinded study staff involved in the management of study participants, the sponsor's study monitor must be notified immediately.

6.1.1.1 CCI Administration

In Stage 1, all participants will receiv CCI [redacted] An experienced and qualified staff member will place the CCI [redacted] The total volume administered will be recorded in the eCRF.

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

Vital signs (BP, temperature, pulse rate, and respiration rate) will be obtained before CCI [redacted] study 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 [redacted] administration, immediately after completion of infusion, and at approximately every 30 minutes for a minimum of 1 hour post-infusion or until stable, whichever is later. The first and last vital signs are to be recorded on the eCRF. Participants will be discharged from the site when they are deemed clinically stable by the investigator and after completion of PK sampling, a minimum of 2 to 4 hours after completion of CCI [redacted] for the CCI [redacted] and a minimum of 1 hour after completion of CCI [redacted] (Weeks 4 and 8).

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

6.1.1.2 CCI Administration

In Stage 1, brazikumab or placebo will be administered to all participants during the Maintenance Period by CCI [redacted] Each CCI [redacted] will be administered by a~~n~~ experienced and qualified staff member who must not be involved in performing assessments on patients. The brazikumab or placebo dose will be administered as 2 CCI [redacted] according to the dosing administration table. Injections will be over no more than 10 minutes total time for all CCI [redacted] and at a distance of at least 2 cm apart. It is advised that the site of study intervention injection be rotated such that the patient receives study intervention at a different anatomical site at each treatment visit. The suggested injection site rotation sequence is presented below (Figure 2). The injection site must be documented in the source at each treatment visit and

recorded in the eCRF. The date and time of all study intervention administrations, as well as any missed doses, should be recorded in the appropriate section of the eCRF.

CCI CCI

CCI

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

Vital signs (BP, temperature, pulse rate, and respiration rate) will be obtained before and immediately after CCI administration during treatment visits outlined in the SoA (Section 1.3). In addition, for the CCI brazikumab doses (Weeks 12 and 16), participants will be monitored for changes in vital signs and/or new symptoms approximately every 30 minutes for a minimum of CCI or until stable, whichever is longer. For the third and subsequent CCI of brazikumab or placebo, participants will be monitored for a minimum of 30 minutes or until stable, whichever is longer. The first and last vital signs (pre- and post-dose) are to be recorded on the eCRF. Discharge from the site will be determined by the investigator. Any injection-site reaction is to be reported as an AESI (see Section 8.3.10.3).

6.1.2 Study Intervention Administration Rescheduling

Every effort should be taken to keep study intervention administration within the scheduled window. If a participant presents with a condition that contraindicates dosing, study intervention 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 or illness or SAE or laboratory abnormality that, in the opinion of investigator, contraindicates dosing.

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

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

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

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

The visit schedule will always be calculated from the Randomization Visit date.

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

6.1.3 Study Supplies

For Stage 1, AstraZeneca will supply the following study interventions:

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

Additional details and instructions for study intervention 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 Study Interventions Administered: Stage 2

Study interventions for Stage 2 of this study are presented in Appendix F 5.

6.3 Preparation/Handling/Storage/Accountability

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Any temperature excursions during storage must be reported and resolved before use of the study intervention.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) All unused study intervention must be stored securely. Unused study intervention should be destroyed locally at the site wherever possible, once expired or at the termination of the study, by the site personnel after accounted for by the monitor. Where local destruction is not possible, then return to the supplying depot can be arranged.

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

Brazikumab and placebo preparation for CCI

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

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

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

A CCI will be administered using an CCI containing CCI A CCI

CCI will be removed from the CCI before addition of CCI of placebo. CCI CCI

Brazikumab and placebo CCI

Brazikumab and placebo CCI are to be administered through an CCI set with a CCI; acceptable configurations include an CCI set containing an in-line filter or the attachment of a separate filter to the distal end of the CCI

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

Other drugs must not be co-administered through the same infusion line.

The CCI will be flushed according to local practices to ensure the CCI Infusion time does not include the final flush time.

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

Brazikumab and placebo preparation for CCI

CCI brazikumab or placebo CCI are required for CCI CCI CCI should be kept at CCI for at least CCI inside the carton prior to administration. The dose of brazikumab or placebo for CCI must be administered at CCI within CCI after removal CCI

Brazikumab and placebo CCI

CCI 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 CCI CCI Avoiding the belly button, ribs, hip bones, scars, or moles, CCI CCI. Brazikumab or placebo will be slowly injected (at least a 5-second duration is recommended) into the CCI using gentle pressure. The area is not to be massaged after CCI are to be CCI and noted in the source documents only. The total volume of CCI will be recorded in the eCRF.

6.4 Measures to Minimize Bias: Randomization and Blinding

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

The randomization assignment procedure will take place only after all eligibility criteria have been satisfied, including the central reader's assessment of the SES-CD endoscopy score, and the calculation of CDAI scores and PRO for LSF and AP.

Study intervention will be administered at the study visits as specified in the SoA (Section 1.3 and Appendix F 2). Refer to the Pharmacy Manual for additional details.

Participants will be randomized in a 5:5:3 ratio for brazikumab CCI brazikumab CCI and placebo groups in Stage 1. Stage 2 randomization information will be provided prior to the first participant screened. Participants will be stratified according to status of prior biologic use, defined as biologic naïve/non-refractory or biologic refractory/intolerant, and current CS use at randomization.

The study will be unblinded, and the Stage 1 primary analysis will be conducted, after the last participant has completed the Week 12 visit. AstraZeneca personnel who are directly involved with the conduct of the study, study site personnel, as well as participants will remain blinded to the treatment assignment for individual participants until the completion of the study. Details on what roles will remain blinded and how trial integrity will be maintained will be documented separately.

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

Ileocolonoscopy video clips will be read centrally for mucosal lesions and endoscopic severity based on the SES-CD score by independent gastroenterologists experienced in IBD who are blinded to the participant's clinical activity and treatment allocation.

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

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

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

6.5 Study Intervention Compliance

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

6.6 Concomitant Therapy

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

6.6.1 Prior Medications Requiring Stable Dose Regimen

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

Table 8 Medications Requiring Stable Dose Regimen

Medication	Stable Dose Required
CCI [redacted]	CCI [redacted]
Oral prednisone up to CCI [redacted] or equivalent	CCI [redacted] opy until Week 12 assessment
CCI [redacted]	CCI [redacted]
Antibiotics	CCI [redacted]
Immunomodulators	
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

The medications listed in Table 8 are to remain at stable doses as defined except for cases of toxicity related to the medication. In cases of toxicity, the medication dose may be decreased or

discontinued; however, the medication dose is not to be increased or restarted once the toxicity has resolved.

6.6.2 Permitted Concomitant Treatments

Investigator, or designee, will collect and record information about concomitant medications as follows:

- All background CD therapy in the 12 months prior to Screening
- All other medications taken for any reason in the 3 months prior to Screening
- Concomitant treatments given during the study (at each study visit)

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 6.6.3. Specifically, participants are to receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with institutional guidelines or local site practice.

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

Table 9 Permitted Concomitant Treatments

Treatment	Details
Oral antibiotics for CD (except for the treatment of acute illness)	Permitted only if being taken at Screening for the treatment of CD. Dose must be kept stable through the Induction Treatment Period and should be continued at stable dose through the Maintenance Treatment Period, if clinically indicated. 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 rest of 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 Randomization (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)

Treatment	Details
NSAIDs	Limited to occasional short courses for less than 7 days. The use of NSAIDs is generally discouraged for IBD patients due to the risk of flares. Chronic NSAID use is exclusionary.
Inactivated/killed vaccination (eg, inactive influenza)	Not allowed within the 7 days before or within 7 days after any study intervention dosing study visit

AE = adverse event; CD = Crohn's disease; CDAI = Crohn's disease activity index; IBD = inflammatory bowel disease; NSAID = non-steroidal anti-inflammatory drug.

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

Background CD medication is not regarded as study intervention and will not be provided by the sponsor.

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

- Indication
- Dates of administration including start and end dates

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.

Corticosteroid study guidelines

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

- The following doses of oral prednisone, oral budesonide, or equivalent dose must be kept stable for at least 2 weeks prior to the Screening ileocolonoscopy.
  - Oral prednisone up to 25 mg per day or equivalent
  - Oral budesonide up to 9 mg per day
- Participants receiving oral CS must attempt CS tapering as per guidelines in Table 10. Corticosteroid tapering should be initiated at Week 12.

When tapering oral CS, follow the guidelines below (Table 10). Additional details are provided in Appendix H.

Table 10 Corticosteroid Tapering Guidelines

Initial corticosteroid dose	Dose reduction
CCI [redacted]	

General tapering guidelines:

- If there are worsening symptoms of CD attributed to the CS 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 treatment unless the dose is above the baseline CS dose. The increase in CS dose is to be recorded in the appropriate eCRF along with the indication for increase.
- If an oral CS 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.

The target goal is to discontinue CS by Week 40, if clinically appropriate.

6.6.3 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, and study intervention must simultaneously be discontinued:

- Anti-TNFα agents

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

Note: The use of other immunosuppressant/biologic 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 all applicable study assessments through the end of the study, including the Safety Follow-up Period.

6.6.4 Rescue Treatment

Although the use of rescue treatment is allowable, the use of rescue treatment should be delayed, if possible, for at least 12 weeks following the initiation of study intervention. The date of rescue treatment administration as well as the name and dosage regimen of the rescue treatment must be recorded.

For study purposes, any new concomitant medication or 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 CS dose back to Baseline dose level for participants undergoing CS tapering within the guidelines in Section 6.6.2 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-aminosalicylates
- Parenteral, oral, or rectal CS
- Oral CS doses above initial Randomization (Day 1) dose
- Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)
- CCI

Administration of rescue treatment constitutes treatment failure. Participants requiring rescue treatment will continue to receive study intervention unless a prohibited treatment is administered as listed in Section 6.6.3. Participants are expected to continue through study completion. Rescue treatments are not to be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety. The use of specific rescue treatment (eg, prohibited interventions) will be exclusionary for the open-label brazikumab study and may preclude participants from enrolling.

While rescue treatment may be considered at any visit, the use of rescue treatment is to be considered by the investigator after the Induction Period at Weeks 16 and 36 if there is worsening or no improvement in CD symptoms as per the rescue criteria (Table 11). The CDAI score must be calculated and the criteria in Table 11 must be met. Unscheduled visits may be performed for CDAI score assessment at any time. An unscheduled endoscopy visit must be performed after Week 16 if rescue treatment is considered during the Maintenance Period. The unscheduled endoscopy may be used for the early termination endoscopy requirement, as applicable, including if the participant qualifies for the open-label brazikumab study.

The following rescue criteria must be met prior to the use of rescue treatment (Table 11):

Table 11 Rescue Criteria

Week of Assessment	Criteria for Use of Rescue Treatment
Weeks 12 to 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.

If the participant meets rescue criteria, the participant may be eligible for the open-label brazikumab study, as applicable, if all other criteria are also met.

6.7 Dose Modification

There is no provision for dose reduction or increase during the Treatment Period. There will be a dosing window of ± 3 days during the Induction Period (from Weeks 1 through 12) and ± 7 days during the Maintenance Period. See Section 6.1.2 for details on dose delays.

6.8 Intervention After the End of the Study

No interventions will be dispensed after the end of the study unless the participant enters the open-label brazikumab study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

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 eCRF.

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

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

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

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

1 Participant requires intra-abdominal surgery during study participation.
2 Participant receives any live vaccine during study participation.
3 Mycobacterial infections, systemic fungal infections, or viral infections requiring hospitalization or parenteral 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 medication listed in Section 6.6.3.
8 Participant becomes pregnant.

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

Abnormal liver function, 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** total bilirubin > 2 × ULN **or** INR > 1.5

- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

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

If a clinically significant finding is identified (including, but not limited to changes from Baseline 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. 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. This review of the ECG printed at the time of collection must be documented.

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

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

7.2 Participant Withdrawal From the Study

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

- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the global study team.
- See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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 are to be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of 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 are to be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- The investigator will ensure that data are recorded on the eCRFs. The web-based data capture system will be used for data collection and query handling. The investigator will ensure the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.
- The maximum amount of blood collected from each participant over the duration of the study (Stage 1), including any extra assessments that may be required, will not exceed CCI Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Primary Efficacy Assessments

8.1.1.1 Ileocolonoscopy

Ileocolonoscopy 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 central 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 who are blinded to the participant's clinical activity and treatment allocation. The worst affected area of each segment is to be assessed for the SES-CD score calculation.

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

The central readers are to promptly notify both the Study Physician/designee and the investigator of the detection of any clinically significant bowel lesions that are not manifestations of CD.

Ileocolonoscopies will be performed according to the SoA (Section 1.3) and may be performed at an unscheduled visit if needed for use of rescue treatment. An ileocolonoscopy performed at an unscheduled visit could serve as an early termination procedure when applicable.

To ensure quality data and standardization, the same endoscopist for a participant is to be used throughout the study whenever possible. Ileocolonoscopies will be read at a centralized reading facility, with the central readers blinded to the participant's clinical activity and treatment allocation.

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 noncompliance), 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.

8.1.1.2 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 patients with CD (Daperno et al, 2004). The score assesses 4 variables in up to 5 segments to yield its final result (Table 12).

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 12 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

SES-CD for each of the 5 segments will be assessed during ileocolonoscopy according to the SoA (Section 1.3).

8.1.1.3 Biopsy

Mucosal biopsies will be collected at each study ileocolonoscopy (see the SOA in Section 1.3). 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 and biomarkers 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 biomarkers from the biopsy specimens.

8.1.1.4 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. 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 score is calculated by summing weighted scores for subjective items (number of liquid or very soft stools, abdominal pain, and general well-being) recorded by a diary during a 1-week period, and objective items (associated symptoms, taking antidiarrheal medications 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. Scores of < 150, 150 to 219, and 220 to 450 represent remission, mild disease, and moderate to severe disease, respectively; whereas scores of > 450 represent very severe disease (Buxton et al, 2007).

The components of the CDAI score (Table 13) are collected as follows:

- Abdominal mass, EIM: physical examination (Section 8.2.1)
- Antidiarrheal medications (Section 6.6.2)
- 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: eDiary (Section 8.1.3.3)
- Patient-reported components (LSF [Appendix I 1], AP [Appendix I 2], and general well-being): eDiary (Section 8.1.3.3). Daily PRO data collected 7 days prior to bowel prep will be used to calculate CDAI.

Table 13 Items Included in CDAI and Their Weights

Item	Weighted factor	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 °C 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 participant Maximum = 10 for underweight participant	×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.

The participant will be prompted to complete the eDiary every evening during the study.

8.1.2 Secondary Efficacy Assessments

- The SES-CD, CDAI, and PROs (LSF and AP) will also be used for secondary assessments.
- Serum brazikumab concentrations for the conduct of population PK analysis and exposure-response model linking of primary endpoints to metrics of model-predicted individual brazikumab exposures
- Serum IL-22 concentrations

- Safety and tolerability of brazikumab (AEs, clinical laboratory values, vital signs, physical examinations, and ECGs)

8.1.3 Additional Efficacy Assessments

8.1.3.1 PRO Assessments

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

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

The device will be programmed at Screening Visit 1, and participants will be required to complete a training module on the device at the site. Site staff must verify the training has been completed before the participant takes the device home.

The investigator or designee will be responsible for monitoring participant adherence with the PROs and follow up as necessary to minimize missing data. Monitoring of participant adherence to the daily PROs (CDAI, LSF, AP, well-being, and temperature) is especially critical between Screening Visit 1 and Screening Visit 2 to ensure that the participant meets applicable criteria for the CDAI eligibility calculation. A minimum of 2 consecutive weeks with evaluable evening diary data (at least 4 days of evening diary data in each 7-day period) is required immediately prior to Screening Visit 2. If the participant does not meet the eligibility requirements, the device will be deactivated and retained at the site for future use.

Participants are expected to bring the device to every site visit. Site staff will review participant compliance with the assessment schedule and ensure completion of available assessments prior to any other study procedures.

8.1.3.2 Bowel Movement eDiary

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

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

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

8.1.3.3 Evening eDiary

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

The participant will be instructed to complete the evening eDiary every night and will be prompted to report any additional bowel movements that they did not enter already in real-time for that day. Participants will also be prompted to report LSF, AP, general well-being, and temperature, captured by the CDAI, over the past 24 hours. In the same evening assessment, participants will record the severity rating of their AP, fatigue, tiredness, weakness, lack of energy, and joint pain over the past 24 hours (Appendix I 2).

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

8.1.3.4 Site Visit Instruments

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

The PGI-S (Appendix I 3.1) is a single item that assesses participants' perceptions of overall severity of CD symptoms for the last 7 days.

The PGI-C (Appendix I 3.2) is a single item that assesses participants' perceptions of overall change in their CD symptoms since starting treatment.

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

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

The EQ-5D-5L (Appendix I 3.5) is a standardized instrument used to measure self-reports of health status and functioning, consisting of 5 elements: mobility, self-care, usual activities,

pain/discomfort, and anxiety/depression. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate an index measuring the value to society of his or her current health. In addition, the EQ-5D-5L includes a 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 (Appendix I 3.6) is a standardized instrument used to measure self-reports of health status and functional well-being, consisting of 8 domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Empirically derived weights can be applied to an individual's responses to the SF-36v2 descriptive system to generate an index measuring the value to society of his or her current health.

8.1.3.5 Participant Qualitative Interview Sub-study

Participants who complete the ICF in English will be invited to participate in a participant qualitative interview sub-study. The overall goal of this sub-study is to supplement and support the interpretation of PRO quantitative trial results through qualitative exploration of the participant disease and treatment experience. The study will highlight the meaningful changes in participant experience and feedback on the feasibility and ease of the eDiary data collection throughout the course of the trial. Up to 25 participants who complete the End of Treatment study visit (Week 52) can be enrolled in the sub-study. The sub-study consists of a one-to-one non-interventional, 60-minute telephone interview conducted in English in the United States, United Kingdom, and Canada. A detailed description of sub-study procedures is available in the Participant Qualitative Interview Sub-study Manual.

Participants will be introduced to the sub-study during the informed consent process using the participant communication materials attached to the Participant Qualitative Interview Sub-study Manual and the Sub-study ICF Addendum. Participants will be contacted according to procedures described in the Participant Qualitative Interview Sub-study Manual. The interview discussion guide is provided as an appendix to the Participant Qualitative Interview Sub-study Manual.

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

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

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

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

8.2 Safety Assessments

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

8.2.1 Physical Examinations

Physical examination will be performed at timepoints as specified in the SoA.

- 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, and 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.

8.2.2 Vital Signs

- 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.
- Height will be measured at Screening Visit 1 only and recorded in centimetres.
- Weight will be recorded in kilograms according to the SoA (see Section 1.3) as part of CDAI.
- Procedure for monitoring vital signs before, during, and after IV and SC administration of study intervention are further detailed in Sections 6.1.1.1 and 6.1.1.2.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc

intervals. Refer to Section 7.1 for QTc withdrawal criteria and additional QTc readings that may be necessary.

8.2.4 Clinical Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the visits indicated in the SoA in Section 1.3. At visits where CDAI is done, a blood sample for determination of hematocrit will be collected if hematology is not required.

All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the Laboratory Manual and the SoA.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date and time of collection will be recorded on the appropriate eCRF.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the study site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.5. The following laboratory variables will be measured (Table 14):

Table 14 Protocol-Required Laboratory Assessments

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

Laboratory assessments	Parameters
	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (reflexively as needed)
Other Screening tests	• QuantiFERON-TB Gold In-Tube • FSH (as needed in women of non-childbearing potential only) [b] • Serum hCG pregnancy test (as needed for women of childbearing potential). Urine hCG is to be performed locally at each visit prior to administering study intervention and as outlined in the SoA. • Serology (HIV antibody, hepatitis B surface antigen, hepatitis B core total antibody, hepatitis B core IgM antibody, and hepatitis C virus antibody with reflex testing when required) • All study-required laboratory assessments will be performed by a central laboratory unless indicated (eg, local urine hCG testing)

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix E.
[b] FSH does not need to be repeated at Week 52 if it was in the post-menopausal range at Screening. If the female participant becomes amenorrhoeic during the course of the study, FSH should be assessed at Week 52.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; IgM = immunoglobulin M; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; SoA = Schedule of Activities; TB = tuberculosis; WBC = white blood cell.

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

- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 18 weeks after the last dose of study intervention are to be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the investigator or sponsor Study Physician/designee.
  - If such values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology is to be identified and the sponsor notified.
  - All protocol-required laboratory assessments, as defined in Table 14, must be conducted in accordance with the laboratory manual and the SoA.
  - 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, AE, or dose modification), then the results will be recorded in the eCRF.

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

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

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

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

8.3.2 Follow-up of AEs and SAEs

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

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

AE variables

'The following variables will be collected for each AE:

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

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

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

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

8.3.3 Causality Collection

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

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

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

8.3.4 AEs Based on Signs and Symptoms

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

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

8.3.5 AEs Based on Examinations and Tests

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

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia vs 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 total bilirubin ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

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, abdominal pain and diarrhea). Events that are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

8.3.8 Reporting of SAEs

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

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

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

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

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

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

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

8.3.9 Pregnancy

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

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

8.3.9.1 Maternal Exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may

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

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

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

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

8.3.9.2 Paternal Exposure

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

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

8.3.10 Adverse Events of Special Interest

8.3.10.1 Infusion Related Reactions and Injection-site Reactions

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

The site of injection will be assessed at every visit during the Induction and Maintenance Periods. CCI [redacted] will be recorded as AEs according to the criteria described in Section 8.3.

8.3.10.2 Malignancies

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

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

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

Participants with a history of cancer, except for basal cell carcinoma and/or squamous cell carcinoma of the skin, or in situ carcinoma of the cervix treated with apparent success with curative therapy within the specified time period, outlined in exclusion criterion #23, will be excluded. Participants with evidence of intestinal epithelial dysplasia on endoscopy and confirmed on biopsy will be excluded.

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

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

Participants with certain ongoing, recent, or latent infections, or at high baseline risk of developing infections, are not to receive brazikumab and will be excluded from the study per Exclusion Criterion #10.

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

8.3.10.4.1 Non-opportunistic Infections

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

8.3.10.4.2 Opportunistic Infections

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

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

8.3.11 Medication Error

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

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

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

8.4 Overdose

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

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

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

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

8.5 Human Biological Samples

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

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

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

8.5.1 Pharmacokinetics

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

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

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

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

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

8.5.1.1 Determination of Drug Concentration

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

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

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

8.5.2 Immunogenicity Assessments

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

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

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

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

8.5.3 Pharmacodynamics

Pharmacodynamic assessments will not be included in this study.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

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

Blood, stool, and biopsy samples will be collected and analyzed to evaluate protein, nucleic acid, metabolic, and cellular BM 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 biomarkers with observed clinical responses over the entire treatment duration of the clinical study and to enhance knowledge 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.

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

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

The IL-22 analyses are a secondary endpoint in Stage 1. All other additional BM analyses are exploratory and will be described in a separate report.

8.7 Optional Genomics Initiative Sample

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

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

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

For storage and destruction of genetic samples see Appendix D.

8.8 Healthcare Resource Utilization

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

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

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

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

9 STATISTICAL CONSIDERATIONS

Statistical considerations for Stage 2 are provided in Appendix F 6.

9.1 Statistical Hypotheses

Stage 1 is a learning phase (Phase 2b study), and inferences will be conducted for the primary and secondary efficacy endpoints to inform the final design and planning for the Phase 3 study (ie, Stage 2).

The primary estimand of Stage 1 is described in Table 15.

Table 15 Key Elements of Stage 1 (Primary Estimand)

Key Elements	
Population	Participants with moderately to severely active CD
Variable	CDAI remission (CDAI < 150) at Week 12
Treatment comparison	Each brazikumab dose vs placebo
Strategy for intercurrent events	A participant who: • discontinues treatment prematurely • takes rescue treatment or meets the rescue criteria • uses prohibited treatment is considered as being unsuccessfully treated ("Composite strategy" - ICH E9 [R1]).
Population level summary	Percentage of participants with CDAI remission

CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; ICH = International Council for Harmonisation.

The null hypothesis is that the percentage of participants achieving CDAI remission at Week 12 for participants dosed with 1 brazikumab dose group is equal to the percentage of participants achieving CDAI remission at Week 12 for participants dosed with placebo. The alternative hypothesis is that the percentage of participants achieving CDAI remission at Week 12 for participants dosed in 1 of the brazikumab dose groups is different to the percentage of participants achieving CDAI remission at Week 12 for participants dosed with placebo, ie:

- H_0: There is no difference in Week 12 CDAI remission rate between 1 brazikumab dose group and placebo treatment group *vs*
- H_1: There is a difference in CDAI remission rate at Week 12 between 1 of the brazikumab dose groups and the placebo treatment group.

These hypotheses will be tested in hierarchical order starting with the largest dose.

9.2 Sample Size Determination

The sample size of this study is assessed for the primary variable and key secondary variable (ie, percentage of participants achieving CDAI remission [CDAI < 150] at Week 12 and percentage of participants achieving endoscopic response at Week 12).

Brazikumab and placebo CDAI remission rates, after a 12-week induction treatment period, are assumed to be 38% and 13%, respectively, considering previous Phase 2a study results in conjunction with the expectation of higher response rates due to increased dose frequency and new induction dose, along with the expected ratio of biologic-naïve to biologic-intolerant or refractory participants 40% to 60%, respectively. Based on these assumptions, a sample size of

85 participants per brazikumab dose and 51 in the placebo group (enrolled after Protocol Amendment 4) provides at least 80% power to detect a difference vs placebo in the CDAI remission rate using continuity-corrected Mantel-Haenszel (Cochran) test of odds ratio = 1 with 2 strata using a 2-sided 0.05 level test.

This sample size will also provide at least 80% power to detect a difference in brazikumab and placebo endoscopic response rates, after a 12-week induction treatment period, assuming the response rates are set to 37% and 13%, respectively.

9.3 Populations for Analyses

The following populations are defined for Stage 1 (Table 16):

Table 16 Populations for Analysis: Stage 1

Population/Analysis set	Description
Full Analysis Set	This population includes all participants who are randomized to a Stage 1 treatment group (as per the ITT principle) after implementation of Protocol Amendment 4.
Safety population	This includes all participants who receive ≥ 1 administration of Stage 1 study intervention.
PK population	The PK population includes all participants who receive at least 1 dose of study intervention and have at least 1 PK sample containing detectable brazikumab concentrations. The Exposure-Response population will be defined in the Modeling and Simulation Plan prior to database lock.

ICF = informed consent form; ITT = intent-to-treat; PK = pharmacokinetics.

9.4 Statistical Analyses

The study will be unblinded and the primary analysis for Stage 1 will be conducted after the last participant has completed the Week 12 visit. AstraZeneca personnel who are directly involved with the conduct of the study, study site personnel, as well as patients will remain blinded to the treatment assignment for individual participants until the completion of the study. Details on what roles will remain blinded and how trial integrity will be maintained will be documented separately.

The final analysis for Stage 1 will be performed after the last participant in Stage 1 completes the Week 52 visit.

9.4.1 General Considerations

For this operationally seamless Phase 2b/3 study, Stage 1 is a dose-ranging, BM+/BM- identification, learning phase, and Stage 2 is a confirmatory phase serving as one of the Phase 3 confirmatory efficacy and safety studies. Participants who are randomized into Stage 1 are exclusive from participants randomized into Stage 2, resulting in 2 distinctive study populations.

Statistical considerations are given separately for Stage 1 (this section) and Stage 2 (Appendix F 6).

Key objectives for Stage 1 are to examine the efficacy and safety of brazikumab, evaluate serum IL-22 concentration as a potentially predictive BM, and evaluate the brazikumab exposure response. Stage 1 will also serve to select an appropriate serum IL-22 concentration cutoff value to define the BM+ and BM- subpopulations and to make a go/no-go decision before proceeding to Stage 2.

Separate Stage 1 and Stage 2 SAPs will be developed. The Stage 1 SAP was approved before any review of blinded data and before implementation of Protocol Amendment 4. The Stage 2 SAP will be approved before the first participant is enrolled. The SAPs will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section summarizes the planned main statistical methodology features of the primary and the key secondary endpoints. The Stage 1 SAP will be revised according to Protocol Amendment 4 before the first participant is enrolled under that amendment.

All efficacy data for participants who were enrolled prior to Protocol Amendment 4 will be listed only; safety data will be summarized together. For Humira patients, safety results will be listed only and not included in the summaries. Specific details will be provided in the SAP.

Missing data for dichotomous variables will be handled using the non-responder imputation method (ie, any participants with missing information on the variables will be assumed as a non-responder). Sensitivity analyses in which missing data are handled differently may be carried out (eg, treatment policy strategy for intercurrent events at the primary timepoint [Week 12] will be performed). Details will be pre-specified in the corresponding SAPs.

Further, supportive analyses may be performed for the primary and key secondary endpoints using alternative strategies for handling intercurrent events (ie, early discontinuation of IP or use of prohibited or rescue treatment).

The use of rescue medication, and in particular, the initiation of CS treatment irrespective of such being foreseen in the protocol should also be considered as a failure of the study drug (composite strategy) independent from the therapeutic intent. If CS that are tapered are used as background medication, a failure to taper CS according to the protocol-planned fixed schedule can be considered as a special case of rescue therapy. However, a minor deviation from the tapering schedule does not necessarily have to be considered as an intercurrent event that should be treated as a treatment failure (European Medicines Agency, 2018). Details will be documented in the corresponding SAPs.

Unless otherwise defined, baseline for efficacy variables is defined as the last non-missing efficacy assessment before the first dose of study intervention upon randomization. The CDAI,

LSF and AP scores assessed at Screening Visit 2 will be used as baseline. More details will be provided in the SAP.

9.4.2 Stage 1 Efficacy

All efficacy analyses will be based on the Full Analysis Set and analyzed according to the ITT principle.

9.4.2.1 Primary Endpoint

The primary efficacy endpoint (percentage of participants achieving CDAI remission at Week 12), will be analyzed using a Cochran-Mantel-Haenszel test controlling for 2 randomization stratification factors (status of prior biologic use and current CCI use [yes or no] at Randomization). In addition, the observed response proportions will be provided by treatment group.

To check the impact of baseline biomarkers to each primary efficacy endpoint, a logistic regression model will be performed controlling for 2 randomization stratification factors (status of prior biologic use and current CCI use [yes or no] at randomization), and baseline serum IL-22 values as covariates. This sensitivity analysis is for the same primary estimand.

9.4.2.2 Secondary Endpoints

The key and all secondary binary variables will be analyzed in the same way as the primary endpoint. Secondary continuous endpoints will be analyzed using mixed models. Immunogenicity and brazikumab serum concentrations will be analyzed by descriptive statistics.

9.4.3 Stage 1 Safety

9.4.3.1 Safety Endpoints

Stage 1 safety data will be summarized descriptively using the Safety population. The safety parameters will include AEs, clinical laboratory assessments, vital signs, physical examinations, and ECG parameters. For each of the clinical laboratory assessments, vital signs, and ECG parameters, the last non-missing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by the number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

9.4.4 Stage 1 Other Analyses

9.4.4.1 Serum IL-22 Concentration Cutoff Identification Based on Stage 1 Primary Analysis

The BM+/BM- populations used in Stage 2 will be defined using serum IL-22 concentrations and CDAI and endoscopy data collected in Stage 1. The IL-22 concentration cutoff, defining the BM+/BM- populations, will be selected as the value that maximizes the difference in CDAI remission and endoscopic response between brazikumab and placebo when comparing the BM+

and BM- population for the pooled doses of brazikumab vs placebo. This cutoff will be algorithmically derived using normalized Z-score across the population of all possible cutoffs.

Should an optimal threshold be determined, it will be selected with consideration to the totality of statistical evidence in conjunction with clinical, regulatory, and commercial relevance.

All primary, secondary, and exploratory efficacy endpoints will be evaluated in the BM+ and BM- populations.

Graphs describing the relationship between baseline IL-22 (on a continuum scale) vs response (both CDAI remission and endoscopic response) will be produced.

In addition, descriptive summaries with the proportions of responders based on different IL-22 cutoff levels together with graphs of the proportion of responders as a function of IL-22 cutoff levels by treatment arm will be produced.

More details will be provided in the SAP.

9.4.4.2 Subgroup Analyses

Subgroup analyses for the primary and secondary efficacy endpoints may include, but are not limited to:

- Serum IL-22 (high vs low)
- Prior biologic use (naïve vs prior use)
- Region/country
- Race
- Gender
- Age group

Serum IL-22 subgroup classification will be specified in the SAP for Stage 1.

9.4.4.3 Other Analyses

Pharmacokinetics, PD, and PRO analyses will be described in the SAP and Modeling and Simulation Analysis plan finalized before database lock. The population PK and PK-PD analyses may be reported separately from the main CSR. Exploratory biomarker analyses other than IL-22 may be defined and presented outside of the SAP and CSR.

9.5 Interim Analyses

The primary analysis for Stage 1 (described in Section 9.4.2.1) will be conducted when all participants have completed their Week 12 visit. Hence, this is an analysis prior to the time point

of the formal completion of the trial.

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 SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing 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 re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

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

A 4 Data Protection

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

A 5 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 CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

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

B 1 Definition of Adverse Events

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

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

B 2 Definition of Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires 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 edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

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

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

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

Intensity Rating Scale

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

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

not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not 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 Adverse Events of Special Interest

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

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

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

B 4 A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue treatment, or standard of care medication in open-label studies, even if an AstraZeneca product

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

B 6 AE and SAE Recording

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

D 1 Use/Analysis of DNA

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

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

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

Inclusion Criteria

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

Exclusion Criteria

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

Withdrawal of Consent for Genetic Research

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

Collection of Samples for Genetic Research

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

Coding and Storage of DNA Samples

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

Ethical and Regulatory Requirements

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

Informed Consent

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

Participant Data Protection

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

Data management

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

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

E 1 Introduction

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

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

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

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

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

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

E 2 Definitions

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

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

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the

same day) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur.

E 3 Identification of Potential Hy's Law Cases

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

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- Total bilirubin ≥ 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 Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

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

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

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

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

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

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

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

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

instructions below.

Where there is an agreed alternative explanation for the ALT or AST and total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for 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 Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

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

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

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

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

E 6 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HbsAg 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 Ab; CMV = Cytomegalovirus; DNA = Deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = Gamma-glutamyl transferase, HAV = hepatitis A virus; HbsAg = Hepatitis B surface antigen; HBc = hepatitis B core; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HEV = Hepatitis E virus; HSV = herpes simplex virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; RNA = ribonucleic acid.

E 7 References

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

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

documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix F Stage 2 Study Design

Protocol sections relevant to Stage 2 of this study will be revised prior to implementation.

F 1 Schema

Figure 3 Study Design (Stage 2)

BM+ = biomarker serum IL-22 concentrations at or above a pre-established cutoff; BM- = biomarker serum IL-22 concentrations below a pre-established cutoff; CCI [redacted]

F 2 Schedule of Activities

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

A single SoA is presented for both the Induction and Maintenance Periods (Table 17) and for the Early Termination Visit and Safety Follow-up Period (Table 18).

Table 17 Schedule of Activities – Induction and Maintenance Periods (Stage 2)

CCI

[redacted]

Study Period	Screening Period	Induction Period (± 3-day visit window for Visits 3 through 9)	Maintenance Period (± 7-day visit window)

CCI

[redacted]

Study Period	Screening Period	Induction Period (± 3-day visit window for Visits 3 through 9)	Maintenance Period (± 7-day visit window)

CCI

[redacted]

Study Period	Screening Period	Induction Period (± 3-day visit window for Visits 3 through 9)								Maintenance Period (± 7-day visit window)																			
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Visit Name	**Screening**	**Baseline**	**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**
Study Day	***-28 to -1***	***1***	***8***	***15***	***29***	***43***	***57***	***71***	***85***	***99***	***113***	***127***	***141***	***155***	***169***	***183***	***197***	***211***	***225***	***239***	***253***	***267***	***281***	***295***	***309***	***323***	***337***	***351***	***365***
Study treatment administration		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of injection-site reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Height is to be measured at Visit 1 only.
[b] The extraintestinal manifestation eCRF is to be completed at all visits starting at Visit 2.
[c] Virology testing at Screening includes Hepatitis B, Hepatitis C, and HIV-1 testing.
[d] Serum pregnancy testing (or FSH when applicable) required at the Screening visit. All other pregnancy testing will consist of urine pregnancy testing performed locally for females of childbearing potential prior to administering study intervention added.
[e] TB testing will consist of QFT-TB test performed by the central laboratory. A tuberculin skin test would additionally be required if the QFT-TB test is not approved/registered in the country. Participants with an indeterminate QuantiFERON-TB test result are to have the test repeated during Screening. If a participant with an indeterminate QFT-TB result is randomized, additional QFT-TB testing will be performed during the course of the study at Visits 9, 15, 23, and 29 (or early termination) (see Inclusion Criterion #6 in Section 5.1).
[f] Participants with a positive purified protein derivative test or an indeterminate QFT-TB test, or participants with a history of using anti-TNFα agents for a treatment course of 1 year or longer, who have discontinued an anti-TNFα agent within 6 months prior to Screening, must obtain a subsequent chest x-ray prior to Visit 2 that shows no evidence of active TB. The chest x-ray may be substituted with documentation of a previous chest x-ray performed within 8 weeks prior to Screening. Please refer to Inclusion Criterion #6 in Section 5.1 for additional details.
[g] All eligible participants will be centrally assigned to randomized study intervention using an IWRS approximately 7 days prior to administration of study intervention at Visit 2 to allow for the shipment of study supplies. All eligibility criteria must be met before a participant can be randomized.
[h] On Day 1 (Visit 2), PK blood samples are to be collected at 0 hour (predose) and at 1 hour (CCI [redacted] and 2 to 4 CCI [redacted] start. After Day 1, *predose* PK samples are to be collected at 0 hours (ie, prior to administration of study intervention).
[i] After Day 1, *postdose* PK samples are to be collected at Visit 3 (CCI [redacted] Visit 4 (CCI [redacted] Visit 6 (CCI [redacted] 2), Visit 8 (CCI [redacted] 3), Visit 10 (CCI [redacted]
CCI [redacted]
[j] CCI [redacted] a whole blood transfusion within 120 days. Participants must provide consent for PAXgene DNA testing. If PAXgene DNA not drawn at Visit 2, it may be taken at any subsequent visit.
[k] Must be collected prior to start of bowel preparation for visits when ileocolonoscopy is needed (eg, Screening, Visits 9 and 29).
[l] SES-CD will be assessed by central reader based on ileocolonoscopy.
[m] Participants will use an electronic device provided by the sponsor to record each bowel movement (occurrence, presence of stool, blood, or mucus in bowel movement, stool consistency, and urgency) on an event-driven basis. At the end of each day, participants will record any bowel movements not reported on an event-driven basis and will complete additional daily PRO assessments (LSF, AP, and well-being items from the CDAI as well as items measuring other salient signs and symptoms) as part of the evening diary. The bowel movement and evening diaries will be available for completion every day during Screening and induction, and during 1 week out of every 4 weeks from Week 12 to Week 47. Starting at Week 48, the bowel movement and evening diaries will be available every day. In addition to the evening diary, the participants will complete 1 additional patient-reported CDAI item about temperature over 100°F (37.8°C) and

CD-PRO signs and symptoms modules as part of the evening diary during Screening, Baseline visit, Week 12, and Week 52; this will be referred to as the extended evening diary. Participants will also fill out the PGI-S-CD, PIS-AP, PII-LBMF, PGIC-CD, and FACIT-F weekly on the collection device. PGI-S-CD, PIS-AP, PII-LBMF, and FACIT-F data collection will begin at Screening, and PGIC-CD will begin at Week 1.

[n] May be performed by investigator or designee. To be collected on a tablet at the site during the study visit.

ADA = anti-drug antibodies; AE = adverse event; AP = abdominal pain; BM = biomarker; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; EQ-5D-5L = European Quality of Life-5 Dimensions; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; IBDQ = Inflammatory Bowel Disease Questionnaire; ICF = informed consent form; IL-22 = interleukin-22; IWRS = interactive web response system; CCI [redacted] LSF = loose stool frequency; PGIC-CD = Patient Global Impression of Change – Crohn's Disease; PGI-S- CD = Patient Global Impression of Severity – Crohn's Disease; PII-LBMF = Patient Impression of Interference-Loose Bowel Movement Frequency; PIS-AP = Patient Impression of Severity-Abdominal Pain; PK = pharmacokinetics; PRO = patient-reported outcome; QFT-TB = QuantiFERON-TB test; RNA = ribonucleic acid; SAE = serious adverse event; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF-36v2 = 36-item Health Survey Version 2; TB = tuberculosis; TNFα = tumor necrosis factor α; W = week; WOCBP = women of childbearing potential.

Table 18 Schedule of Activities–- Early Termination Visit and Safety Follow-up Period (Stage 2)

Study Period	**Induction or Maintenance Period**	**18-week Follow-up[a]**	
Visit Number	**Early Termination Visit**	**Follow-up 1**	**Follow-up 2**
Week	**At Study Withdrawal or Premature Discontinuation of Study intervention**	**8 Weeks Post-last Dose**	**18 Weeks Post-last Dose**
Extra-intestinal manifestation assessment	X	X	X
AE/SAE assessment	X	X	X
Concomitant medications	X	X	X
Physical examination, vital signs, and weight	X	X	X
ECG	X		
Serum chemistry, hematology, C-reactive protein, and urinalysis	X	X	X
Urine pregnancy test	X	X	X
PK blood sample	X	X	X
Immunogenicity blood sample	X	X	
BM blood sample	X		
Serum IL-22 and [redacted]	X	X	X
Stool for fecal calprotectin and exploratory BMs[b]	X		
Stool for *C difficile* test[b]	X		
Ileocolonoscopy	X		
Terminal ileum and colon mucosal biopsies	X		
SES-CD assessment	X		
CDAI clinician-reported assessments	X		

Study Period	**Induction or Maintenance Period**	**18-week Follow-up[a]**	
Visit Number	**Early Termination Visit**	**Follow-up 1**	**Follow-up 2**
Week	**At Study Withdrawal or Premature Discontinuation of Study intervention**	**8 Weeks Post-last Dose**	**18 Weeks Post-last Dose**
CD-PRO weekly recall modules[c]	X		
IBDQ[c]	X		
EQ-5D-5L[c]	X		
SF-36[c]	X		
Review participant PRO eDiary	X		
Assessment of injectionsite reactions	X	X	

[a] For participants offered the opportunity to enroll into the open-label extension study of brazikumab based on qualification of eligibility criteria, the Safety Follow-up Period will not be applicable. The follow-up periods are based on the last brazikumab/brazikumab placebo dose.
[b] Must be collected prior to start of bowel preparation for ileocolonoscopy
[c] To be collected on a tablet at the site during the study visit
AE = adverse event; BM = biomarker; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; ECG = electrocardiogram; EQ-5 D-5L = European Quality of Life-5 Dimensions; IBDQ = Inflammatory Bowel Disease Questionnaire; IL-22 = interleukin-22; CCI [redacted] PK = pharmacokinetics; PRO = patient-reported outcome; SAE = serious adverse event; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF-36 = 36-item Health Survey.

F 3 Rationale for the Stage 2 Active Comparator

Humira® will be used as an active comparator for Stage 2 of this study. Humira was chosen as the appropriate active comparator for this protocol because it is used extensively to treat patients with CD and is considered an acceptable standard of care treatment in patients who have failed conventional non-biologic treatments [including antibiotics, CS, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate)]. Humira is an acceptable alternate therapy in patients who have failed to demonstrate a response or have lost response to infliximab. Furthermore, practical considerations for participants were considered when selecting Humira as the comparator such as the long-term SC dosing and the lower complexity needed to implement a double-dummy blinding strategy. Brazikumab (after the 3 IV infusion doses) and Humira are both administered SC for the duration of the study. A detailed description of Humira can be found in the manufacturer's prescribing information or local package insert (Humira Package Insert).

F 4 Objectives and Endpoints

Table 19 Stage 2 Objectives and Endpoints

Stage 2 Objectives	Stage 2 Endpoints
Primary	
• To compare the efficacy of brazikumab with that of Humira to achieve endoscopic response and clinical remission at Week 52 in participants who are BM+	• **Co-primary**: Endoscopic response at Week 52 • **Co-primary**: Clinical remission at Week 52
Secondary	
• To compare the efficacy of brazikumab with that of Humira to achieve sustained endoscopic response and clinical remission at both Week 12 and Week 52 in participants who are BM+	• **Key Secondary:** Endoscopic response at both Week 12 and Week 52 • **Key Secondary:** Clinical remission at both Week 12 and Week 52
• To compare the efficacy of brazikumab with that of Humira in achieving endoscopic remission and clinical remission at Week 52 in participants who are BM+	• **Key Secondary:** Endoscopic remission at Week 52 • **Key Secondary:** Clinical remission at Week 52
• To compare the efficacy of brazikumab with that of Humira to achieve CS-free endoscopic remission and clinical remission at Week 52 in participants who are BM+	• **Key Secondary:** CS-free endoscopic remission at Week 52 • **Key Secondary:** CS-free clinical remission at Week 52
• To compare the efficacy of brazikumab with that of Humira to achieve CS-free endoscopic remission and clinical remission at Week 52 in participants taking CS at Baseline and BM+	• CS-free endoscopic remission at Week 52 for participants taking CS at Baseline • CS-free clinical remission at Week 52 for participants taking CS at Baseline
• To compare the efficacy of brazikumab with that of Humira to achieve endoscopic response and clinical remission at Week 12 in participants who are BM+	• Endoscopic response at Week 12 • Clinical remission at Week 12
• To compare the efficacy of brazikumab with that of Humira to achieve endoscopic response at Week 12 and endoscopic remission at Week 52 and clinical remission at both Week 12 and Week 52 in participants who are BM+	• Endoscopic response at Week 12 and endoscopic remission at Week 52 • Clinical remission at both Week 12 and Week 52
• To compare the efficacy of brazikumab with that of Humira to achieve CS-free endoscopic response and clinical remission at Week 52 in participants who are BM+	• Endoscopic response at Week 52 • Clinical remission at Week 52
• To evaluate PK and immunogenicity of brazikumab in participants who are BM+	• Population PK model of serum concentrations of brazikumab and analysis for serum anti-brazikumab antibodies
• To characterize the exposure-response relationships of brazikumab in participants who are BM+	• Exposure-response model linking primary endpoints to metrics of model-predicted individual brazikumab exposures

Stage 2 Objectives	Stage 2 Endpoints
• To evaluate the safety and tolerability of brazikumab in participants who are BM+	• AEs, clinical laboratory values, vital signs, physical exams, ECGs
Additional	
• To compare the efficacy of brazikumab with that of Humira to achieve CS-free endoscopic response at Week 12 and CS-free endoscopic remission at Week 52 and CS-free clinical remission at both Week 12 and Week 52 in participants who are BM+	• CS-free endoscopic response at Week 12 and endoscopic remission at Week 52 • CS-free clinical remission at both Week 12 and Week 52
• To evaluate the impact of brazikumab on the signs and symptoms of CD in participants who are BM+	• Change from Baseline at Week 12 and Week 52 in signs and symptom scores (eg, LSF, AP, urgency, fatigue) derived from the BSFS, NRS, CD-PRO, PGI-S-CD, PIS-AP, PII-LBMF, PGIC-CD, and FACIT-F
• To evaluate the impact of brazikumab on HRQoL in participants who are BM+	• Change from Baseline at Week 12 and at Week 52 in IBDQ, SF-36, and EQ-5D-5L
• To explore changes in signs and symptoms and HRQoL using a range of measures in participants who are BM+	• Exploratory analysis of subscale scores from BSFS, CD-PRO, IBDQ, and additional PRO items developed for the brazikumab program.

AE = adverse event; AP = abdominal pain; BM+ = biomarker serum IL-22 concentrations at or above a pre-established cutoff; BSFS = Bristol Stool Form Scale; CD = Crohn's disease; CS = corticosteroid; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life-5 Dimensions; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; LSF = loose stool frequency; NRS = Numerical Rating Scale; PGIC-CD = Patient Global Impression of Change – Crohn's Disease; PGI-S-CD = Patient Global Impression of Severity – Crohn's Disease; PII-LBMF = Patient Impression of Interference-Loose Bowel Movement Frequency; PIS-AP = Patient Impression of Severity-Abdominal Pain; PK = pharmacokinetics; PRO = patient-reported outcomes; SF-36 = 36-item Health Survey.

F 5 Study Intervention

F 5.1 Study Interventions Administered

Participants who satisfy all inclusion and exclusion criteria (Sections 5.1 and 5.2) and are randomized in Stage 2 will receive study intervention, defined as any investigational treatment or placebo intended to be administered to a study participant according to the study protocol. Table 20 presents details regarding study intervention and administration for Stage 2.

Table 20 Stage 2 Study Interventions

Study intervention Name	Brazikumab CCI	Brazikumab CCI	CCI	Placebo
Route of administration	CCI [redacted]			
Dose (mg)				

Study intervention Name	Brazikumab CCI	Brazikumab CCI	Humira	Placebo
	CCI		40 (Day 29 and every 2 weeks through Week 50)	
Dosing instructions[a]	CCI [redacted]			
Packaging and labeling	[redacted]			
Provider	AstraZeneca	AstraZeneca	AstraZeneca	AstraZeneca

[a] F CCI [redacted] contents of vials will be added to an CCI [redacted] of dextrose solution to a total volume of CCI [redacted] then administered by CCI [redacted] CCI [redacted] CCI [redacted]

F 5.2 Double-dummy Dosing Regimen

In Stage 2 of this protocol, brazikumab is administered as a 60-minute CCI [redacted] infusion for the CCI [redacted] and CCI [redacted] for all subsequent doses; all Humira® doses are administered as a SC injection. Therefore, because the preparations of brazikumab and Humira are distinct in appearance and volume, special precautions need to be taken to ensure the double-blind nature of the study. The double-dummy technique will be used to maintain the blind when administering the treatments because the brazikumab and Humira treatments cannot be made identical. All participants will be administered the same number and type (CCI [redacted] of treatments throughout the study regardless of treatment group assignment. For example, during the Induction Period, an CCI [redacted] and CCI [redacted] will be administered to each participant for induction doses on CCI [redacted] injections will be administered on CCI [redacted] Table 21 presents the by-visit double-dummy administration schedule for the Induction Period. The SC injection is to be administered after CCI [redacted] to maintain consistency in procedures during the Induction Period Further details regarding dosage formulation and dosing

procedures for the study intervention may be found in the Pharmacy Manual.

For the double-blind Maintenance Period, all participants will receive SC injections every 2 weeks per the double-dummy administration schedule (Table 22). They will receive either 3 SC injections or 1 SC injection at alternating visits 2 weeks apart. Please refer to the Pharmacy Manual for additional details regarding the administration schedule for study intervention.

All study interventions will be handled by a pharmacist (or appropriately qualified individual) and handed over to the qualified site staff who will administer the study intervention to participants according to the brazikumab investigational directions for use. The pharmacist will be responsible for preparing the CCI [redacted] and CCI [redacted] according to the Pharmacy Manual. A study monitor will perform study intervention accountability. In the event that the treatment allocation for a participant becomes known to the investigator or other blinded study staff involved in the management of study participants, the sponsor's study monitor must be notified immediately.

Table 21 Double-dummy Dosing Administration Schedule for Stage 2 Induction Period

Day (Visit Number, Visit Name)	Treatment Group			
	Brazikumab		Humira	
	CCI [redacted]		CCI [redacted]	
	CCI [redacted]	Humira placebo (# administered)	CCI [redacted]	Humira (# administered)
1 (2, Baseline)	CCI [redacted]			
CCI [redacted]				
CCI [redacted]				
CCI [redacted]				
CCI [redacted]				
CCI [redacted]				

#CCI [redacted]

Table 22 Double-dummy Dosing Administration for Stage 2 Maintenance Period

Day (Visit Number, Visit Name)	Treatment Group			
	Brazikumab		Humira	
	CCI [redacted]		CCI [redacted]	
	Brazikumab (# administered)	Humira placebo	Brazikumab placebo (# administered)	Humira
CCI [redacted]				

Day (Visit Number, Visit Name)	Treatment Group			
	Brazikumab		Humira	
	CCI [redacted]			
	Brazikumab (# administered)	Humira placebo	Brazikumab placebo (# administered)	Humira
CCI [redacted]				

F 5.2.1 Intravenous Administration

All participants will receive 1 CCI [redacted] of study intervention (brazikumab, sham placebo) on Days 1, 29, and 57 (Visits 2, 5, and 7) of the Induction Period. An experienced and qualified staff member will place the CCI [redacted] The total volume administered will be recorded in the eCRF.

The CCI [redacted] intervention (brazikumab or sham placebo) will be delivered in CCI [redacted] in water in a volume of CCI [redacted] over a minimum of CCI [redacted] using an infusion pump. Before and after the CCI [redacted] the CCI [redacted] will be flushed with CCI [redacted] of CCI [redacted] in water.

Vital signs (BP, temperature, pulse rate, and respiration rate) will be obtained before IV study 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 CCI [redacted] administration, immediately after completion of infusion, and at approximately every 30 minutes for a minimum of 1 hour post-infusion or until stable, whichever is later. The first and last vital signs are to be recorded on the eCRF. Participants will be discharged from the site when they are deemed clinically stable by the investigator, a minimum of 1 hour after completion of CCI [redacted] for the initial 2 infusions (Visits 2 and 5). The monitoring time after the third infusion (Visit 7) may be reduced to a minimum of 30 minutes at the discretion of the investigator.

Infusion related reactions have been reported with the administration of CCI [redacted] antibodies. 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, or procedures for

emergency treatment must be in place. Study personnel must be trained to recognize and take appropriate action for emergency measures according to local guidelines. Any infusion related reaction and/or hypersensitivity reaction is to be reported as an AESI (see Sections 8.3.10.1 and 8.3.10.3).

F 5.2.2 Subcutaneous Administration

Brazikumab, Humira, or sham placebo will be administered to all participants during the Induction and Maintenance Periods by CCI at the visits specified in Table 21 and Table 22. Each SC dose will be administered to the participant's anterior abdominal wall by an unblinded, experienced and qualified staff member. The brazikumab, Humira, or sham placebo dose will be administered as a single or multiple CCI according to the double-dummy dosing administration table. CCI will be on alternating (left or right) sites on the participant's anterior abdominal wall over no more than CCI total time for all CCI and at a distance of at least CCI.

For CCI the person administering the dose will wipe the CCI surface of the participant's abdomen with alcohol and allow the skin to air dry. The skin will be pinched to isolate the CCI. Avoiding the belly button, ribs, hip bones, scars, or moles, the needle will be inserted at a CCI approximately halfway into the CCI Brazikumab or Humira will be slowly injected (at least a CCI is recommended) into the CCI using gentle pressure. The area is not to be massaged after CCI. CCI are to be CCI and noted in the source documents only. The total volume of dose administered will be recorded in the eCRF.

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

F 5.3 Study Supplies

AstraZeneca will supply the following study interventions for the study:

1 Brazikumab CCI
2 Brazikumab pack containing CCI
3 Brazikumab placebo pack containing CCI

4 Humira CCI
5 Humira placebo CCI
6 Brazikumab placebo CCI

Additional details and instructions for study intervention use are provided in the Pharmacy Manual.

Any defects in study intervention or prefilled syringes (including malfunction, use error, and inadequate labeling) shall be reported by the investigator as described in the Pharmacy Manual.

F 6 Statistical Considerations

F 6.1 Stage 2 Statistical Hypotheses

Stage 2 is a confirmatory phase for efficacy and safety. Efficacy analyses will be performed primarily for the BM+ group. The null and alternative hypotheses for the 2 co-primary endpoints are:

H0: There is no difference in Week 52 endoscopic response rate or Week 52 clinical remission rate between each of the 2 brazikumab dose groups and the Humira® CCI treatment group.

versus

H1: There is a difference in both endoscopic response rate and clinical remission rate at Week 52 between at least 1 of the brazikumab dose groups and the Humira CCI treatment group.

For a key secondary endpoint, the null hypothesis is that there is no difference between each of the brazikumab CCI and brazikumab CCI treatment groups and the Humira CCI treatment group, and the alternative hypothesis is that there is a difference between at least 1 brazikumab dose group and the Humira CCI treatment group.

F 6.2 Stage 2 Sample Size Determination

For Stage 2 of the study, if initiated, a total of approximately 690 participants will be randomized into 3 treatment groups, brazikumab CCI brazikumab CCI and Humira CCI with a CCI The randomization will be stratified by BM+ and BM- status in a 2:1 ratio. A total of 459 BM+ participants and a total of 231 BM- participants will be randomized. Therefore, approximately 153 BM+ and 77 BM- participants will be randomized per treatment group. The analyses for efficacy endpoints will be based on the BM+ group. One hundred fifty-three participants per treatment group will provide at least CCI to detect the treatment difference between each of the 2 brazikumab doses and

Humira for the co-primary and key secondary efficacy endpoints, using a 2-sided test at a significance level of α = 0.025 for each brazikumab dose. The power calculations are based on assumed rates for the BM+ group listed in Table 23. These rates are estimates based on available brazikumab data and limited published data for Humira for the CDAI LSF and AP symptoms and SES-CD assessments. There are no completed studies for either brazikumab or Humira that have assessed the exact endpoints at the specified timepoints below.

Table 23 Assumed Response/Remission Rates in Stage 2 for the BM+ Group and Estimated Power for Co-primary and Secondary Efficacy Endpoints

Endpoint	Assumed Rate			Power	
	Brazikumab CCI	Brazikumab CCI	Humira CCI	Brazikumab CCI vs. Humira CCI	Brazikumab CCI vs. Humira CCI
CCI [redacted]					

BM+ = biomarker serum IL-22 concentrations at or above a pre-established cutoff.

The sample size for Stage 2 may be amended before its initiation based on the Stage 1 primary (Week 12) analysis results. The sample size for Stage 2 may be further adjusted based on the Stage 1 final (Week 52) analysis results when all participants in Stage 1 complete the 52-week Treatment Period. Since the final analyses for Stage 2 will not use Stage 1 data, such sample size adjustment will not introduce bias to the statistical validity of conclusions. Similarly, since the target participants population for Stage 2 is for the BM+ group, the ratio of 2:1 for BM+:BM- in the current sample size calculation may be adjusted as well based on Stage 1 data.

F 6.3 Stage 2 Populations

There are 2 analysis populations for Stage 2:

- The ITT population: This includes all participants who are randomized to a Stage 2 treatment group.

– The safety population: This includes all participants who receive ≥ 1 administration of Stage 2 study intervention.

F 6.4 Statistical Analyses

A separate Stage 2 SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned main statistical methodology features of the primary and the key secondary endpoints.

If initiated, Stage 2 will enroll all participants regardless of BM status, but randomization to Stage 2 will be stratified by BM+/BM- status. The key statistical efficacy objective for Stage 2 is to test the superiority of brazikumab dose(s) versus the active comparator in the BM+ participants cohort.

An overall 5% Type 1 error rate will be applied to the confirmatory Stage 2 and will be controlled for the comparison of any brazikumab dose group versus the Humira 160 mg control for the primary and the key secondary endpoints. For Stage 2 as well as Stage 1, all statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects, unless stated otherwise; and all confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. Those tests done for Stage 1, however, will be considered as exploratory only.

Baseline for efficacy variables is defined as the last non-missing efficacy assessment before the first dose of study intervention upon randomization.

F 6.4.1 Efficacy Analysis

Stage 1 and Stage 2 efficacy data will be analyzed and reported separately.

The efficacy analysis for Stage 2 of the study will be based on the ITT population from Stage 2 participants. Since Stage 2 of the study is designed and planned for the BM+ group, all planned statistical inference will be based on the BM+ group. Analyses results for the BM- group will be presented as well, but primarily as a reference group to provide at least some estimate of the effect in that group and may also potentially provide an overall risk–benefit assessment for brazikumab in the overall study population. There is no interim analysis planned for Stage 2.

Stage 2 will be considered as a successful or positive Phase 3 study if, in the BM+ group, at least 1 brazikumab dose, each primary endpoint is demonstrated to be statistically superior for brazikumab over the Humira CCI control (at the 2-sided 5% significance level).

F 6.4.1.1 Efficacy Endpoints for Stage 2

Primary Efficacy Endpoints

There are 2 primary efficacy endpoints in Stage 2:

- Co-primary: Endoscopic response CCI
- Co-primary: Clinical remission CCI

Secondary Efficacy Endpoints

The key secondary efficacy endpoints for Stage 2 are:

Sustained endoscopic response and clinical remission:

- Endoscopic response at CCI
- Clinical remission at CCI

Endoscopic remission and clinical remission at CCI

- Endoscopic remission CCI
- Clinical remission at CCI

CS-free endoscopic remission and clinical remission at CCI

- CS-free endoscopic remission at CCI
- CS-free clinical remission at CCI

Other secondary efficacy endpoints for Stage 2 are:

CS-free endoscopic remission and clinical remission at Week 52 in participants taking CS at Baseline:

- CS-free endoscopic remission at Week 52 for participants taking CS at Baseline
- CS-free clinical remission at Week 52 for participants taking CS at Baseline

Endoscopic response and clinical remission at CCI

- Endoscopic response at CCI
- Clinical remission at CCI

Sustained endoscopic response/remission and clinical remission:

- Endoscopic response at CCI and endoscopic remission at CCI
- Clinical remission at both CCI

CS-free endoscopic response and clinical remission at CCI

- Endoscopic response CCI

- Clinical remission at Week 52

Additional Efficacy Endpoints

Additional efficacy endpoints for Stage 2 of the study are:

- CS-free endoscopic response at Week 12 and endoscopic remission at Week 52
- CS-free clinical remission at both Week 12 and Week 52
- Change from Baseline at Week 12 and Week 52 in signs and symptom scores (eg, LSF, AP, urgency, fatigue) derived from the BSFS, NRS, CD-PRO, PGI-S-CD, PIS-AP, PII-LBMF, PGIC-CD, and FACIT-F
- Change from Baseline at Week 12 and at Week 52 in IBDQ, SF-36, and EQ-5D-5L
- Exploratory analysis of subscale scores from BSFS, CD-PRO, IBDQ, and additional PRO items developed for the brazikumab program

F 6.4.1.2 Missing Data Imputation for Efficacy Endpoints

For both Stage 1 and Stage 2 of the study, missing data for dichotomous variables will be handled using the non-responder imputation method, ie, any participants with missing information on the variables will be assumed as a non-responder.

Further, for Stage 2, for both the co-primary and key secondary endpoints, additional sensitivity analyses that account for missing remission data due to reasons of early discontinuation or due to other reasons that led to 1 or more missing data points will be explored to assess the robustness of the primary efficacy and key secondary analysis results. Participants who take prohibited or rescue treatment will also be explored. These will be explored based on blinded trial data along with historical data (if available) and then be documented in the final Stage 2 SAP of this study.

F 6.4.1.3 Analyses for Efficacy Endpoints for Stage 2

The co-primary and key secondary efficacy analyses are defined in the following sections. All analyses for other efficacy endpoints will be defined in the Stage 2 SAP.

Analyses for Primary Efficacy Endpoints

For each primary endpoint for Stage 2 of the study, the observed response proportions will be provided by BM status and treatment group. For each BM+ cohort, each of the efficacy endpoints will be analyzed using a Cochran-Mantel-Haenszel test controlling for stratification factors (status of prior biologic use and CS use [yes or no] at randomization).

The respective comparisons of brazikumab versus Humira is the primary analysis for the BM+ group.

Analyses for Secondary Efficacy Endpoints

For each key secondary efficacy endpoint, the observed response proportions will be analyzed

using the same methods used for co-primary efficacy endpoints for Stage 2 of the study.

Multiple Comparisons Procedure for Primary and Secondary Endpoints

For Stage 2 of the study, a graphical approach by (Bretz et al, 2009) will be used to control the overall type I error rate for multiple comparisons across the brazikumab doses and the primary and secondary efficacy endpoints. The co-primary efficacy endpoints will serve as the gatekeepers of the secondary endpoints. The test order for the secondary endpoints will be determined after the primary analysis of Stage 1 and/or the Stage 1 final (Week 52) analysis when all participants in Stage 1 complete the 52-week Treatment Period. Recycling of weights between the 2 doses is also allowed.

Using graphical approach with the weighted Bonferroni-based closed-test procedure, the endpoints are represented by circles with associated weights inside the circle. The weight is the fraction of α, representing local significance levels. The fraction in the rectangle, associated with a line connecting 2 circles, indicates the fraction of the local significance level of the circle at the beginning of the line which is added to the local significance level of the circle at the end of the line, if the null hypothesis at the beginning circle is rejected (Figure 4 and Table 24).

Figure 4 Multiple Comparisons Procedure

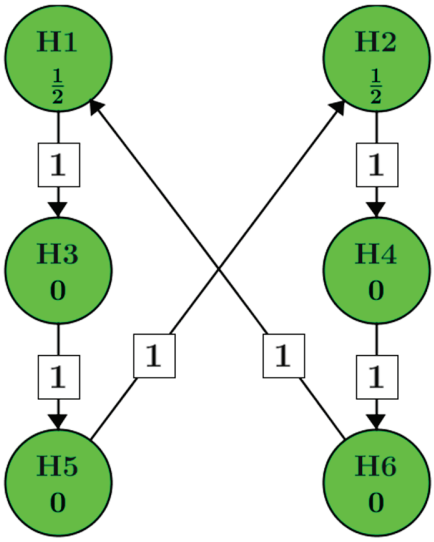


Table 24 Multiple Comparisons Procedure Definitions

Circle	Alternate Hypothesis	Weight	Local Significance Level
CCI [redacted]			

F 6.4.1.4 Serum IL-22 Concentration Cutoff Identification Based on Stage 1 Primary Analysis

In Stage 2 (Phase 3) of this study, Humira is chosen as an active comparator. The rationale for the choice of comparator is discussed in Appendix F 3. The primary and key secondary objectives of Stage 2 are to show that brazikumab is superior to Humira in the BM+ subgroup. Therefore, the selection of the serum IL-22 concentration level cutoff will be based on the efficacy result of brazikumab versus Humira from Stage 1 (Phase 2b) of this study.

The serum IL-22 concentration cutoff will be chosen to be the superior active comparator point defined as the smallest serum IL-22 concentration value where the posterior mean response rate for the endoscopic response endpoint of brazikumab is better than the mean response rate of Humira, the standard of care comparator used in the study. The superior active comparator point will be estimated using a model for the response rate under the endoscopic response endpoint as a function of treatment group and log (IL-22) value described in the Stage 1 primary analysis plan for serum IL-22 concentration cutoff Determination and Stage 2 Go/No-go Suggestion for Efficacy in Section 9.4. The superior active comparator point will be primarily estimated using the endoscopic response endpoint and further assessed for the clinical remission endpoint incorporating both the CDAI LSF and AP items to confirm the superior active comparator point is also valid for clinical remission endpoint.

F 6.4.2 Safety Analyses

The safety analyses will be performed using the Safety Population. Stage 1 and Stage 2 data

will be analyzed separately. In addition, for Stage 2, the safety analyses will be further presented by BM+ and BM- group. The safety parameters will include AEs, clinical laboratory, vital sign, physical exams, and ECG parameters. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of study intervention will be used as the Baseline for all analyses of that safety parameter. Continuous variables will be summarized by the number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

F 6.4.2.1 Adverse Event

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

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

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

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

- By system organ class and preferred term
- By system organ class, preferred term, and severity.

The number and percentage of participants reporting treatment-related TEAEs in each study intervention 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 summarization by severity.

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

In addition, AESIs as defined in Section 8.3.10 will also be summarized.

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

F 6.4.2.2 Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at Baseline, postbaseline, and changes from Baseline at each postbaseline assessment will be presented by treatment group for each clinical laboratory assessment.

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

F 6.4.2.3 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 by treatment group.

Vital sign values will be considered as a PCS if they meet both the observed value criteria and the change from Baseline value criteria that will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants who have available Baseline values or non-PCS Baseline values for parameters with only observed value criterion and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

F 6.4.2.4 Electrocardiograms

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 by treatment group.

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

F 6.4.3 Other Analyses

PK, PD, and IL22 data will be described in the SAP and PK analysis plan finalized before database lock. The population PK analysis and PK-PD as well as BM for exploratory analyses will be presented separately from the main CSR.

F 6.5 Interim Analyses

There is no planned interim analysis for Stage 2, the confirmatory Phase 3 registration study.

Sample size or brazikumab dose arm adaptation, if needed, will be based entirely on and determined by the observed Week 52 data from Stage 1.

Appendix G Procedures for Tuberculosis Testing From Screening

Testing for TB will be performed as specified in the SoA (Table 2). The following guidelines for TB testing are to be followed at Screening and during the study period:

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

Appendix H Corticosteroid Tapering

Table 25 Corticosteroid Tapering for Prednisone/Budesonide in mg/Day

CCI

[redacted]

Table 26 Approximate Equivalent Doses of Oral Prednisone

Oral prednisone equivalents	Equivalent doses

CCI

[redacted]

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

I 1 Bowel Movement Diary

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

I 2 Evening Diary

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

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

I 3 Site Visit Instruments

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

I 3.1 Patient Global Impression of Severity-Crohn's Disease

Overall, how would you rate your Crohn's disease symptoms in the past 7 days?

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

I 3.2 Patient Global Impression of Change-Crohn's Disease

Compared to before you started this study, how would you rate your Crohn's disease symptoms overall?

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

I 3.3 FACIT-F Scale (Version 4)

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

I 3.4 Inflammatory Bowel Disease Questionnaire

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

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

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.

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

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

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

I 3.6 SF-36v2® Health Survey

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

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

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

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

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

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

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

Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary (eg, remote visits). Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Table 2 or Table 17. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

Rescreening of Participants to Reconfirm Study Eligibility

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

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the Screening window specified in Table 1 or Table 17, 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 or Table 17 must be undertaken to

confirm eligibility using the same randomization 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 participant's home or other remote location as per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

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

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

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

At-home or Remote Location Study Intervention Administration Instructions

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

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

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

Data Capture During Telemedicine or Home/Remote Visits

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

Appendix K Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ANA	antinuclear antibody
Anti-LKM	anti-liver/kidney microsomal Ab
ALT	alanine aminotransferase
AP	abdominal pain
ASMA	anti-smooth muscle Ab
AST	aspartate aminotransferase
aTT	activated thromboplastin time
AUC	area under the serum concentration time-curve
AUC_{0-28}	area under the curve from time 0 to 28 days
BM	biomarker
BM-	biomarker serum IL-22 concentrations below a pre-established cutoff
BM+	biomarker serum IL-22 concentrations at or above a pre-established cutoff
BP	blood pressure
BSFS	Bristol Stool Form Scale
BUN	blood urea nitrogen
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CD-PRO	Crohn's Disease Patient-Reported Outcome Scale
CI	confidence interval
clinical 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
clinical response	minimum 25% reduction in LSF subscore or AP subscore from Baseline
C_{max}	maximum concentration
CMV	cytomegalovirus
CRP	C-reactive protein
CS	corticosteroids
CS-free	free of corticosteroids for the last 12 weeks before the assessment
CSP	clinical study protocol
CTCAE	Common terminology criteria for adverse events
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid

Abbreviation or special term	Explanation
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
E/D	Early Study Intervention Discontinuation
EDC	Electronic Data Capture
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EIM	extraintestinal manifestations
endoscopic remission	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
endoscopic response	Minimum of 50% decrease from Baseline in SES-CD total score
EQ-5D-5L	5-level European Quality of Life - 5 Dimensions
ET	Early Termination
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	*same as* intent-to-treat
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAV	hepatitis A virus
HBc	hepatitis B core
HBV	hepatitis B virus
HCV	hepatitis C virus
hCG	human chorionic gonadotropin
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HSV	herpes simplex virus
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

Abbreviation or special term	Explanation
IFNγ	interferon-gamma
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IL-22	interleukin-22
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRT	Interactive Response Technology
ITT	intent-to-treat
CCI	CCI
IWRS	interactive web response system
IxRS	Interactive Voice/Web Response System
CCI	CCI
LDH	lactate dehydrogenase
LS	least squares
LSF	loose stool frequency
MACE	major adverse cardiac events
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
NCI	National Cancer Institute
NRI	non-responder imputation
NRS	Numeric Rating Scale
NSAID	non-steroidal anti-inflammatory drug
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PGIC-CD	Patient Global Impression of Change-Crohn's Disease
PGI-S-CD	Patient Global Impression of Severity-Crohn's Disease
PII-LBMF	Patient Impression of Interference-Loose Bowel Movement Frequency
PIS-AP	Patient Impression of Severity-Abdominal Pain
PK	pharmacokinetic(s)

Abbreviation or special term	Explanation
Primary symptom remission	for participants with Baseline LSF subscore of ≥ 5 and AP subscore < 2: Average daily LSF subscore of ≤ 3 AND no worsening of Baseline AP subscore as assessed on the CDAI OR for participants with Baseline AP subscore of ≥ 2 and LSF subscore < 5: Average daily AP subscore of ≤ 1 AND no worsening of Baseline LSF subscore as assessed on the CDAI
PRO	patient-reported outcomes
PR	time from beginning of the P wave until the beginning of the QRS complex
PT	prothrombin time
Q4W	every 4 weeks
QFT-TB	QuantiFERON-TB test
QRS	time from beginning of the Q wave to end of the S wave in heart's electrical cycle
QT	time from beginning of the Q wave to end of the T wave in heart's electrical cycle
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RBC	red blood cell
RNA	ribonucleic acid
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
CCI	CCI
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36	Short-Form 36 Health Survey
SoA	schedule of activities
SOP	standard operating procedure
SV	Screening Visit
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNFα	tumor necrosis factor-alpha
TPV	third-party vendor
UC	ulcerative colitis
UK	United Kingdom
ULN	upper limit of normal
UNS	Unscheduled

Abbreviation or special term	Explanation
W	week
WBC	white blood cell
WOCBP	women of childbearing potential
w/v	weight/volume

Appendix L Protocol Amendment History

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

Amendment 3 (August 2020)

Overall Rationale for the Amendment:

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

Section No. and Name	Description of Change	Brief Rationale
Throughout	Change sponsor to AstraZeneca and change study number to AstraZeneca study number	The sponsor of the study is changing to AstraZeneca and an AstraZeneca study code will be used moving forward
Throughout	Change Medical Safety Physician (MSP) to Study Physician.	This changed is being made to align with AstraZeneca terminology.
Title Page	Change in Sponsor Name and Legal Registered Address	The Sponsor name and address were changed to AstraZeneca AB
Title Page	Emergency Telephone number removed	The Allergan emergency number was removed from the title page. This will be provided directly to investigators
Title Page	SAE Reporting Fax Number/email removed	The Allergan SAE reporting Fax number/email were removed. Safety reporting information will be provided directly to investigators.
Title Page	Sponsor signatory was removed	The Allergan sponsor signatory was removed
Section 3, Objectives and Endpoints; Section 9.4.1.3.3, Additional Efficacy Endpoints 9.4.1.3.6, Additional Efficacy Endpoints	Changed "Exploratory analysis of subscale scores from BSFS, CD-PRO, IBDQ, and Allergan-developed items to "…and additional PRO items developed for the brazikumab program."	Revised text to be more generic and remove previous sponsor.
Section 6.1, Study Intervention	Changes made to reflect that AstraZeneca will be providing study interventions	With the sponsor change, AstraZeneca will be providing study interventions.
Section 6.1.2, Study Supplies	Allergan was changed to AstraZeneca	AstraZeneca will supply the test articles for the study.
Section 8.3.1, Time Period and Frequency for Collecting AE and SAE information	The Allergan specific AE reporting information was removed.	AstraZeneca will provide safety reporting information directly to investigators.

Section No. and Name	Description of Change	Brief Rationale
Section 8.3.3, Follow-up of AEs and SAEs Section 8.3.8.1 Potential Hy's Law Cases		
Section 10.3, Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The Allergan specific AE reporting information was removed. AstraZeneca protocol language was added.	AstraZeneca language was added due to change in Sponsor. AstraZeneca will provide safety reporting information directly to investigators.
Section 10.9, 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 2 (November 2018)

This amendment changes the infusion time for IV administration of brazikumab and placebo from 30 minutes to 60 minutes.

Overall Rationale for the Amendment:

Preliminary data from Phase 1 Study 3150-101-008 suggests that the brazikumab exposure following a 30-minute IV infusion is not comparable to a 60-minute infusion so Study 3150-301-008 will not evaluate brazikumab in a 30-minute infusion.

Summary of Changes:

On the Title Page the Sponsor name was corrected from Allergan to Allergan, Ltd.

In the following sections, Table 1-1 (footnote h), Section 2.2, Section 4.3, Table 6-1, Section 6.1.1, Section 6.1.1.1, and Section 8.5, the infusion time of 30 minutes (0.5 hour) was replaced with an infusion time of 60 minutes (1 hour).

The following sentence was added to the end of Section 2.2, "In Study 3150-301-008 the brazikumab and brazikumab placebo induction doses will be administered in a 60-minute IV infusion."

Amendment 1 (November 2018)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

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

Section No. and Name	Description of Change	Brief Rationale
Global	Minor editorial and document formatting revisions	Minor, therefore have not been summarized
Global	Changed Stage 1 endpoints from "Co-primary" to "Primary"	For clarity
Section 1.2 Schema	Replaced schema	To correct an error in Humira dosing
Section 1.3 Schedule of Activities, Table 1-1	Deleted fecal microbiome from stool sample testing	Fecal microbiome not analyzed
Section 1.3 Schedule of Activities, Table 1-2	Deleted fecal microbiome from stool sample testing	Fecal microbiome not analyzed
Section 5,1 Inclusion Criteria, criterion #1	Added language about local regulations regarding the minimum age of adult consent	For clarity
Section 5.2 Exclusion Criteria, criterion #7	Deleted "or evidence of obstruction"	To remove unnecessary text
Section 5.2 Exclusion Criteria, criterion #24	Added text to include relevant subpopulations	For clarity
Section 5.2 Exclusion Criteria, criterion #26	Replaced QTcF intervals with "determined on central ECG"	To align with central ECG parameters and include participants under 18 years old
Section 5.2 Exclusion Criteria, criterion #27, b	Added text to clarify that the Schwartz equation is to be used	For clarity
Section 5.2 Exclusion Criteria, criterion #28	Added text to allow Screening window to be extended after discussion with medical monitor	To provide site flexibility
Section 6.1 Study Interventions Administered, Table 6-1	Deleted Dosage Formulation and fixed footnote	Dosage formulation will only be included in the Pharmacy Manual
Section 6.1.1 Double-dummy Dosing Regimen	Changed text to remove dosage formulation and added text to refer to the Pharmacy Manual	For clarity and internal consistency
Section 6.1.1 Double-dummy Dosing Regimen, Table 6-2	Deleted dosage formulations and added visit numbers and visit names to the table	For clarity and internal consistency
Section 6.1.1 Double-dummy Dosing Regimen, Table 6-3	Deleted dosage formulations and added visit numbers and visit names to the table	For clarity and internal consistency

Section No. and Name	Description of Change	Brief Rationale
Section 6.1.1 Double-dummy Dosing Regimen, Table 6-4	Deleted dosage formulations and added visit numbers and visit names to the table	For clarity and internal consistency
Section 6.1.1 Double-dummy Dosing Regimen, Table 6-5	Deleted dosage formulations and added visit numbers and visit names to the table	For clarity and internal consistency
Section 6.1.1.1 Intravenous Administration	Added text to clarify how sites must be prepared to deal with infusion reactions	For clarity
Section 6.1.1.2 Subcutaneous Administration	Deleted text about injection volumes	For clarity
Section 6.1.1.2 Subcutaneous Administration	Change injection angle of subcutaneous injection from 90° to 45°	To change the method of administration for Humira
Section 6.1.2 Study Supplies	Deleted dosage formulations and added additional study supplies	For clarity and internal consistency
Section 6.1.2 Study Supplies	Deleted text concerning investigators reporting medical device incidents	For clarity and to prevent unintentional unblinding
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Added text to clarify site specific measures will be implemented to maintain the blind for participants and blinded site personnel	For clarity and to prevent unintentional unblinding
Section 6.5.1 Prior Medications Requiring Stable Dose Regimen	Added “and aminosalicylates”	To clarify the types of drugs in Table 6-6
Section 6.5.4 Rescue Therapies	Corrected text for when rescue therapy is to be considered and added text to clarify the definition of worsening or no improvement of symptoms	To fix an error and for clarity
Section 7.1 Discontinuation of Study Intervention	Edited text to clarify reasons for discontinuation of study intervention	For clarity and to align with other studies in the program
Section 8.3.8 Medical Device Incidents (Including Malfunctions)	Added text to clarify that the injector is also responsible for detection and documentation of events	For clarity and to prevent unintentional unblinding
Section 8.3.8.2 Follow-up of Medical Device Incidents	Added text to clarify measures will be implemented to maintain the blind for AE reporting	For clarity and to prevent unintentional unblinding

Section No. and Name	Description of Change	Brief Rationale
Section 8.3.8.3 Prompt Reporting of Medical Device Incidents to Sponsor	Added text to clarify that the injector is also responsible for reporting events	For clarity and to prevent unintentional unblinding
Section 8.3.8.4 Regulatory Reporting Requirements for Medical Device Incidents	Added text to clarify that the injector is also responsible for prompt reporting of events	For clarity and to prevent unintentional unblinding
Section 8.3.9.2 Infusion Reactions and Injection-site Reactions	Changed text to say infusion related reactions may be observed	For clarity
Section 8.3.9.3 Malignancies	Added squamous cell carcinoma to include relevant subpopulations	For clarity
Section 8.4 Treatment of Overdose	Added text concerning who to contact and how	For clarity
Section 9.3.1 Stage 1 Populations	Edited text to clarify study populations	For clarity
Section 9.3.2 Stage 2 Populations	Edited text to clarify study populations	For clarity
9.4.1.5 Missing Data Imputation for Efficacy Endpoints	Deleted “or concomitant”	For clarity
Section 10.4, Appendix 4: Abbreviations and Trademarks	Added MDRD	MDRD added to text
Section 10.8, Appendix 8: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting, Documenting Medical Device Incidents	Deleted “in accordance with the investigator’s normal clinical practice”	For clarity and to prevent unintentional unblinding
Section 10.8, Appendix 8: Medical Device Incidents: Definition and Procedures for Recording, Device Deficiency	Deleted entire section	For clarity and to prevent unintentional unblinding

AE = adverse event; ECG = electrocardiogram; MDRD = modification of diet in renal disease QTcF = QT interval corrected for heart rate using the Fridericia formula.

11 REFERENCES

Ahern et al, 2008
Ahern PP, Izcue A, Maloy KJ, Powrie F. The interleukin-23 axis in intestinal inflammation Immunological Reviews. 2008;226:147-159.

Andoh et al, 2005
Andoh A, Zhang Z, Inatomi O, Fujino S, Deguchi Y, Araki Y, et al. Interleukin-22, a member of the IL-10 subfamily, induces inflammatory responses in colonic subepithelial myofibroblasts. Gastroenterology. 2005;129:969-984.

Best et al, 1976
Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70:439-444.

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

Brand et al, 2006
Brand S, Beigel F, Olszak T, Zitzmann K, Eichhorst ST, Otte JM, et al. IL-22 is increased in active Crohn's disease and promotes proinflammatory gene expression and intestinal epithelial cell migration. Am J Physiol Gastrointest Liver Physiol. 2006;290:G827-G838.

Brazikumab, 2020
Brazikumab (MEDI2070) Investigator's Brochure, 2020; Edition 7.1.

Bretz et al, 2009
Bretz F, Maurer W, BrannathW, Posch M. A graphical approach to sequentially rejective multiple test procedures. Statist. Med. 2009;28:586–604.

Burger and Travis, 2011
Burger D, Travis S. Conventional medical management of inflammatory bowel disease. Gastroenterology. 2011;140:1827-1837.

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

Buxton et al, 2007
Buxton MJ, Lacey LA, Feagan BG, Niecko T, Miller DW, Townsend RJ. Mapping from disease-specific measures to utility: an analysis of the relationships between the Inflammatory

Bowel Disease Questionnaire and Crohn's Disease Activity Index in Crohn's disease and measures of utility. Value Health. 2007;10:214-20

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

Daperno et al, 2004
Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60:505-512.

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

European Medicines Agency, 2018
European Medicines Agency: Guideline on the development of new medicinal products for the treatment of Crohn's Disease (CPMP/EWP/2284/99 Rev. 2); 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-development-new-medicinal-products-treatment-crohns-disease-revision-2_en.pdf, February 2021

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

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

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

Gordon et al, 2012
Gordon K, Langley R, Gottlieb, Papp KA, Krueger GG, Strober BE, et al. A phase III, randomized, controlled trial of the fully human IL-12/23 mAb briakinumab in moderate-to-

severe psoriasis. J Invest Dermatol. 2012;132:304-314.

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

Guyatt et al, 1989
Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989 Mar; 96(3):804-810.

Higgins et al, 2013
Higgins PD, Harding G, Patrick DL, Revicki DA, Globe G, Viswanathan HN, et al. Development of the Crohn's Disease Patient-Reported Outcomes (CD-PRO) Questionnaire. Gastroenterology. 2013;44(5), Suppl 1, S-768 (Abstract Tu1124).

Hue et al, 2006
Hue S, Ahern P, Buonocore S, Kullberg MC, Cua DJ, McKenzie BS, et al. Interleukin-23 drives innate and T cell–mediated intestinal inflammation. J Exp Med. 2006;203:2473-2483.

Humira Package Insert
Humira® Package Insert. Abbvie Inc, North Chicago, IL, USA.

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

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

Kullberg et al, 2006
Kullberg, MC, Jankovic D, Feng CG, Hue S, Gorelick PL, McKenzie BS, et al. IL-23 plays a key role in Helicobacter hepaticus-induced T cell-dependent colitis. J Exp Med. 2006;203:2485-2494.

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

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

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

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

Maca et al, 2006
Maca J, Bhattacharya S, Dragalin V, Gallo P, and Krams, M. Adaptive seamless Phase II/III designs—background, operational aspects, and examples. Drug Inf 2006;40:463-475.

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

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

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

Rutgeerts et al, 2003
Rutgeerts P, Van Deventer S, Schreiber S. Review article: the expanding role of biological agents in the treatment of inflammatory bowel disease - focus on selective adhesion molecule inhibition. Aliment Pharmacol Ther. 2003;17:1435-1450.

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

Sandborn et al, 2020
Sandborn WJ, Ferrante M, Bhandari BR, Berliba E, Feagan BG, Hibi T, et al. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Ulcerative Colitis. Gastroenterology. 2020;158(3):537-549.

Sands and Ooi, 2005
Sands BE, Ooi CJ. A survey of methodological variation in the Crohn's disease activity index. Inflamm Bowel Dis. 2005;11:133-138.

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

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

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

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

Uhlig et al, 2006
Uhlig HH, McKenzie BS, Hue S, Thompson C, Joyce-Shaikh B, Stepankova R, et al. Differential activity of IL-12 and IL-23 in mucosal and systemic innate immune pathology. Immunity. 2006;25:309-318.

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

Yen et al, 2006
Yen D, Cheung J, Scheerens H, Poulet F, McClanahan T, McKenzie B, et al. IL-23 is essential

for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. J Clin Invest. 2006;116:1310-1316.

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