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

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LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AP	Abdominal pain
AST	Aspartate aminotransferase
BM	Biomarker
BMD	Bowel movement diary
BSFS	Bristol stool form scale
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDL	Clinical data lock
CRP	C-reactive protein
CS	Corticosteroid
CSP	Clinical study protocol
CSR	Case study report
ECG	Electrocardiogram, electrocardiographic
eCRF	Electronic case report form
EIM	Extraintestinal manifestation
EQ-5D-5L	European Quality of Life- 5 Dimensions
ET	Early termination
FAS	Full Analysis Set
FCP	Fecal calprotectin
HRQoL	Health-related quality of life

Abbreviation/Term	Definition
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed consent form
IL-22	Interleukin-22
IP	Investigational Product
IPD	Important protocol deviations
IV	Intravenous
LLN	Lower limit of normal
LOCF	Last observation carried forward
LSF	Loose stool frequency
Max	Maximum
MCSc	Mental Component Score
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
nAb	Neutralizing antibody
NRI	Non-responder imputation
NRS	Numerical Rating Scale
PCS	Potentially Clinically Significant
PCSc	Physical Component Score
PK	Pharmacokinetic
PRO	Patient reported outcome
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{½}$)

Abbreviation/Term	Definition
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous(ly)
SD	Standard deviation
SE	Standard error
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36	Short-Form 36 Health Survey
SI	Le Système International d'Unités (International System of Units)
SoA	Schedule of activities
SOC	System organ class
TBL	Total bilirubin
ULN	Upper limit of normal
VAS	Visual Analog Scale
WHO	World Health Organization

AMENDMENT HISTORY

The table below is pre-populated with 'N/A' for the first edition of the SAP, where the first entry into the table is to be the date of initial sign off, showing 'Initial Approved SAP' in the Description of Change column.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	xx xxx 2022 (Version 1.0)	Initial approved SAP	N/A	N/A

1 INTRODUCTION

This is a global, multicenter, open-label extension study of brazikumab limited to participants previously enrolled in Stage 1 of Study D5271C00001 (Legacy #3150-301-008) (hereinafter referred to as the "lead-in (LDI) study"). Participants in the lead-in study are eligible to enroll in Study D5271C00002 (Legacy #3150-303-008) provided they continue to meet eligibility criteria and have not had adverse experiences considered to be related to study medication that resulted in discontinuation of the initial lead-in study intervention, or that in the judgment of the investigator, would disqualify them from participating. Participants will be eligible for inclusion into this study if they have completed the lead-in study, or have completed 12 weeks of treatment in the lead-in study, but were subsequently discontinued due to lack of efficacy. Eligible participants do not need to complete the 18-week safety follow-up period of the lead in study if they rollover into this study after they complete the Week 52 visit of the lead in study.

It is anticipated that the enrolled population will consist of participants who have had varying endoscopic and clinical symptom responses during the lead-in study, ranging from complete endoscopic and clinical remission to no response or worsening of their signs and symptoms of Crohn's disease (CD). Participants who roll over to this open-label extension study (Study D5271C00002 [Legacy #3150-303-008]) within 28 days of completing their final visit (Week 52 or Early Termination Visit) assessments in the lead-in study may use the assessments from the final visit of the lead-in study as screening assessments for this study.

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the most recent Clinical Study Protocol (CSP) (Amendment 4 version 5, dated 04 Apr 2022). Specifications of tables, figures, and data listings are contained in a separate document. The advanced analysis of pharmacokinetic data may be specified in a separate analysis plan and reported outside of the Clinical Study Report (CSR).

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

The 240 mg subcutaneous (SC) dose of brazikumab will be administered every 4 weeks to all who completed requirements through Week 52 and met Crohn's disease activity index (CDAI) response (CDAI score of < 150 points or CDAI reduction from Baseline of ≥ 100 points) without ongoing rescue treatment at Week 52 in the lead-in study. Participants who met criteria for early termination due to lack of efficacy (rescure treatment criteria) or who did not meet CDAI response at Week 52 in the lead-in study are considered inadequate/non-responders, and will receive intravenous (IV) induction dosing with 1440 mg of brazikumab

at Week 0, Week 4, and Week 8 followed by maintenance dosing of brazikumab 240 mg SC every 4 weeks thereafter up to Week 52.

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

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

For reporting purposes, there will be 3 treatment groups in the extension study, defined by treatment in the lead-in study: Brazikumab/Brazikumab, Placebo/Brazikumab, and Adalimumab/Brazikumab. Adalimumab/Brazikumab will be excluded from analyses and only listed for safety reporting. As part of the changes to the development program in the lead-in study, the adalimumab (Humira®) arm has been removed from Stage 1 in the Protocol Amendment 4 of study D5271C00001 (Legacy #3150-301-008).

For listings, active treatment details for the lead-in and OLE studies will be footnoted as in Table 1-1.

Table 1-1 Treatment Details Footnotes for Listings

Footnote	***Study treatment***	***Footnote text***
a	LDI Brazikumab	Brazikumab 720 mg IV + 240 mg SC
b	LDI Brazikumab	Brazikumab 1440 mg IV + 240 mg SC
c	LDI Adalimumab	Adalimumab 160/80/40 mg SC
d	OLE Brazikumab	Brazikumab 240 mg SC
e	OLE Brazikumab	Brazikumab 1440 mg IV + 240 mg SC

LDI = Lead-in; OLE = Open-label extension.

The schedule of activities for the open label extension study can be found in the Clinical Study Protocol (CSP) Section 1.3, Tables 1, 2, and 3.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

This SAP has been authored to account for the different protocol versions, assuring that all data collected will be presented in an appropriate fashion.

Differently from what initially planned in the CSP, the additional classification (participants starting the OLE study with the Induction dose or the Maintenance dose) is no longer of interest in terms of splitted reporting. In particular, the following sentence from CSP is ignored: "In addition, brazikumab patients in this extension study will be further classified and separated by those that needed induction and those that received maintenance dose directly". Moreover, the CS-free endpoints described in the CSP will not be analyzed.

In order to maintain consistency with the efficacy analyses conducted in the LDI study, the estimand framework established in the LDI study is utilized. Handling of intercurrent events is described in Section 4.2.3.1. This is in contrast to the following sentence from CSP: "The efficacy analyses will be based on the FAS population using the observed-cases approach".

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The analysis will be undertaken after the last participant has completed the last visit of the study (second safety follow-up visit) or discontinued early.

3.2 Analysis Populations

The following populations are defined in Table 3-1:

Table 3-1 Populations for Analysis

Population/Analysis set	Description
Screened Analysis Set	All participants who are screened for the study.
Full Analysis Set (FAS)	All participants who are assigned to an IV or SC brazikumab study intervention in the OLE study, excluding participants randomized prior to Amendment 4 in the LDI study. Participants will be summarized according to the randomized study treatment group in the LDI study. Treatment groups will be presented as Brazikumab/Brazikumab for participants randomized to brazikumab study intervention in the LDI study, and Placebo/Brazikumab for participants randomized to placebo study intervention in the LDI study.

Safety Analysis Set	All participants who receive ≥ 1 administration of study intervention in the OLE study. Participants will be summarized according to the actual study treatment received in the LDI study. Treatment groups will be presented as Brazikumab/Brazikumab for participants who received brazikumab study intervention in the LDI study, and Placebo/Brazikumab for participants who received placebo study intervention in the LDI study. Participants who received Adalimumab/Brazikumab will only be included in listings.
PK Analysis Set	All participants who receive ≥ 1 administration of study intervention in the OLE study and have at least 1 PK sample containing detectable brazikumab concentration. Participants will be summarized according to the actual study treatment received in the LDI study.
ADA Evaluable Analysis Set	All participants who receive ≥ 1 administration of study intervention in the OLE study, have non-missing baseline ADA result and at least one non-missing post-baseline ADA result. Participants will be summarized according to the actual study treatment received in the LDI study.

ADA = anti-drug antibody; IV = intravenous; LDI = lead-in; PK = pharmacokinetic; SC = subcutaneous.

3.3 General Considerations

Statistical analysis will be performed using SAS Software, Version 9.4 or higher.

Study-related raw data for enrolled participants, including derived data, will be presented in data listings. Unless otherwise stated, listings will be sorted for presentation in order of treatment group, study site, participant number, date of event, and parameter name (if applicable).

Unless otherwise specified, descriptive statistics for continuous variables include the number of participants (n), mean, standard deviation (SD), median, 1st (Q1) and 3rd (Q3) quartiles, minimum (Min), and maximum (Max). Summary statistics for categorical variables include the number of participants (n) and percent (%). All efficacy and safety data will be analyzed based on the analysis visits. The details of analysis visit windowing rules are described in Section 3.3.3.

Unless otherwise specified, presentation will be up to 3 decimal places and as follows: Minimum, and maximum will be presented to the same number of decimal places as in the recorded data. Mean, median, Q1, and Q3 will be presented to 1 more decimal place than the

recorded data. SD and standard error (SE) will be presented to 2 more decimal places than the recorded data. Percentages will be rounded to 1 decimal place, except 0 and 100%, which will be displayed without any decimal places.

3.3.1 General Study Level Definitions

3.3.1.1 Study Day 1

Day 1 will be defined as the date of first dose of study intervention in this open-label study. If a participant is assigned to a treatment group but discontinues participation without receiving any study intervention, then his Study Day 1 will be undefined.

3.3.1.2 Baseline

For participants who were previously enrolled in the lead-in study, the baseline from the lead-in study will be used for the analyses, with the following exceptions:

- For PK and ADA analyses, baseline for participants who received Brazikumab/Brazikumab is the same as the baseline in the double-blind lead-in study (as treated with brazikumab during the lead-in study); however, for participants who received Placebo/Brazikumab, baseline is the last non-missing assessment before the first dose of study intervention administration in this open-label extension study (as never treated with brazikumab during the lead-in study).

Change from Baseline is defined as (Value at Visit X – Value at Baseline).

Percent Change from Baseline is defined as (Value at Visit X – Value at Baseline)/(Value at Baseline)*100

3.3.1.3 Study Periods

The study periods defined in this section are different from the safety reporting periods for Adverse Events (AE) defined in Section 4.6.2.1.

Screening period

All assessments made at the final visit of the lead-in study will be used as screening assessments for this study, unless Week 0 for this study occurs greater than 28 days from the final assessment(s) of the lead-in study, in which case the participant will need to complete all required screening assessments, except the ileocolonoscopy and CDAI. A repeat ileocolonoscopy is not required for participants who discontinue from the lead-in study after Week 12 and prior to Week 16.

Treatment Period

The Treatment Period consists of:

- For participants who receive maintenance therapy only, the Maintenance Period (Days 1 to 365)
- For participants who receive Induction therapy, Induction Period (Days 1 to 85 until first administration of SC brazikumab) through Maintenance Period (Day 85 from first administration of SC brazikumab to Day 365).

Safety Follow-up Period

The Safety Follow-up Period consists of the 18 weeks after the last dose of brazikumab (Follow-up Visit 1 [8 weeks after last dose] and Follow-up Visit 2 [18 Weeks after last dose]) for all treatment groups.

3.3.2 Visit Window

3.3.2.1 Study day

For assignment of data to analysis windows, study days will be defined in reference to Study Day 1 as defined in Section 3.3.1.1.

For any analysis visit time windows, if the assessment date is on or after the date of first dose of study intervention, the study day is calculated by:

assessment date – date of first dose of study intervention + 1.

If the assessment date is before the date of first dose of study intervention, the study day is calculated by:

assessment date – date of first dose of study intervention.

Therefore, a negative day indicates a day before the start dose of the study intervention.

If the assessment date is unavailable, the visit date will be used instead.

3.3.3 Conventions for the analysis windows

Table 3-2 presents the analysis windows assigned for efficacy (except daily data parameters) and safety analyses and the corresponding range of treatment days (window) during which data for a particular nominal visit may be collected. The analysis windows will be calculated from the date of first dose of study intervention. These are analysis windows that contain, but are not the same as, the actual visit windows. Each analysis window is equidistant between the neighboring Scheduled Visit Days. For example Week 4 = Day 29 and Week 8 = Day 57 (Table 3-2): the center of the analysis window is calculated as the average between the two Visit Days, that is (29+57)/2 = 43. Therefore the end of the Week 4 analysis window is Day 42 and the beginning of the analysis window for Week 8 is Day 43.

Similarly, for Follow-up Visit 1 and Follow-up Visit 2 scheduled at (last dose + 8 weeks) and (last dose + 18 weeks), the middlepoint is (last dose + 13 weeks), which is considered as the limit of the analysis windows during follow-up.

Table 3-2 Analysis Windows

Derived Visit	***Scheduled Visit Day***	***Analysis Window***
Lead-in Baseline		See Section 3.3.1.2
Screening OLE, last visit in LDI[a]		Last assessment in the LDI
Screening OLE[a]	-28	Days [-28,-1]
Week 0	Day 1[b]	Day 1
Week 4	Day 29	Days [2,42]
Week 8	Day 57	Days [43,70]
Week 12	Day 85	Days [71,98]
Week 16	Day 113	Days [99,126]
Week 20	Day 141	Days [127, 154]
Week 24	Days 169	Days [155, 182]
Week 28	Day 197	Days [183,210]
Week 32	Day 225	Days [211,238]
Week 36	Day 253	Days [239, 266]
Week 40	Day 281	Days [267,294]
Week 44	Day 309	Days [295,322]
Week 48	Day 337	Days [323,350]
Week 52	Day 365	Day ≥ 351 to (last dose + 4 weeks)
End of Treatment Period[c]	The earliest of Week 52 and Early Termination Visit	
Follow-up Visit 1	(last dose + 4 weeks + 1) to (last dose + 13 weeks)	
Follow-up Visit 2	(last dose + 13 weeks + 1) to End of Study	

[a] Mapped to "Screening OLE" in Tables and Figures, and presented separately in listings. Any repeated screening assessments or the final assessment for the lead-in study will be presented in the listings.
[b] Relative to the date of the first dose of study intervention in the Treatment Period. Day 1 = the date of the first dose of study intervention in the Treatment Period. There is no Day 0.
[c] Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs.

3.3.3.1 Early termination visits

Early termination (ET) visits for either discontinuation of study intervention or early discontinuation from study will be mapped to analysis windows following the conventions in Table 3-2. ET visits will only be used in analysis if the nominal scheduled visit result is missing.

3.3.3.2 Multiple observations

All observations will be assigned to their corresponding analysis window following the conventions in Table 3-2. If multiple assessments are recorded in a single analysis window, the following rules will be followed, unless otherwise specified:

- If there are 2 or more observations within the same analysis window, then the observation closest to the Visit where study intervention was given will be used in the analysis.
- If there are 2 Visits with study intervention, the observation closest to the planned protocol Scheduled Visit day will be used. The other observation(s) will not be used for analysis but will be included in listings.
- If 2 observations are equidistant from the Visit where the study intervention was given, the observation with the earlier collection date will be used in the analysis.
- Where study intervention is not scheduled, then the observation closest to the Scheduled Visit day will be used in the analysis.

3.3.4 Handling of Unscheduled Visits

If the study intervention cannot be administered during a scheduled study visit, the rescheduled dose will be administered as an unscheduled visit.

Post-baseline unscheduled visits will be mapped to a visit based on the analysis windows in Table 3-2. Both unscheduled and scheduled visits will be used in case of multiple observations within an analysis visit window and same rules as in Section 3.3.3.2 will be applied.

Data from unscheduled visits will be presented in data listings.

3.3.5 Multiplicity/Multiple Comparisons

Efficacy endpoints are exploratory in this extension study. No formal hypothesis testing will be performed and no multiplicity adjustments will be made.

3.3.6 Handling of Protocol Deviations in Study Analysis

A per-protocol (PP) analysis is not planned for this study. Important protocol deviations will be listed and tabulated in the Clinical Study Report (CSR). Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

The definitions, process for identification, and assessment of protocol deviations are detailed in a separate protocol deviation plan.

4 STATISTICAL ANALYSIS

4.1 Study Population

The study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medications, and study intervention compliance.

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Enrolled/Screened

A participant is enrolled if they, or their legally acceptable representative, sign the informed consent form (ICF).

Screen failure

Screen failures are defined as participants who consent to participate in this open-label clinical study but subsequently do not receive open-label study intervention, because they do not meet all eligibility criteria.

Treatment assignment

This is an open-label trial and participants are not randomized. Instead, each participant is assigned to one of two treatments (Induction or Maintenance Brazikumab) based on their clinical response in the lead-in study. Treatment groups will be defined for presentation as specified in Section 1.

Study discontinuation

A study 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.

The day of discontinuation is the Study day of last visit (or contact), that is, the date of discontinuation – date of first dose + 1.

Discontinuation of Study intervention

A study intervention discontinuation will occur if a participant who has taken at least one dose of the open-label study intervention is discontinued from the study intervention before the completion of protocol-defined study procedures.

Study intervention completion

Study intervention completion for a participant means that the protocol-defined study procedures related to the study intervention are completed.

Study completion

Study completion for a participant means that the protocol-defined study procedures related to the study are completed.

4.1.1.2 Presentation

Listings and summaries will be presented for the Screened Analysis Set. The listings will include but not be limited to completion status, including reasons for premature termination. The summary will include the number and percentage of participants in the Screened Analysis Set who:

- Were screened
- Failed screening, and reasons
- Were assigned to treatment
- Were assigned to treatment, not treated and reasons
- Started treatment
- Discontinued treatment in the Induction Period (if applicable), and reasons
- Completed the Induction Period (if applicable)
- Entered Maintenance Period
- Discontinued treatment in the Maintenance Period, and reasons
- Completed Maintenance treatment
- Completed Week 52
- Withdrew from the study, and reasons
- Completed the Safety Follow-up Period

Participants will be summarized overall and by treatment group.

Summary of global/country situation A summary of disposition due to the global/country situation will be provided by treatment group, to include the number of participants who

- Completed treatment
- Discontinued treatment due to the global/country situation, and reasons
- Completed the study
- Withdrew from the study due to the global/country situation

In addition, global/country situation disruptions will be summarized for the FAS by treatment group, to include the number of participants with at least one disruption due to global/country situation:

- Visit impacted
- Study drug impacted
- Concomitant medication impacted
- Discontinued treatment due to global/country situation
- Withdrew from the study due to global/country situation

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The following analysis populations are defined for the open label extension study:

Screened Analysis Set

This analysis set includes all participants screened for the study.

The Full Analysis Set (FAS)

This analysis set includes all participants who are assigned to an IV or SC brazikumab study intervention in the OLE study, excluding participants randomized prior to Amendment 4 in the LDI study. Participants will be summarized according to the randomized study treatment group in the LDI study. The FAS will be used for all efficacy analyses unless otherwise indicated.

The Safety (SAF) Analysis Set

This analysis set includes all participants who receive 1 or more administration of study intervention in the OLE study. Participants will be summarized according to the actual study treatment received in the LDI study.

Participants randomized to adalimumab in the double-blind lead-in study are excluded from the safety summaries, but will be included in the safety listings.

The PK Analysis Set

This includes Safety Set participants having at least 1 PK sample containing detectable brazikumab concentrations. Participants will be summarized according to the actual study treatment received in the LDI study. To be noted that if 5 or more patients have received Adalinumab, they will be included in the summaries; otherwise the patients who received Adalinumab will only be listed.

The ADA Evaluable Analysis Set

This includes Safety Set participants having a non-missing baseline ADA result and at least one non-missing post-baseline ADA result. Participants will be summarized according to the actual study treatment received in the LDI study. To be noted that if 5 or more patients have received Adalinumab, they will be included in the summaries; otherwise the patients who received Adalinumab will only be listed.

4.1.2.2 Presentation

The number of participants in each analysis set will be listed and summarized by treatment group as defined in Section 1 and overall, including reasons excluded from the Full analysis set, Safety analysis set, PK analysis set, and ADA evaluable analysis set.

Recruitment per country and site will also be summarized for each analysis set.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

The definition and derivation of important protocol deviations (IPDs) is described in a separate Protocol Deviation plan. These IPDs will be reviewed and documented before the clinical data lock.

4.1.3.2 Presentation

The participants with IPDs will be listed. The number and percentages of participants with at least one IPD will be summarized overall and by treatment group.

Important Protocol Deviations include:

- Violations of inclusion criteria
- Violations of exclusion criteria
- Discontinuation Criteria for study intervention are met but the participant was not withdrawn from study intervention
- Discontinuation Criteria for withdrawal from study are met but the participant was not withdrawn from the study

- Excluded medication taken
- Deviations related to study procedures
- Other important protocol deviations

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic variables will include age, sex, region, country, race and ethnicity. Patient age is entered into the eCRF in years. Age will be further categorized in 3 groups (<40, 40-65, and >65).

Participants who reported multiple races will be counted in the category "multiple".

4.1.4.2 Presentation

Demographic variables will be listed and summarized by treatment group and overall for the FAS and include:

- Age
- Age group [<40, 40-65, and >65]
- Sex
- Region [US and Non-US]
- Country
- Race
- Ethnicity

4.1.5 Disease Characteristics

4.1.5.1 Definitions and Derivations

Disease characteristics to be collected at Baseline are listed in Table 4-1.

Table 4-1 Disease Characteristics to be Summarized at Baseline

Disease Characteristics at Baseline	• Disease duration of CD (years) • Current immunomodulator use • Baseline disease location • Fistula • Extra-intestinal manifestations

	• Prior biologic use • Current CS use • Number of prior biologics • Number of different mechanisms of action of biologics
Inadequate Responder status on previous Crohn's medications (Intolerance, Primary failure, Secondary failure)	• Anti-TNF (Infliximab, Adalimumab, Certolizumab, Golimumab) • Integrin receptor antagonist (Vedolizumab, Ustekinumab) • Other Biologic • Immunomodulator (Azathioprine, Methotrexate, 6-mercaptopurine) • Other immunomodulator
SES-CD (assessed during ileocolonoscopy)	• Total score • Score by baseline disease location subgroup (per subgroup of participants with ileum, right colon, transverse colon, left colon, and rectum-colonic disease)
CDAI (calculated from PRO, physician assessment and laboratory markers)	• 220-450 moderate to severe disease • >450 very severe disease
Evening Diary (daily average over 7 days)	• CDAI LSF • CDAI AP • General Well-being • Temperature • NRS AP • Fatigue • Tiredness • Weakness • Lack of energy • Joint pain

Disease duration will be calculated as the (Date of First Study Intervention – Date of Onset of Crohn's disease)/365.25 yrs from the form Crohn's Location Details.

Immunomodulators will include either prior or concomitant use of azathioprine, methotrexate, 6-mercaptopurine, or other immunomodulator.

Baseline disease location will be collected with locations anus, rectum, sigmoid, descending colon, transverse colon, ascending colon, cecum, gastric, duodenum, extraintestinal, jejunum, and other. Any of these locations with the response = "Current" will be included.

Extra-intestinal manifestations (EIM) will be entered into the form Extra-intestinal manifestations. Responses will be categorized as

- Morning stiffness
- Arthropathy (peripheral arthropathy, axial arthropathy)
- Iritis/uveitis
- Skin problems (erythema nodosum, pyoderma gangrenosum, aphthous stomatitis/aphthous ulcers, anal fissures, anal abscess, non-anal abscess, fistula
- Other

The number of prior biologics: prior biologics used will be entered into the form Crohn's Meds Hx – Biologic Agents. The number of prior biologics is the number of unique entries with the question "Is the medication still ongoing?" = "No" or the end date of the medication is prior to the date of enrolment.

Number of different mechanisms of action of prior biologics: for each of the prior biologics identified above, categorize as anti-TNF, integrin receptor antagonists, or IL-12 and -23 antagonist per Table 4-2. The number of different mechanisms will be 0, 1, 2, or 3.

Table 4-2 Drug Names and ATC Codes

Category	Drug name	ATC code
Immunomodulators	Azathioprine	L04AX01
	6-mercaptopurine	L01BB02
	Methotrexate	L01BA01/L04AX03
	Other	
BIOLOGICS		
Anti-TNF	Infliximab	L04AB02
	Adalimumab	L04AB04
	Certolizumab	L04AB05
	Golimumab	L04AB06
	Etanercept	L04AB01
Integrin receptor antagonists	Vedolizumab	L04AA33

	Natalizumab	L04AA23
IL-12 and -23 antagonist	Ustekinumab	L04AC05

CDAI baseline

CDAI is defined in Appendix 7.1. CDAI Baseline from lead-in study will be used.

SES-CD

The SES-CD score is an endoscopic activity score used to assess the status and change of mucosal lesions. The score assesses 4 variables in up to 5 segments to yield its final result. 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

Each segment is assessed for four qualities: size of ulcers, ulcerated surface, affected surface, and presence of narrowing. The total score is the sum of these 20 components (see Section 4.2.3.1 for more details).

4.1.5.2 Presentation

The disease characteristics will be listed and summarized descriptively by treatment group and overall for the FAS.

4.1.6 Medical History and Concomitant Disease

4.1.6.1 Definitions and Derivations

Crohn's disease Medical History

Participants Crohn's disease medical history will be collected, including surgical history, chest x-ray, family history of colorectal cancer, substance use, tuberculosis history, and vaccination history.

Family history, and substance use are only collected during the lead-in study.

General Medical and Surgical History

Verbatim terms on the eCRF form Medical History, Surgical History, and Concurrent Procedures will be mapped to system organ class (SOC) and preferred term (PT). For Medical History, the item will be concurrent if it is ongoing at the time of enrollment.

Participants' medical and surgical histories and concurrent procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 or newer.

4.1.6.2 Presentation

Crohn's disease medical history as described in Section 4.1.6.1 will be listed and summarized by treatment group, and overall for the FAS. Chest x-ray, vaccination history, family history of colorectal cancer, substance use, and tuberculosis history will be presented in a listing.

General medical and surgical histories will be summarized applying MedDRA terms. Each SOC and PT will be summarized separately for data from the lead-in study, and for any new medical history as collected from the OLE eCRF, by treatment group, and overall for the FAS. Concurrent procedures will also be presented in a listing.

4.1.7 Prior and Concomitant Medications

4.1.7.1 Definitions and Derivations

The World Health Organization (WHO) Drug Dictionary Enhanced, September 2021 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Prior medication

Prior medication is defined as any medication discontinued before the first dose of the study intervention in the OLE study.

Concomitant medication

Concomitant medication is defined as any medication taken on or after the date of the first dose of the study intervention in the OLE study.

Any medications taken later than 18 weeks after the last dose of study intervention date will not be presented in the summary tables but will be included in the participant data listings.

Permitted Crohn's disease medication

Permitted Crohn's disease medications should be recorded as concomitant medications. See CSP Section 6.5.1 and Table 4-3 for details of permitted Crohn's disease medications. Participants may continue treatment with corticosteroids during the study.

Prohibited Crohn's disease medications

Prohibited Crohn's disease medication should not be taken during the course of the study. These are considered exclusionary and are not permitted through the course of the study. See CSP Section 6.5.4 for details. In addition to the list specified in the CSP, Upadacitinib is considered prohibited medication. In most cases, if prohibited medications are taken, the study intervention must be discontinued.

Rescue treatment

Permitted rescue medications are allowed as per investigator judgment. Participants will continue to receive study intervention unless a prohibited medication is used.

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. Any **new** initiation (or dose increase) of medications or interventions listed in Table 4-3 will be considered rescue treatment and will not require stopping study intervention.

Table 4-3 Permitted Rescue Medications

Medication	***ATC code***
5-aminosalicylates	A07EC02
Corticosteroids Parenteral, oral, or rectal CS Oral CS doses above Day 1 dose	 L04AD01 L04AD01
Immunomodulators Azathioprine 6-mercaptopurine Methotrexate	 L04AX01 L01BB02 L01BA01/L04AX03
IV immunoglobulin	J06BA02

An increase in CS dose that does not exceed the Week 0 dose level, for participants underoing CS tapering within the guidelines in CSP Section 6.5.2 is not considered rescue treatment.

Other investigational products are not permitted to be used as rescue treatment. Use of rescue medication after Day 1 constitutes treatment failure. The use of rescue medication (eg, prohibited interventions) in the lead-in study will be exclusionary for this study.

4.1.7.2 Presentation

Medications will be summarized for the FAS by the number and percentage of participants in each treatment group and overall receiving each medication within WHO drug class and preferred term. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once

for the coded drug name or therapeutic class. Any prior and concomitant medications will be included in listings, including corticosteroid medications.

The following summaries will be provided:

- Prior medication use
- Prior corticosteroid use for Crohn's disease
- Prior immunomodulator use (for Crohn's disease and for other indication than Crohn's disease)
- Concomitant rescue medication use during the lead-in study for Crohn's disease
- Concomitant rescue medication use during the OLE study for Crohn's disease
- Permitted concomitant medications
- Concomitant corticosteroid use (for Crohn's disease and for other indication than Crohn's disease)
- Concomittant immunomodulator use (for Crohn's disease and for other indication than Crohn's disease)
- Prohibited concomitant medication use

Prior medication use will be reported for the time periods "prior to the first dose in the lead-in study", and "after the first dose during the lead-in study but before the first dose in the OLE".

4.1.8 Study Intervention Compliance

4.1.8.1 Definitions and Derivations

Participants are dosed under the direct supervision of study center personnel. The date and time of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. Study intervention compliance will measure the number of doses received and will be calculated as the total number of doses taken during that period divided by the number of expected doses, multiplied by 100.

4.1.8.2 Presentation

Study intervention compliance will be listed and summarized for the Induction Period with number and proportion of expected participants dosed for each Visit by treatment group and overall using the FAS. Mean study intervention compliance will also be descriptively summarized for the Maintenance Period and full treatment period by treatment group and overall.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses, including primary, secondary, and exploratory endpoints.

The purpose of this OLE study is to permit participants who previously enrolled in the double-blind lead-in study to receive brazikumab, allowing for long-term observation of safety and efficacy in these participants treated with brazikumab. There are no formal hypotheses to be tested.

In this SAP, the exploratory endpoints “Endoscopic Enhanced Remission” and “PRO remission” (as defined in the CSP OLE) are named “SES-CD total score of 0-2” and “Clinical remission” respectively, to be consistent with the terminology used in the LDI study.

Table 4-4 Objectives and Endpoints

Statistical category	*Endpoint*	*Analysis Population*	*Intercurrent event strategy*	*Population level summary (analysis)*	*Details in section*
Objective 1: To assess the safety of long-term treatment with brazikumab in CD participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from the Study D5271C00001 (Legacy #3150-301-008) at or after Week 12 due to lack of efficacy					
Primary	• AEs • Clinical laboratory values • Vital signs • Physical exams • ECGs	Safety		Summary tables	4.6
Objective 2: To assess the efficacy of long-term treatment with brazikumab in CD participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from the Study D5271C00001 (Legacy #3150-301-008) at or after Week 12 due to lack of efficacy					
Exploratory	SES-CD: • Endoscopic Response at Week 52 • Endoscopic Remission at Week 52 • SES-CD total score of 0-2 at Week 52	FAS	NRI	Descriptive statistics	4.2.3
Exploratory	CDAI: • CDAI Response at Weeks 0, 12*, and 52 • CDAI Remission at Weeks 0, 12*, and 52	FAS	NRI	Descriptive statistics	4.2.4
Exploratory	PRO – Evening Diary: • Clinical remission at Weeks 0, 12*, and 52	FAS	NRI	Descriptive statistics	4.2.5
Exploratory	PRO – Site Visits: Change from Baseline in • IBDQ at Weeks 0, 12*, and 52 • SF-36 at Weeks 0, 12*, and 52 • EQ-5D-5L at Weeks 0, 12*, and 52	FAS	Treatment policy strategy	Descriptive statistics	4.2.6 4.2.7 4.2.8
Objective 3: To evaluate the PK and immunogenicity of brazikumab					

Statistical category	*Endpoint*	*Analysis Population*	*Intercurrent event strategy*	*Population level summary (analysis)*	*Details in section*
Exploratory	• Serum concentration of brazikumab at Weeks 0, 12*, 24 and 52	PK		Descriptive statistics	4.4
	• Serum ADAs at Weeks 0, 24, and 52	ADA		Descriptive statistics	4.5
Objective 4: To explore transcriptional, histological, protein, microbiome, and clinical biomarkers in CD participants who previously completed Study D5271C00001 (Legacy #3150-301-008) or discontinued from the Study D5271C00001 (Legacy #3150-301-008) at or after Week 12 due to lack of efficacy, and the effect of long-term brazikumab treatment on these biomarkers					
Exploratory	• Serum, plasma, fecal, or gut tissue proteins; whole blood or gut transcriptional changes; histological, microbiome, and clinical lab assessments	FAS		Descriptive statistics will be presented for IL-22, CRP, and FCP. Analysis for other assessments to be developed in separate SAP and reported outside of the CSR.	4.3

ADA = Anti-drug antibodies; AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; CS = corticosteroids; CSR = Clinical study report; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life-5 Dimensions; FAS = Full analysis set; FCP = Fecal calprotein; IBDQ = Inflammatory Bowel Disease Questionnaire; IL-22 = Interleukin-22; NRI = Non-responder imputation; PGA = Physician's Global Assessment; PK = Pharmacokinetic(s); PRO = Patient reported outcome; SAP = Statistical analysis plan; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF36-v2 = Short-Form 36 Health Survey version 2.

* Data at Week 12 are collected from participants who have IV induction only.

4.2.1 Primary Endpoint

The primary endpoints are safety endpoints (see Section 4.6).

4.2.2 Secondary Endpoint

There are no secondary endpoints in this study.

4.2.3 Exploratory Endpoints: SES-CD

4.2.3.1 Definition

The SES-CD total score is an endoscopic activity score, described in Appendix 7.3.

Following the estimand framework established in the lead-in study, intercurrent events include:

- Discontinues the study intervention prematurely before Week 52
- Takes rescue treatment before Week 52
- Uses prohibited medication before Week 52

Participants who experience any of these intercurrent events are considered as being unsuccessfully treated and non-responders for the relevant endpoints.

The SES-CD endpoints include:

- Endoscopic Response at Week 52
- Endoscopic Remission at Week 52
- SES-CD total score of 0-2 at Week 52

4.2.3.2 Derivation

Endoscopic response will be derived using the following formula:

If ((baseline total SES-CD - total SES-CD at Week 52)/baseline total SES-CD > 0.5) endoscopic response will be set to 1 (endoscopic responder), otherwise it will set to 0 (endoscopic non-responder). SES-CD total score is described in Appendix 7.3. Baseline is defined in Section 3.3.1.2.

Endoscopic remission is defined as SES-CD total score of 0-2, or SES-CD total score of ≤ 4 and at least 2-point reduction from lead-in Baseline with no subscore > 1.

Each endpoint is the the proportion of participants who meet the criteria.

4.2.3.3 Handling of Dropouts and Missing Data

If a post-baseline SES-CD segment is missing, the subscore for that SES-CD segment will be imputed to zero. The imputed segment scores will then be used for the SES-CD total score calculation.

If the SES-CD total score is missing, then the endoscopic endpoint will be imputed as a nonresponder.

4.2.3.4 Primary Analysis of Exploratory Endpoints

Descriptive statistics will be calculated for the FAS for each endpoint.

4.2.3.4.1 Presentation

Descriptive statistics will be presented by treatment group and overall.

4.2.4 Exploratory Endpoints: CDAI score

4.2.4.1 Definition

The CDAI is a composite index with weighted domains that quantifies the global disease severity in a single numerical score, described in Appendix 7.1.

CDAI endpoints include:

- CDAI response at Week 12 for participants who receive IV induction dosing
- CDAI remission at Week 12 for participants who receive IV induction dosing
- CDAI response at Week 52
- CDAI remission at Week 52

4.2.4.2 Derivation

The CDAI score is described in Appendix 7.1.

A participant will have achieved **CDAI response** if their CDAI score < 150 or reduction from Baseline CDAI score of ≥ 100 points.

A participant will have achieved **CDAI remission** if their CDAI score < 150.

Participants will be considered nonresponders if they experience any of the intercurrent events as described in Section 4.2.3.1. For the endpoints assessed at Week 12, non-responders are those participants who experience any of the intercurrent events before Week 12.

4.2.4.3 Handling of Dropouts and Missing Data

1. Missing total CDAI score due to PRO components missing

If the CDAI score is missing due to missing PRO components, apply the following algorithm to impute the missing components: if there are at least 4 days of information, calculate the subscore for each item as the mean value from available days × 7. If the CDAI score still cannot be calculated, then the endpoints will be imputed as nonresponder.

2. Missing total CDAI score due to other than PRO components missing

If the CDAI total score is missing due to reasons other than PRO components missing, then the CDAI score will be missing and the endpoints will be imputed as nonresponder.

3. Missing total CDAI score due to both PRO and non-PRO components missing

If both PRO and non-PRO components are missing, then the CDAI score will be missing and the endpoints will be imputed as nonresponder.

See Appendix 7.1 for more details on the calculation of the total CDAI score.

4.2.4.4 Primary Analysis of Exploratory Endpoints

Descriptive statistics will be calculated for the FAS for each endpoint.

4.2.4.4.1 Presentation

Descriptive statistics will be presented by treatment group and overall.

Additionally, the number and percent of participants who are nonresponders due to each intercurrent event will be presented for CDAI remission at Week 12 (for participants who receive IV induction only) and Week 52 by treatment group and overall. If a participant experiences more than one category of intercurrent event, that participant will be counted in each category.

In addition, a listing will be presented which includes, but is not limited to, whether the participant is a responder and which (if any) intercurrent events occurred.

4.2.5 Exploratory Endpoint: PRO – Evening Diary

4.2.5.1 Definitions

The CDAI loose stool frequency (LSF) item is the average daily LSF subscore from the Evening Diary, based on the average of the 7 days prior to initiation of bowel prep for the ileocolonoscopy. The CDAI abdominal pain (AP) item is the average daily abdominal pain score from the Evening Diary, based on the 7 days prior to initiation of bowel prep for the ileocolonoscopy.

The evening diary endpoint includes the clinical remission.

4.2.5.2 Derivations

Clinical remission is defined as

- 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

Participants will be considered nonresponders if they experience any of the intercurrent events as described in Section 4.2.3.1.

4.2.5.3 Handling of Dropouts and Missing Data

Missing CDAI elements (LSF and AP) will be handled as described in Appendix 7.2. If the Week 52 CDAI elements cannot be imputed, then clinical remission will be imputed to nonresponder.

4.2.5.4 Primary Analysis of Exploratory Endpoint

Descriptive statistics of PRO remission will be calculated based on the FAS.

4.2.5.4.1 Presentation

Descriptive statistics will be presented by treatment group and overall.

4.2.6 Exploratory Endpoints: Change in The Inflammatory Bowel Disease Questionnaire (IBDQ)

4.2.6.1 Definition

The IBDQ is presented in Appendix F 2.1 of CSP, and measures Health Related Quality of Life (HRQoL) in patients with inflammatory bowel disease (IBD). It will be assessed during the site visit at Baseline and Weeks 0, 12, and 52, or ET (Week 12 for Induction groups only). It covers how the participant has been feeling in the past two weeks (Guyatt et al, 1989). Four dimensions are covered: 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 (from 1 [worse] to 7 [better]). The total score is obtained by summing the score from each item, yielding a global score in the range 32 to 224 (with higher scores indicating better quality of life).

4.2.6.2 Derivation

The total score is obtained by summing each item, and will range from 32 to 224. Change from Baseline is calculated as described in Section 3.3.1.2. A positive Change from Baseline value indicates increased quality of life compared to Baseline.

4.2.6.3 Handling of Dropouts and Missing Data

The IBDQ will be administered at the site. If a participant discontinues early or misses a Visit, the scores for that Visit will be set to missing.

If more than half of the items in a subscore are missing for the IBDQ, the total score will be set to missing as well as that subscore. Otherwise, substitution of the mean of the remaining items in the subscore can be imputed for that subscore (W. Y. Cheung, 2002).

4.2.6.4 Primary Analysis of Exploratory Endpoints

Descriptive statistics will be calculated for IBDQ total score for each Visit, by treatment group and overall.

4.2.6.4.1 Presentation

Descriptive statistics will be presented for observed values and changes from baseline for each Visit, by treatment group and overall. Week 12 results will only be reported for participants receiving Induction treatment.

4.2.7 Exploratory Endpoint: Change in SF-36

4.2.7.1 Definition

The SF-36v2 (SF-36) is presented in Appendix F 2.3 of the CSP, and will be assessed at Baseline and during site visits at Weeks 0, 12, and 52, or ET (Week 12 for Induction groups only). It is a standardized instrument used to measure self-reports of health status and functional well-being. It consists of 8 domains: physical functioning (10 questions, #3a to 3j), role physical (4 questions, #4a to 4b), bodily pain (2 questions, #7 and 8), general health (5 questions, #1,11a to 11d), vitality (4 questions, #9a, 9e, 9g, 9i), social functioning (2 questions, #6, #10), role emotional (3 questions, #5a to 5c), and mental health (5 questions, #9b to 9d, 9f, 9h). The subscores from the 8 dimensions can be directly calculated. Two summary indices can be scored: the Physical Component Score (PCSc) and the Mental Component Score (MCSc). The lower the score, the more disability (Brazier, Roberts, and Deverill, 2002).

4.2.7.2 Derivations

The SF-36 will be scored using the algorithm provided by Optum with the instrument license (Health Outcomes™ Scoring Software 4.5 or higher). Change from Baseline is calculated for the PCSc and MCSc.

4.2.7.3 Handling of Dropouts and Missing Data

The SF-36 will be administered at the site. If a participant discontinues early or misses a Visit, the scores for that Visit will be set to missing.

Missing items and subscores are handled by the algorithm provided by Optum.

4.2.7.4 Primary Analysis of Exploratory Endpoint

Descriptive statistics will be calculated for SF-36 PCSc and MCSc separately for each Visit, by treatment group and overall.

4.2.7.4.1 Presentation

Descriptive statistics will be presented for observed values and changes from baseline for each Visit, by treatment group and overall. Week 12 results will only be reported for participants receiving Induction treatment.

4.2.8 Exploratory Endpoint: Change in EQ-5D-5L

4.2.8.1 Definition

The EQ-5D-5L is presented in Appendix F 2.2 of the CSP, and will be assessed at Baseline and during site visits at Weeks 0, 12, and 52, or ET (Week 12 for Induction groups only). The EQ-5D-5L includes a Visual Analog Scale (VAS) that allows respondents to rate their own current health on a 101-point scale ranging from 100 = “best imaginable” to 0 = “worst imaginable” health.

4.2.8.2 Derivations

Change from Baseline is calculated for the 101-point scale. A negative Change from Baseline value indicates a worse health state.

4.2.8.3 Handling of Dropouts and Missing Data

The EQ-5D-5L will be administered at the site. If a participant discontinues early or misses a Visit, the score for that Visit will be set to missing.

Per the EQ-5D-5L user guide (EQ-5D-5L User Guide, 2019), missing values should be coded as ‘9’, or ‘999’ for the VAS. These should be set to missing prior to analysis.

4.2.8.4 Primary Analysis of Exploratory Endpoint

Descriptive statistics will be calculated for the EQ-5D-5L VAS for each Visit, by treatment group and overall.

4.2.8.4.1 Presentation

Descriptive statistics will be presented for observed values and changes from baseline for each Visit, by treatment group and overall. Week 12 results will only be reported for participants receiving Induction treatment.

4.3 Pharmacodynamic Endpoints

Pharmacodynamic variables collected for this study include IL-22, serum C-reactive protein (CRP), and fecal calprotectin (FCP). Absolute values, Change from Baseline, and percentage Change from Baseline will be listed and summarized by treatment group using descriptive statistics for the FAS. Mean absolute values, mean Change from Baseline, and mean percentage Change from Baseline will be presented graphically by treatment group.

4.4 Pharmacokinetics

Serum samples for determination of brazikumab concentrations will be collected at Baseline prior to first study intervention administration, and pre-dose at Weeks 0, 12, 24 and 52, or ET. (Week 12 sample will be collected for participants receiving Induction only).

Individual brazikumab serum concentrations will be listed and summary descriptive statistics will be presented for each nominal sampling time and plotted versus time for the PK analysis set. Individual brazikumab serum concentrations will be graphically illustrated and summarized by ADA status.

For each time point, the geometric mean, geometric standard deviation, coefficient of variation (CV), arithmetic mean, SD, median, minimum, and maximum will be reported as summary statistics.

Linear and log-linear mean (± SE) concentration profile plots against time will be produced for each lead-in treatment group, with nominal sampling time on the x-axis.

These descriptive statistics will be reported in the CSR. Further model-based evaluation of PK will be detailed in a separate PK analysis plan and reported outside the CSR.

4.5 Immunogenicity

Serum samples to measure the presence of anti-drug antibodies (ADAs) against brazikumab (binding antibodies and neutralizing antibodies) will be collected at Week 0, Week 24, and Week 52, or ET. ADA results from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of nAb will be tested for all ADA-positive samples.

4.5.1 Derivations

The number and percentage of ADA-evaluable participants in the following ADA categories in each lead-in treatment group and overall will be determined. The number of ADA-evaluable participants in the lead-in treatment group will be used as the denominator for percentage calculation.

- ADA positive at any visit (at baseline and/or post-baseline). The percentage of these participants in a population is known as ADA prevalence.
- Treatment-emergent ADA positive (either treatment-induced ADA positive, or treatment-boosted ADA positive). The percentage of these participants in a population is known as ADA incidence.
- Treatment-induced ADA positive (ADA negative at baseline and ADA positive at >=1 post-baseline assessment).
- Treatment-boosted ADA positive (baseline ADA titer that was boosted by ≥4-fold following OLE study intervention administration).
- Non-Treatment emergent ADA positive (ADA positive but not fulfilling the definition of TE-ADA positive).
- ADA positive at baseline and post-baseline.
- ADA positive at baseline and not detected post-baseline.
- Treatment-emergent ADA (TE-ADA) persistently positive, defined as treatment-emergent ADA positive participants having at least 2 post-baseline ADA positive measurements at least 16 weeks (112 days) between the first and last positive measurement, or an ADA positive result at the last available assessment.
- Treatment-emergent ADA (TE-ADA) transiently positive is defined as treatment-emergent ADA positive participants not fulfilling the conditions for TE-ADA persistently positive.
- Neutralizing Antibody (nAb) positive is defined as nAb positive at any time baseline and/or post-baseline (nAb prevalence).
- Treatment-induced nAb positive (nAb incidence) is defined as nAb negative at baseline (or ADA negative at baseline) and nAb positive at >=1 post-baseline assessment.
- Treatment-emergent ADA positive with maximum titer > median of maximum titer (calculated based on the maximum titer for each ADA positive participant within each treatment group).

4.5.2 Primary Analysis of ADA

A summary of the number and percentage of participants who developed positive ADA by ADA categories (Section 4.5.1) in different treatment groups and overall will be presented based on the ADA evaluable analysis set. In addition, descriptive statistics of the maximum titer will be presented by ADA category. ADA results and titers will be summarized by visit and treatment group.

Additional immunogenicity outcomes may be described in separate analysis plans and will be reported separately.

4.6 Safety Analyses

Safety data will be summarized descriptively using the Safety analysis set. Participants who received Adalimumab/Brazikumab will only be included in listings. The safety parameters will include AEs, clinical laboratory, vital signs, physical examinations, and ECG parameters. 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.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Duration of Exposure to the study intervention will be calculated as the number of days from the first study intervention to 28 days after the last study intervention for the study for the Safety analysis set. Any gaps in dosing will be ignored when calculating the total.

Total dose will be calculated as the IV doses given for Induction (from the form Exposure - Intravenous) during Week 0, 4, and 8, plus the SC doses given for Maintenance (from the form Exposure - Subcutaneous).

4.6.1.2 Presentation

Duration of Exposure (in days) and total dose will be listed and summarized by treatment group and overall for the Safety analysis set.

4.6.2 Adverse Events

Adverse events (AE) will be coded by system organ class and preferred term using the MedDRA, version 24.0 or newer.

4.6.2.1 Definitions and Derivations

Adverse event data will be categorized according to their onset date based on the last dose of investigational product as follows:

- An AE occurring during the Treatment Period is defined as an AE with a date of onset ≥ the first dose of investigational product in the OLE and ≤ 28 days after the last dose of investigational product.
- An AE occurring during the Study Period is defined as an AE that occurs during treatment including follow-up is defined as an AE with a date of onset ≥ day of first dose of investigational product in the OLE and ≤ 18 weeks after the last dose of investigational product.
- An AE occurring during the LDI Treatment Period and is still ongoing during the OLE Treatment Period, is defined as an AE occurring during the LDI+OLE Treatment Period with a date of onset ≥ day of first dose of investigational product in LDI and ≤ 28 days after the last dose of investigational product in the OLE.

Per case report form instructions, a new AE record will be created for any AE that worsens.

Treatment related

An AE will be considered as treatment related if the investigator considers that there is a reasonable possibility that the event may have been caused by the investigational product.

Serious

An AE will be considered a serious AE (SAE) if it is an AE that additionally meets any SAE criteria (as recorded on the AE form of the eCRF).

Missing Severity Assessment

Adverse events with missing severity are assumed to be severe. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

Missing Causal Relationship to Study Intervention

There will be no imputation of missing causal relationship for any non-serious AEs. For SAEs, if the causal relationship to the study intervention is missing for an SAE that started on or after the date of the first dose of the study intervention, a causality of yes will be assigned. The imputed values for causal relationship during the Treatment Period will be used for the incidence summary; the values will be shown as missing in the data listings.

Missing Date Information for Adverse Events

See Appendix 7.5 for missing date imputation rules.

4.6.2.2 Presentation

Adverse Events will be reported for the Treatment Period and Study Period (Treatment Period + Safety Follow-up Period). The end of the Treatment Period is defined as the date of last dose of study intervention + 28 days. The end of the Follow-up Period is defined as the date of last dose of study intervention + 18 weeks.

For the Safety analysis set, the following will be summarized by treatment group and overall:

- Overall summary of AE, including
  - Any AE
  - Any SAE
  - Any SAE with outcome death
  - Any AE leading to discontinuation of IP
  - Any possibly related AE
  - Any possibly related SAE
- AE by SOC and PT
- AE sorted by decreasing frequency on preferred term level
- AE by maximum reported intensity on preferred term level
- Possibly related AE by SOC and PT
- AE per subject year by SOC and PT.
- Adverse events of special interest (AESI)
- SAE with outcome death by SOC and PT
- SAE by SOC and PT
- Possibly related SAE by SOC and PT
- AE leading to discontinuation of investigational product by SOC and PT

The incidence of common (> 5% of participants in any treatment group) non-serious AEs will be summarized by system organ class, preferred term, and treatment group.

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 severity for the summaries by severity. Similarly, the participant will be counted using the closest relationship for summaries by causality.

Listings of AEs, deaths, SAEs and AEs leading to discontinuation of the investigational product by participant will be presented, to include key participant information. Key participant information will be presented for the Treatment Period and Study Period (Treatment Period + Safety follow-up Period). In addition, key participant information for participants with an AE that occurred during the LDI study and has led to discontinuation of investigational product due to that AE in the OLE study will also be presented for the LDI+OLE Treatment Period.

AESI will be summarized and include infusion related reactions/injection-site reactions, malignancies, hypersensitivity (including anaphylaxis), and infections.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

The following are protocol-required laboratory parameters as listed in Table 4-5 through Table 4-7. All laboratory assessments will be done at Screening. Clinical chemistry, hematology (including hematocrit), and C-reactive protein (CRP) will be carried out at Weeks 12, 24, 36, 52, unscheduled visits, ET, and safety follow-up visits.

Table 4-5 Protocol-Required Laboratory Assessments

Laboratory Assessments	***Parameters***			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV MCH % Reticulocytes		WBC count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	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	• Fecal calprotectin • Fecal lactoferrin			
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (reflexively as needed)			
Other Screening Tests	• FSH (as needed in women of non-childbearing potential only) • Urine hCG is to be performed locally at each visit prior to administering study intervention and as outlined in the SoA • All study-required laboratory assessments will be performed by a central laboratory unless indicated (eg, local urine hCG testing)			

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

Table 4-6 Normal Ranges for Laboratory Values (Central Laboratory Services Manual)

Laboratory Parameter	***LLN - Male***	***ULN- Male***	***LLN – Female***	***ULN- Female***	***SI Unit***
Hematology					
Hemoglobin	Age 12-59: 127 Age >59: 125	Age 12-59: 181 Age >59:170	Age 12-59: 116 Age >59: 115	Age 12-59: 164 Age >59: 158	g/L
Hematocrit	Age 12-59: 0.39 Age >59: 0.37	Age 12-59: 0.54 Age >59: 0.51	0.34	0.48	ratio
RBC	Age 12-59: 4.5	Age 12-59: 6.4	Age 12-59: 4.1	Age 12-59: 5.6	TI/L

Laboratory Parameter	***LLN - Male***	***ULN- Male***	***LLN – Female***	***ULN- Female***	***SI Unit***
	Age >59: 4.0	Age >59: 5.8	Age >59: 3.9	Age >59: 5.5	
Eosinophils	0.00	0.57	0.00	0.57	GI/L
Neutrophils	40.5	75.0	40.5	75.0	%
Basophils	0.00	0.20	0.00	0.20	GI/L
Monocytes	0.12	0.92	0.12	0.92	GI/L
Lymphocytes	Age 18-59: 0.91 Age >59: 0.80	Age 18-59: 4.28 Age >59:3.00	Age 18-59: 0.91 Age >59: 0.80	Age 18-59: 4.28 Age >59: 3.00	GI/L
Absolute neutrophil count	1.96	7.23	1.96	7.23	GI/L
Platelet count	Age 12-60: 140 Age > 60: 130	Age 12-60: 400 Age > 60: 394	Age 12-60: 140 Age > 60: 130	Age 12-60: 400 Age > 60: 394	10^9/L
Clinical chemistry					
Albumin	Age 18-69: 33 Age >69: 33	Age 18-69: 49 Age >69: 46	Age 18-69: 33 Age >69: 33	Age 18-69: 49 Age >69: 46	g/L
Alkaline phosphatase	Age 18-19: 55 Age >19: 40	Age 18-19: 149 Age > 19: 129	Age 18-19: 45 Age > 19: 35	Age 18-19: 87 Age > 19: 104	U/L
Alanine aminotransferase (ALT)	Age 18-69: 6 Age > 69: 6	Age 18-69: 43 Age > 69: 35	Age 18-69: 6 Age > 69: 6	Age 18-69: 34 Age > 69: 32	U/L
Aspartate aminotransferase (AST)	11	36	9	34	U/L
Gamma-glutamyl transferase (GGT)	Age 18-59: 10 Age >59: 10	Age 18-59: 61 Age >59: 50	Age 18-59: 4 Age >59: 5	Age 18-59: 49 Age >59: 50	U/L
Blood urea nitrogen or Urea	1.4	Age 18-70: 8.6 Age >70: 10.4	1.4	Age 18-70: 8.6 Age >70: 10.4	mmol/dL
Calcium	2.07	2.64	2.07	2.64	mmol/dL
Chloride	94	112	94	112	mmol/L
Creatinine	40	Age 18-50: 110 Age 50-70: 119 Age >70: 137	31	Age 18-70: 101 Age >70: 110	µmol/L
Glucose, nonfasting	3.9	5.6	3.9	5.6	mmol/L
Magnesium	Age 18-20: 0.70 Age 20-60: 0.66 Age >60: 0.66	Age 18-20: 0.90 Age 20-60: 1.07 Age >60: 0.98	Age 18-20: 0.70 Age 20-60: 0.66 Age >60: 0.66	Age 18-20: 0.90 Age 20-60: 1.07 Age >60: 0.98	mmol/L
Potassium	3.5	5.2	3.5	5.2	mmol/L
Sodium	Age 18-59: 132 Age >59: 135	Age 18-59: 147 Age >59: 145	Age 18-59: 132 Age >59: 135	Age 18-59: 147 Age >59: 145	mmol/L
Total bilirubin	3	21	3	21	µmol/L

Laboratory Parameter	*LLN - Male*	*ULN- Male*	*LLN – Female*	*ULN- Female*	*SI Unit*
Total protein	Age 18-59: 61 Age >59: 60	Age 18-59: 84 Age >59: 80	Age 18-59: 61 Age >59: 60	Age 18-59: 61 Age >59: 60	g/L
Uric acid or Urate	Age 18-50: 125 Age > 50: 149	Age 18-50: 488 Age >50: 494	Age 18-50: 125 Age >50: 149	Age 18-50: 428 Age >50: 446	mg/dL

Blood urea nitrogen or Urea are the same parameters, and Uric acid or Urate are the same parameters.
LLN = lower limit of normal; ULN = upper limit of normal laboratory reference range.

Table 4-7 Criteria for Potentially Clinically Significant Laboratory Values

Laboratory Parameter	*SI Unit*	*Conversion Factor*[a]	*Conventional Unit*	*PCS Criterion*[b] *Low Value*	*PCS Criterion*[b] *High Value*
Hematology					
Hemoglobin	g/L	0.1	g/dL	< 0.9 × LLN	—
Hematocrit	Volume fraction	100	%	< 0.9 × LLN	—
Eosinophils	%	1	%	—	> 10
Neutrophils	%	1	%	< 30	> 90
Basophils	%	1	%	—	> 6
Monocytes	%	1	%	—	> 20
Lymphocytes	%	1	%	< 10	> 60
Absolute neutrophil count	$\times 10^9$/L	1	1000/μL	< 1.0	—
Platelet count	$\times 10^9$/L	1	1000/μL	≤ 75	≥ 700
White blood cell count with differential	$\times 10^9$/L	1	1000/μL	≤ 2.5	≥ 15
Chemistry					
Albumin	g/L	0.1	g/dL	< 0.9 × LLN	> 1.1 × ULN
Alkaline phosphatase	U/L	1	U/L	—	≥ 3 × ULN
Alanine aminotransferase (ALT)	U/L	1	U/L	—	≥ 3 × ULN
Aspartate aminotransferase (AST)	U/L	1	U/L	—	≥ 3 × ULN
Gamma-glutamyl transferase (GGT)	U/L	1	U/L	—	≥ 3 × ULN
Blood urea nitrogen or Urea	mmol/L	2.8011	mg/dL	—	> 1.2 × ULN

Laboratory Parameter	*SI Unit*	*Conversion Factor*[a]	*Conventional Unit*	*PCS Criterion*[b] *Low Value*	*PCS Criterion*[b] *High Value*
Calcium	mmol/L	4.008	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	1	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Creatinine	µmol/L	0.0113	mg/dL	—	> 1.3 × ULN
Glucose, nonfasting	mmol/L	18.018	mg/dL	< 0.8 × LLN	> 1.2 × ULN
Magnesium	mmol/L	2	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	1	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	1	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Total bilirubin	µmol/L	0.0585	mg/dL	—	> 1.5 × ULN
Total protein	g/L	0.1	g/dL	< 0.9 × LLN	> 1.1 × ULN
Uric acid or Urate	µmol/L	0.0168	mg/dL	—	> 1.1 × ULN

[a] Conversion factor from SI units to conventional (traditional) units.
[b] Criteria refer to SI units.
Blood urea nitrogen or Urea are the same parameters, and Uric acid or Urate are the same parameters.
LLN = lower limit of normal; PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal laboratory reference range.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 4-7 (using the same periods as defined for AEs in Section 4.6.2.1). If Visit 1 for this study is the last visit from the lead-in study, the safety value at Visit 1 will not be included in the PCS evaluation, as it had been evaluated in the lead-in study, but it will be included in the change-from-baseline summary analysis.

4.6.3.2 Presentation

Observed, and Change from Baseline by visit for Hematology and clinical chemistry parameters will be listed and summarized in SI units by treatment group for the Safety analysis set.

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

The number and percentage of participants who have PCS post baseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available baseline values and at least 1 post baseline assessment. The numerator will be the total number of participants with available baseline values and at least 1 PCS post baseline value. A supportive tabular display of participants with PCS post baseline values will be provided, including the participant identifier, baseline and all post baseline (including non-PCS) values.

In addition, a listing with key participant information showing all AEs that occurred in participants who had PCS post baseline clinical laboratory values will be provided.

Chemistry lab results will be similarly listed and summarized with descriptive statistics.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Urinalysis will be carried out at Screening, Week 52, unscheduled visit, ET, and safety follow-up visits. Routine urinalysis includes specific gravity, pH, glucose, protein, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase, all of which are considered a high value if 2+. In addition, pH normal range is ≥ 5 to ≤ 8. Microscopic examination is performed as needed.

4.6.4.2 Presentation

Listing of urinalysis results, including Lead-in Baseline, for the Safety analysis set will be provided. A shift table from Baseline to the end of the Treatment Period will be presented by treatment group. Treatment emergent urinalysis abnormalities will be summarized by treatment group.

4.6.5 Other Laboratory Evaluations

4.6.5.1 Definitions and Derivations

Other laboratory testing is presented in Table 4-5.

4.6.5.2 Presentations

Positive pregnancy and other screening tests will be listed.

4.6.6 Physical Examinations

4.6.6.1 Definitions and Derivations

A complete physical examination will include assessments of the following:

- general appearance
- respiratory
- cardiovascular
- abdomen
- skin

- head and neck (including ears, eyes, nose, and throat)
- lymph nodes
- thyroid
- muscular-skeletal (including spine and extremities)
- neurological systems
- Fistula exam (as applicable)

Physical examinations will be performed at Screening, Weeks 0, 12, 24, 36, 52, unscheduled visit, and ET.

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.

4.6.7 Vital Signs

4.6.7.1 Definitions and Derivations

Vital signs will be collected at every Visit and include:

- Pulse rate
- Respiratory rate
- Temperature
- Blood pressure
- Weight, recorded in kilograms

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion detailed in Table 4-8.

Table 4-8 Criteria for Potentially Clinically Significant Vital Signs

Parameter	***Flag***	***Criteria***[a]	
		Observed Value	*Change from Baseline*
Sitting systolic blood pressure, mm Hg	High	≥ 140	Increase of ≥ 20
	Low	< 90	Decrease of ≥ 20
Sitting diastolic blood pressure, mm Hg	High	≥ 90	Increase of ≥ 15
	Low	< 60	Decrease of ≥ 15
Sitting pulse rate, bpm	High	≥ 100	Increase of ≥ 15
	Low	≤ 60	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%

[a] A post baseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.
bpm = beats per minute; hG = Mercury.

4.6.7.2 Presentation

A listing and summary of descriptive statistics for vital signs (systolic and diastolic blood pressures, pulse rate, body temperature, respiratory rate, and weight) values at Lead-in Baseline, Week 0 (i.e., the last assessment prior to first OLE dose), all post baseline visits, and change from baseline values at each post baseline timepoint will be presented by lead-in treatment group for the Safety analysis set. This by-visit summary is based on the visit name as collected in eCRF.

The number and percentage of participants who have PCS post baseline vital sign values will be tabulated by treatment group for each assessment. The percentages will be calculated relative to the number of participants who have available baseline values and at least 1 post baseline assessment. The numerator will be the total number of participants with at least 1 PCS post baseline value. A supportive listing of participants with PCS post baseline values will be provided.

In addition, a listing showing all AEs that occurred in participants who had PCS post baseline vital sign values will be provided.

4.6.8 Electrocardiogram

4.6.8.1 Definitions and Derivations

Single 12-lead ECGs will be obtained at Screening, Week 52, unscheduled visit, and ET using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The upper limit for each measure is shown in Table 4-9.

Table 4-9 Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	*Unit*	*Low Value*	*Low Decrease*	*High Value*	*High Increase*
RR interval	msec	< 500	NA	> 1500	NA
PR interval	msec	NA	NA	≥ 240	NA
QRS duration	msec	≤ 60	NA	≥ 140	NA
QT	msec	≤ 300	NA	> 450	> 60
QTcF	msec	≤ 300	NA	> 480	> 60
QTcB	msec	≤ 300	NA	> 480	> 60

QTc = QT interval corrected for heart rate.
QTcB = QT interval corrected for heart rate using the Bazett formula.
QTcF = QT interval corrected for heart rate using the Fridericia formula.

The outcome of the ECG evaluation is to be recorded as normal or abnormal in the eCRF, with any abnormalities recorded as either not clinically significant, or clinically significant.

4.6.8.2 Presentation

A listing and summary of descriptive statistics for ECG parameters (i.e., heart rate, PR interval, QRS interval, QT interval, and QTc interval) at Baseline, Week 0 (i.e., the last assessment prior to first OLE dose), Week 52, and change from baseline values at Week 52 will be presented by lead-in treatment group for the Safety analysis set.

ECG parameter values are considered PCS if ECG values meet the value listed in Table 4-9. The number and percentage of participants with PCS post baseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with an available non-PCS baseline value and at least one post baseline assessment. The numerator will be the total number of participants with an available non-PCS Baseline value and at least one PCS post baseline ECG value. A supportive listing of participants with PCS post baseline values will be provided and will include the participant number and the Baseline and post baseline values.

A listing of all AEs for participants with PCS ECG values will also be provided.

4.6.9 Other Safety Assessments

4.6.9.1 Definitions and Derivations

Potential Hy's Law criteria is defined as a post baseline elevation of ALT or AST ≥ 3x ULN, and Total Bilirubin (TBL) ≥ 2x ULN, where at least one time TBL ≥ 2x ULN occurred after the first occurrence of AST ≥ 3x ULN or ALT ≥ 3x ULN after start of treatment with investigational product.

Hy's Law is defined as ALT or AST ≥ 3x ULN together with TBL ≥ 2x ULN, where for no other reason, other than study intervention, can be found to explain the combination of increases (e.g., elevated alkaline phosphatase indicating cholestasis, viral hepatitis, or another drug).

More information can be found in the Clinical Study Protocol, Appendix D2.

4.6.9.2 Presentations

Participants with elevated liver tests based on measured laboratory values will be summarized for the Safety analysis set. Participants who meet the potential Hy's Law criteria from the first dose of the study intervention to within 18 weeks after the last dose of the study intervention will be listed and summarized by treatment group for the Safety analysis set.

5 INTERIM ANALYSIS

No interim analysis is planned for this study.

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7 APPENDIX

7.1 Crohn's Disease Activity Index

The CDAI is a composite index with weighted domains that quantifies the global disease severity in a single numerical score in a range from 0-600. The CDAI measures the severity of active disease using symptom scores that are monitored over the previous week and includes participant-reported symptoms, physician-assessed signs, and laboratory markers (Best 1976, Sands 2005). The CDAI score is calculated by summing weighted scores for subjective items (number of liquid or very soft stools [LSF], the degree of abdominal pain over a week [AP] and general well-being) recorded by a diary during a 1-week period, and objective items (associated symptoms, taking antidiarrheal such as loperamide/opiates, abdominal mass, hematocrit, daily morning temperature, and body weight). The CDAI scores range approximately 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 are shown in Table 7-1.

Table 7-1 Components of the CDAI score

Physical examination	Abdominal mass EIM (peripheral/axial arthropathy, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis/aphthous ulcers, anal fissures, anal abcess, non-anal abscess, fistula, other) Weight
Antidiarrheal medications	Antidiarrheal medications
Laboratory assessment	Hematocrit
Vital signs	Weight
Evening Diary	Temperature
Patient-reported components	LSF AP General well-being

The PRO symptoms scores (LSF, AP, and General Well-being) will be calculated by summing the individual daily scores over 7 days (see below for missing data conventions). This is in contrast with the average daily LSF and AP, which are calculated by taking the mean of the entries over the 7 days (see Appendix 7.2). If there is an ileocolonoscopy done the same day as the CDAI assessment, the PRO items will be collected for the 7 days prior to bowel prep; otherwise they will be collected for the 7 days prior to CDAI assessment.

The CDAI score is calculated by summing the weighted scores for the items in Table 7-2.

Table 7-2 Items Included in CDAI and Their Weights

Item	***Timing of assessment***	***× weight***	***Total***
Total number of liquid or very soft stools over past week (LSF)	7 days prior*	× 2	X_1
Total abdominal pain (AP) score (rating:0-3) over past week (range: 0-21)	7 days prior*	× 5	X_2
Total general well-being score (rating: 0-4) over past week (range: 0-28)	7 days prior*	× 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. Erthema 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)	 Assessed at Visit Assessed at Visit Assessed at Visit Assessed at Visit Assessed at Visit Assessed at Visit 7 days prior	× 20	X_4
Antidiarrheal use (E.g., Diphenoxylate hydrochloride) (0=none, 1=yes)	Assessed at Visit	× 30	X_5
Abdominal mass (none=0, equivocal=2, present=5)	Assessed at Visit	× 10	X_6
Deviation of Hematocrit levels (minimum value = 0) 47 – hematocrit (males) 42 – hematocrit (females)	Lab collected at Visit	× 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 (if value < -10, enter -10, if value > 10, enter 10)	Assessed at Visit	× 1	X_8 *(if value < -10, enter -10, if value > 10, enter 10)*
		CDAI score	$\sum_{i=1}^{8} X_i$

Standard body weight (IBW)(men) = 50 kg + 2.3 kg × (height, in – 60)
Standard body weight (IBW)(women) = 45.5 kg + 2.3 kg × (height, in – 60)
Note: this formula is only an approximation and is generally only applicable for people 60 inches (5 foot) tall or greater.
* If the CDAI calculation is done on the same day as an ileocolonoscopy, then the PRO elements will be collected during the 7 days prior to bowel prep.

Convention for calculations of CDAI scores:

1. Identify the CDAI calculation date as the completion date of the physician reported CDAI components using the Visit Window conventions in Section 3.3.2.
2. Calculate the 3 Diary subscores (liquid/soft stool frequency, abdominal pain and general well-being):
   a. If 4 or more days of diary are non-missing, the subscore is calculated as the (average of non-missing diary x 7), multiplying the factor appropriate for the given subscore then rounding to the nearest integer
3. Calculate Extra-intestinal manifestations of Crohn's Disease Subscore, usage of Lomotil/Imodium/opiates for diarrhea and abdominal mass.
   a. The EIM subscore will be the sum of the six items as listed in Table 7-2
   b. Assign 1 point for use of diarrhea treatment
   c. Abdominal mass is scored as none=0, equivocal=2, present=5
4. Calculate Hematocrit subscore as follows:
   a. Identify the Hematocrit (%) results using the visit window defined in Section 3.3.2. Select the value closest to the CDAI calculation date in (1). If two hematocrits are in the visit window, follow the rules in Section 3.3.3.2.
   b. If a hematocrit is missing, use the previous Week's value, if available.
   c. To calculate the corresponding subscore subtract 47 from males and 42 for females, multiply by a factor of 6 and round to the nearest integer. If the hematocrit subscore is < 0, set it to 0.
5. Calculate Body Weight subscore as follows:
   a. Identify the body weight result reported on the CDAI calculation date.
   b. Identify the standard weight based on the participant's gender and baseline height (in)
      1) Standard body weight (IBW)(men) = 50 kg + 2.3 kg × (height, in – 60)
      2) Standard body weight (IBW)(women) = 45.5 kg + 2.3 kg × (height, in – 60)
   c. Calculate the subscore as (1-(Body weight/Standard weight)) x 100. If the subscore is below -10, set to -10. If the subscore is greater than 10, set to 10.
6. Calculate total score as the weighted sum of the 8 subscores only if none of the subscores are missing. Otherwise, the total score is set to missing for the visit. In addition, the following set of rules will be applied:

If any of the subscores cannot be completed using the guidelines above, , then rules explained in Section 4.2.4.3 will apply.

Any total CDAI score < 0 will be considered as 0 in the analysis.

7.2 Participant-completed PRO Diary: LSF and AP

Patient Reported Outcomes Questionnaire was removed due to copyrights.

7.3 Simple Endoscopic Score for Crohn's Disease (SES-CD)

Patient Reported Outcomes Questionnaire: SES-CD was removed due to copyrights.

Patient Reported Outcomes Questionnaire: SES-CD was removed due to copyrights.

7.4 Evening Diary

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

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

7.5 Missing start and stop dates

For adverse events and prior or concomitant medications, including rescue medications, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

7.5.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

If the start date is missing, then it will be set to the date of the first study intervention, unless the end date suggests that the start date could be prior to the date of the first study intervention. In that case, set the start date to January 1 of the same year as the end date.

Missing month and day
The start date will be set to January 1 of the year of occurrence.

If the start year is the same as the year of the first study intervention, then the start date will be set to the date of first study intervention.

Missing month only
If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only
The missing start day will be set to the first day of the month of occurrence, if the start month and year is after the month and year of the first study intervention.

If the month and year of the incomplete start date are the same as the month and year of the first dose of the study intervention, the day of the first dose of the study intervention will be assigned to the missing day.

If the month and year of the incomplete start date is before the month and year of the first study intervention, the date of informed consent will be assigned to the incomplete date.

7.5.2 Incomplete Stop Date

Because participants will receive their double-blind study intervention doses under the direct supervision of study center personal, the date of dose of study intervention will always be known. The following rules will be applied to impute missing date fields for an incomplete AE, prior, or concomitant medication stop date. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

If the end date is missing and the event is not recorded as ongoing, then set the end date as the date of the first study intervention, if the start date is prior to the date of the first study intervention. If the start date is on or after the date of first study intervention, set the end date to the date of last visit.

Missing month and day

If the year of occurrence is the same as the last study intervention year, then the incomplete date will be set to the date of last study intervention. If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields.

If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* of the year of occurrence will be assigned to the missing fields, that is, the stop date will be set to December 31 of the year of occurrence. If the participant died in the same year, the stop date will be set to the date of death.

Missing month only

If only the month is missing, the day will be treated as missing and both the month and the day will be replaced as described in Section 7.5.1.

Missing day only

If the month and year of the incomplete stop date are after the month and year of the first study intervention, then the missing end day will be set to the last day of the month of the occurrence.

If the participant died, the end date will be set to the death date.

If the month and year of the incomplete stop date are the same as the month and year of the last dose of study intervention, the day of the last dose of study intervention will be assigned to the missing day.

If either the year of the incomplete stop date is before the year of the date of the last dose of study intervention or if both years are the same, but the month of the incomplete stop date is before the month of the date of the last dose of study intervention, the last day of the month will be assigned to the missing day.

If either the year of the incomplete stop date is after the year of the date of the last dose of study intervention or if both years are the same, but the month of the incomplete stop date is after the month of the date of the last dose of study intervention, the first day of the month will be assigned to the missing day.

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