Janssen Pharmaceutical K.K.*

Statistical Analysis Plan

A Phase 3, Open-label, Multicenter Study to Evaluate the Safety and Efficacy of Guselkumab in Participants with Moderately to Severely Active Crohn's Disease

Protocol CNTO1959CRD3003; Phase 3

CNTO1959 (guselkumab)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan.

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Compliance: The study described in this document will be performed according to the principles of Good Clinical Practice.

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VERSION HISTORY

This statistical analysis plan for Study CNTO1959CRD3003 is based on the protocol dated 24 March 2025.

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	15-Oct-2025	Not Applicable	Initial release

LIST OF ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AP	abdominal pain
AST	aspartate aminotransferase
AZA	Azathioprine
BIO-Failure	biologic therapy failure or intolerance
CDAI	Crohn's Disease Activity Index
CON-Failure	conventional therapy failure or intolerance
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
IA	interim analysis
ICF	informed consent form
INR	international normalized ratio
IV	Intravenous
LTE	long-term extension
NAb	Neutralizing antibody
PD	Pharmacodynamic
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SB	small bowel
SC	Subcutaneous
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SID	Study Intervention Discontinuation
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell (count)

1. INTRODUCTION

The protocol CNTO1959CRD3003 is a Phase 3 open label study in participants with moderately to severely active Crohn's Disease (CD). There will be 2 interim analyses planned at Week 24 database lock (DBL) as well as Week 48 DBL. The final DBL will occur after the end of long-term extension (LTE) phase. The analysis for the final DBL will be conducted after the final DBL occurred.

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for the final DBL. The analyses for Week 24 DBL and Week 48 DBL will be covered under 2 separate SAPs, respectively.

1.1. Objectives

Primary Objective

- To evaluate the safety of guselkumab in participants with CD

Secondary Objectives

- To evaluate the efficacy of guselkumab in participants with CD
- To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of guselkumab, including changes in C-reactive protein (CRP) and fecal calprotectin

Exploratory Objective

- To assess the efficacy of guselkumab on small bowel (SB) lesions

1.2. Study Design

This is a Phase 3, open-label, multicenter study to evaluate the safety and efficacy of guselkumab in participants with moderately to severely active CD who have demonstrated an inadequate response or failed to tolerate the previous conventional therapy (ie, 6-mercaptopurine [6-MP], azathioprine [AZA], or corticosteroids) [CON-failure] or biologic therapy (ie, TNFα antagonists, vedolizumab) [BIO-failure].

A target of 25 participants will be enrolled in this study. Participants will receive following guselkumab treatment in an open-label fashion;

- Weeks 0, 4, and 8: Guselkumab 200 mg IV administration (induction)
- Every 4 weeks after Week 8 until the end of the study: Guselkumab 200 mg SC administration (maintenance)

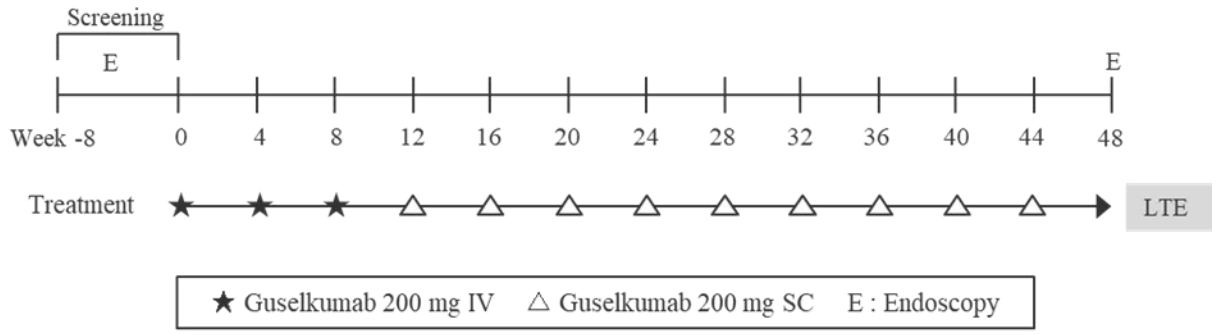
The study will be conducted in 3 phases: a maximum 8-week screening phase, a 48-week treatment phase followed by LTE phase, and a posttreatment follow up visit (12 weeks after the participant's last dose of study intervention to collect any adverse events since the last study visit). The duration of individual participation will be approximately 68 weeks if a participant ends the study participation at the end of treatment phase and does not enter the LTE.

Participants who have a concurrent or history of small bowel (SB) disease activity confirmed by radiography, imaging and/or endoscopy may be eligible to participate in the substudy for additional SB assessment by device-assisted enteroscopy (DAE).

Key safety assessments will include the monitoring of adverse events, vital sign measurements, and clinical laboratory tests including inflammatory biomarkers. Key efficacy assessments include Crohn's Disease Activity Index (CDAI) and its components, endoscopic assessments by either ileocolonoscopy or DAE (if a participant agrees to perform additional SB assessment).

A diagram of the study design is provided as below:

Figure 1: Schematic Overview of the Study



2. STATISTICAL HYPOTHESIS

The primary objective is to evaluate the safety of guselkumab in participants with Crohn's disease. No hypothesis testing will be performed in this study.

2.1. Multiplicity Adjustment

No multiplicity adjustment will be performed due to no hypothesis testing.

3. ANALYSIS SETS

Analysis Sets	Description
Enrolled Analysis Set	All participants who sign the ICF.
Full Analysis Set (FAS)	All enrolled participants who receive at least 1 dose of guselkumab.
SB Full Analysis Set (SBFAS)	All enrolled participants who receive at least 1 dose of guselkumab and have at least 1 SB assessment by device-assisted enteroscopy after their first dose of guselkumab.
Safety Analysis Set	All enrolled participants who receive at least 1 dose of guselkumab.
LTE Safety Analysis Set	All enrolled participants who receive at least 1 dose of guselkumab during the LTE phase.
Pharmacokinetics (PK) Analysis Set	All enrolled participants who receive at least 1 complete dose of guselkumab and have at least 1 valid blood sample drawn for PK analysis after their first dose of guselkumab.
Pharmacokinetics/ Pharmacodynamics (PK/PD) Analysis Set	All enrolled participants who have evaluable data of both PK and PD at the same visit which includes Week 12, Week 24, Week 48 or Week 96 visit.
Immunogenicity Analysis Set	All enrolled participants who receive at least 1 dose of guselkumab and have at least 1 observed postdose immune response data.

4. STATISTICAL ANALYSES

4.1. General Considerations

Unless otherwise noted, efficacy analysis will include all participants in the FAS, which is defined as all enrolled participants who had at least 1 dose of guselkumab in the study.

Baseline is defined as the last observation prior to or on the day of the first study intervention, unless otherwise specified.

4.1.1. Analysis Visit Windows

Unless otherwise specified, scheduled visits will be used for over time summaries and listings with no visit windows applied. However, the Unscheduled visits (USV), the Study Intervention Discontinuation (SID) and Final Efficacy and Safety (FES) visits will be slotted to scheduled visits according to the following mapping rules:

1. Assign a visit number to USV, SID or FES visit based on the visit day as illustrated in Table 2.
2. If USV, SID or FES visit falls in the window of a scheduled visit and there are not already data for the scheduled visit, assign the scheduled visit number to the USV, SID or FES visit. If there are already data for a same scheduled visit, those data will be used in lieu of the USV, SID or FES visit data.

Table 2: USV, SID and FES Visit Slotting

Week 4	Day 2-42
Week 8	Day 43-70
Week 12	Day 71-98
Week 16	Day 99-126
Week 20	Day 127-154
Week 24	Day 155-182
Week 28	Day 183-210
Week 32	Day 211-238
Week 36	Day 239-266
Week 40	Day 267-294
Week 44	Day 295-322
Week 48	Day 323-350
Week 52	Day 351-378
Week 56	Day 379-406
Week 60	Day 407-434
Week 64	Day 435-462
Week 68	Day 463-490
Week 72	Day 491-518
Week 76	Day 519-546
Week 80	Day 547-574
Week 84	Day 575-602
Week 88	Day 603-630
Week 92	Day 631-658
Week 96	Day 659-686
Week 100	Day 687-714
Week 104	Day 715-742
Week 108	Day 743-770
Week 112	Day 771-798
Week 116	Day 799-826

Week 120	Day 827-854
Week 124	Day 855-882
Week 128	Day 883-910
Week 132	Day 911-938
Week 136	Day 939-966
Week 140	Day 967-994
Week 144	Day 995-1022
Week 148	Day 1023-1050
Week 152	Day 1051-1078
Week 156	Day 1079-1106
Week 160	Day 1107-1134
Week 164	Day 1135-1162
Week 168	Day 1163-1190
Week 172	Day 1191-1218
Week 176	Day 1219-1246
Week 180	Day 1247-1274
Week 184	Day 1275-1302
Week 188	Day 1303-1330
Week 192	Day 1331-1358
Week 196	Day 1359-1386
Week 200	Day 1387-1414
Week 204	Day 1415-1442
Week 208	Day 1443-1470
Week 212	Day 1471-1498
Week 216	Day 1499-1526
Week 220	Day 1527-1554
Week 224	Day 1555-1582
Week 228	Day 1583-1610
Week 232	Day 1611-1638
Week 236	Day 1639-1666
Week 240	Day 1667-1694

When an endoscopy by either ileocolonoscopy or DAE is performed at a USV, SID or FES visit, then an endoscopy that occurs from Days 309-365, 645-701, 981-1037, 1317-1373 or 1653-1709 inclusive, will be slotted to Week 48, 96, 144 192 or 240, respectively.

Descriptive summary statistics, such as n, mean, standard deviation (SD), median, inter quantile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize data as appropriate unless otherwise specified.

4.2. Efficacy Analysis

The following efficacy endpoints will be included in the efficacy analysis based on FAS:

- Clinical response at each visit during LTE (tabularly and graphically)
- Clinical remission at each visit during LTE (tabularly and graphically)
- Endoscopic response at each visit during LTE
- Endoscopic remission at each visit during LTE
- Change in CDAI score from baseline at each visit during LTE

- Clinical-biomarker response at each visit during LTE
- PRO-2 remission at each visit during LTE (tabularly and graphically)
- Abdominal pain score (daily average based on the CDAI assessment) ≤1 at each visit during LTE, among participants with daily average AP score >1 at baseline
- Number of liquid or very soft stools (daily average based on the CDAI assessment) ≤3 at each visit during LTE, among participants with daily average number of liquid or very soft stools >3 at baseline
- Change in SES-CD score from baseline at each visit during LTE
- Endoscopic healing at Week each visit during LTE
- Proportion of participants having any Crohn's disease-related hospitalizations and/or surgeries during the study
- Summary of the change from baseline in the average daily prednisone equivalent (P.Eq) oral corticosteroids dose (mg/day; excluding budesonide) at each visit during LTE; participants who were receiving oral corticosteroids other than budesonide at baseline
- Plot of mean average daily prednisone equivalent (P.Eq) corticosteroid dose (excluding budesonide) during LTE among participants receiving steroids at baseline

In addition, below efficacy endpoints will be analyzed based on SBFAS:

- Change in mSES-CD score from baseline at each visit during LTE
- Endoscopic healing in small bowel at each visit during LTE
- Endoscopic healing at each visit during LTE
- Mucosal activity in small bowel at each visit during LTE

4.2.1. Definition of Endpoints

- **Clinical response:** ≥100-point reduction from baseline in CDAI score or CDAI score <150
- **Clinical remission:** CDAI score<150
- **PRO-2 remission:** an AP mean daily score at or below 1 and an SF mean daily score at or below 3, and no worsening of AP or SF from baseline
- **Clinical-biomarker response:** clinical response based on CDAI score and ≥50% reduction from baseline in CRP or fecal calprotectin
- **Endoscopic response:** at least 50% improvement from baseline in the SES-CD score or SES-CD score ≤2
- **Endoscopic remission:** SES-CD ≤4 with at least a 2-point reduction from baseline and no subscore greater than 1 in any individual subcomponent
- **Endoscopic healing:** absence of mucosal ulcerations

The following endpoints are defined for SB substudy only.

- **Mucosal activity in small bowel**: defined as no mucosal activity (modified SES-CD=0), mild disease (1≤modified SES-CD<5) and ulcerative disease (modified SES-CD≥5) (Takenaka 2018).
- **Endoscopic healing in small bowel**: modified SES-CD<5 (Takenaka 2018).

Crohn's Disease Activity Index (CDAI)

The CDAI will be assessed by collecting information on 8 different CD-related variables (Best 1976). These 8 variables are:

- Extraintestinal manifestations
- Abdominal mass
- Weight
- Hematocrit
- Use of antidiarrheal drug(s) and/or opiates
- Total number of liquid or very soft stools
- Abdominal pain/cramps
- General well-being

The last 3 variables are scored over 7 days by the participant on a diary card. For the total number of liquid or very soft stools, abdominal pain/cramps, and general well-being, if only 5 days or 6 days of data are available for the calculation, the weights of 7/5 and 7/6, respectively, will be used for the calculation; if the values are recorded for less than 5 days, the component will not be calculated. The CDAI score calculation algorithm is presented in Appendix 10 of the protocol.

At each timepoint, the CDAI score will only be calculated if ≥ 4 of the 8 components are available. If the CDAI score cannot be calculated (ie, <4 components available), the CDAI score will be considered missing. When at least 4 of the 8 components are available, any missing components will be imputed by carrying forward the last nonmissing component. The **PRO-2** includes the unweighted CDAI components of the total number of liquid or very soft stools and the AP score.

Daily average abdominal pain (AP) score

Daily average abdominal pain score is defined as: the sum of abdominal pain/cramps ratings in previous 7 days in a dairy card ÷ total days assessment performed. Daily average abdominal pain score at a scheduled visit will not be calculated if the total days of assessment is less than 5.

Daily average stool frequency (SF) score

Daily average stool frequency score is defined as: total number of liquid or very soft stools in previous 7 days in a dairy card ÷ total days assessment performed. Daily average stool frequency score at a scheduled visit will not be calculated if the total days of assessment is less than 5.

Simplified endoscopic activity score for Crohn's disease (SES-CD)

The Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) is a scoring system developed to provide a more granular evaluation of endoscopic disease severity in patients with Crohn's disease. It is constructed based on the evaluation of 4 endoscopic components across 5 predefined ileocolonic segments. The 4 endoscopic components within each segment are: the presence/size of ulcers, the proportion of mucosal surface covered by ulcers, the proportion of mucosal surface affected by any other lesions, and the presence/ type of narrowing (also commonly referred to as strictures/ stenosis clinically). Each endoscopic component is scored from 0 to 3 for each segment, and a total score is calculated as a sum of all the component scores across all the segments, as outlined in Table 3. The total SES-CD score ranges from 0 to 56.

Table 3: Sample score sheet and scoring definitions for the Simple Endoscopic Score for Crohn's Disease (SES-CD)

	Ileum	Right Colon	Transverse Colon	Left Colon	Rectum	Total
1. Presence and size of ulcers (0-3)						15 max
2. Extent of ulcerated surface (0-3)						15 max
3. Extent of affected surface (0-3)						15 max
4. Presence and type of narrowings (0-3)						11 max*
					Total 1 + 2 + 3 + 4 =	SES-CD (56 max)

	Score = 0	Score = 1	Score = 2	Score = 3
Size of ulcers	None	Aphthous ulcers (ø 0.1 – 0.5 cm)	Large ulcers (ø 0.5 – 2.0 cm)	Very large ulcers (ø > 2.0 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

* The maximum subscore for narrowings (ie, stricturing) is 11 points. The presence of a narrowing that cannot be passed can be only observed once.
ø =Diameter.

Calculation of the SES-CD score:

Main approach (SES-CD calculated based on all segments available):

The total SES-CD score at a visit will be calculated based on all segments scored at the visit. If the total SES-CD score cannot be calculated (ie, no segment is scored) at a visit, the total SES-CD score will be considered missing.

Modified SES-CD

Modified SES-CD will be used to evaluate endoscopic improvement in SB lesions. While 3 endoscopic components except for presence/type of narrowing/strictures for the evaluation of modified SES-CD is the same as that for original SES-CD score instead of 5 ileocolonic segments for original SES-CD score; terminal ileum (≤ 10 cm from ileocecal valve), proximal ileum (10-300 cm from the ileocecal valve) and jejunum (SB proximally beyond the section defined as the

proximal ileum), ranged from 0-27. The modified SES-CD score will be calculated based on all 3 segments scored.

4.2.2. Analysis Methods

The following are the intercurrent events considered for this study:

1. A Crohn's disease-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc)
2. A prohibited change in CD medication (for details, see Appendix 8)
3. Discontinuation of study agent due to lack of efficacy or due to an AE of worsening Crohn's disease
4. Discontinuation of study agent due to COVID-19 related reasons (excluding COVID-19 infection)
5. Discontinuation of study agent for reasons other than those specified in ICE 3 and 4

Intercurrent events (ICEs) in categories 1-3 and 5 will be handled with the **Composite Strategy**. ICE category 4 will be handled by the **Treatment Policy Strategy**. Note that the application of ICE 1-3 overrides that of ICE 4. The number of participants who experienced ICEs during the study will be summarized based on the FAS.

The occurrence of ICE 1-3 and 5 is considered as an unfavorable outcome. For continuous variables, the records collected after ICE 1-3 and 5 will be replaced by the baseline observation value. Take CDAI for example. If the ICE occurs between Week 4 and Week 8 visit, the baseline CDAI will be used as the CDAI scores for Week 8 and onward. For binary response variables, participants will be treated as nonresponders after ICE 1-3 and 5. Participants with ICE 4 will use their observed data after the ICE.

After accounting for all ICEs, no imputation method will be utilized for participants with missing observations for continuous efficacy endpoints unless otherwise specified. For participants with missing observations for dichotomous efficacy endpoints except for endoscopic endpoints, participants will be considered as not having achieved the respective endpoints (eg, participants with a missing CDAI score will be considered not in clinical response/clinical remission), unless otherwise specified. Because endoscopic assessments can be performed at discretion of the investigator, missing observations at each visit will be excluded from the analyses after accounting for all ICEs for endoscopic endpoints including endoscopic response, endoscopic remission, endoscopic healing, endoscopic healing in small bowel, mucosal activity in small bowel.

As no statistical hypothesis testing is planned in this study, no comparison will be performed.

Continuous variables will be summarized by descriptive summary statistics, such as n, mean, standard deviation (SD), median, inter quantile range, minimum, and maximum. After imputed for missing data, response rate and its 2-sided Clopper-Pearson exact 95% confidence interval (CI) will be provided for binary response variables unless otherwise specified.

4.3. Safety Analyses

All safety analyses will be based on Safety Analysis Set, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

4.3.1. Extent of Exposure

The number and percentage of participants who receive study intervention during the study will be summarized based on Safety Analysis Set. The duration of treatment, cumulative dose (IV and SC) and number of administrations (IV and SC) of study intervention received will be summarized during the study.

In addition, the number of administrations (IV and SC), average duration of study participation follow-up in weeks, defined by latest follow-up visit date during the study, will be summarized as part of the adverse event tables.

Study intervention compliance will be summarized descriptively. See Appendix 6 for further details.

4.3.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) are AEs with onset during the intervention phase or that are a consequence of a preexisting condition that has worsened since baseline. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized. Since safety should be assessed relative to exposure and follow-up, all AE summary tables will summarize the average weeks of follow-up and average exposure (number of administrations).

Summary tables will be provided for TEAEs during the study based on Safety Analysis Set and during LTE based on LTE Safety Analysis Set

- Frequency and type of AEs*
- Frequency and type of SAEs*
- Frequency and type of reasonably related AEs as assessed by the investigator
- Frequency and type of reasonably related SAEs as assessed by the investigator
- Frequency and severity of AEs

- Frequency and type of AEs leading to discontinuation of study intervention*
- Frequency and type of infections
- Frequency and type of AEs temporally associated with infusion
- Frequency and type of injection-site reactions
- Frequency and type of AEs by onset period (within Week 48, Week 48-Week 96, Week 96-Week 144, Week 144-Week 192 beyond Week 192)
- Frequency and type of AEs with frequency of at least 3% by preferred term

* Adverse events will also be summarized as events per 100 subject years of follow-up during the study.

In addition to the summary tables, listings will be provided for participants with:

- TEAEs
- SAEs
- TEAEs leading to discontinuation of study intervention
- Death
- COVID-19 related TEAEs

Information for TEAE occurred after self-administration at home but not after administration by healthcare provider at site will be included in the listings.

These summary tables will provide the count and percentage of participants with 1 or more of the specified TEAEs by system-organ class and preferred term. AESIs or AEs of interest as described in Appendix 7 will either be presented in a table, listing or described in the clinical study report.

4.3.3. Additional Safety Assessments

4.3.3.1. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The following tests will be performed by the central laboratory unless otherwise specified or approved by the medical monitor.

- **Hematology assessments** will include but are not limited to the following: hemoglobin, hematocrit, platelet count, total and differential WBC count.
- **Blood chemistry assessments** will include but are not limited to the following: chemistry panel (total and direct bilirubin, ALT, AST, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, glucose, and creatinine).

Clinical laboratory test values are to be graded based on CTCAE version 5.0 (Appendix 9) except ALT, AST, total bilirubin, and alkaline phosphatase which will be using the predefined upper limit of normal (ULN) thresholds. The laboratory tests not included in Appendix 9 or the predefined ULN thresholds of liver tests will not be presented in the corresponding tables or listings.

The following analyses and summaries of clinical laboratory tests will also be provided for participants in the Safety Analysis Set:

1. Descriptive statistics of observed values and change from baseline for selected chemistry, hematology laboratory tests at scheduled time points during the study.
2. Line plots of the observed values and changes from baseline over time during the study for liver function (ALT, AST, total bilirubin, and alkaline phosphatase).
3. Summary of maximum National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grade for postbaseline laboratory values during the study for the predefined hematology and chemistry lab parameters except liver tests (ie ALT, AST, total bilirubin, and alkaline phosphatase).
4. Shift tables for maximum NCI-CTCAE toxicity grade from baseline during the study will be summarized for the predefined hematology and chemistry lab parameters except liver tests (ie ALT, AST, total bilirubin, and alkaline phosphatase).
5. Summary of maximum postbaseline measurement during the study for liver tests (ie ALT, AST, alkaline phosphatase and total bilirubin) relative to ULN threshold. This summary will be provided by normal/abnormal measurements at baseline.
6. Change in CRP from baseline at each visit during the study.
7. Change in fecal calprotectin from baseline at each visit during the study.

Change from baseline is defined to be the assessment at the postbaseline visit minus the assessment at baseline. There will be no imputation for missing laboratory values.

Listings will be provided for participants with any of the following:

- Abnormal postbaseline lab values of NCI-CTCAE grade ≥ 2 except liver tests
- Postbaseline elevated liver tests of ALT or AST ≥ 5x ULN, or total bilirubin ≥2x ULN, or alkaline phosphatase ≥ 2x ULN
- Postbaseline elevated liver test with combined ALT/AST ≥ 3x ULN and (total bilirubin ≥ 2x ULN or INR > 1.5).

4.3.3.2. Vital Signs

Continuous vital sign parameters including temperature, pulse, weight, respiratory rate, blood pressure (systolic and diastolic) will be summarized at each assessment time point during the study. Change from baseline will be summarized at scheduled time points during the study. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Incidence of markedly abnormal vital signs during intervention, as defined in Table 4, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign. A listing of participants with markedly abnormal vital signs will be presented, along with a listing of all vital sign measurements.

Table 4: Markedly Abnormal Vital Signs

Vital Sign	Criteria
Pulse	>120 bpm and with >30 bpm increase from baseline
	<50 bpm and with >20 bpm decrease from baseline
Systolic blood pressure	>180 mm Hg and with >40 mm Hg increase from baseline
	<90 mm Hg and with >30 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >30 mm Hg increase from baseline
	<50 mm Hg and with >20 mm Hg decrease from baseline
Temperature	>38ºC and with >=1ºC increase from baseline
Weight	increase 10% kg from baseline
	decrease 10% kg from baseline

4.3.3.3. Other Safety Parameters

4.3.3.3.1. Suicidal Ideation and Behavior

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used as a screening tool to prospectively evaluate suicidal ideation and behavior in this study, as part of a comprehensive evaluation of safety. The C-SSRS is an investigator-administered questionnaire (Best 1976; Mundt 2013) that defines five subtypes of suicidal ideation and 4 possible suicidal behaviors, as well as nonsuicidal self-injurious behavior and completed suicide.

The baseline is defined as the most severe/maximum score at screening and Week 0.

Suicidal ideation and behavior will be analyzed by the most severe/maximum post baseline C-SSRS outcome or AE of suicidal ideation or behavior during the study.

Participants with positive (ie, score >0 postbaseline ideation and behavior) during the study will be presented in a data listing.

4.4. Other Analyses

4.4.1. Pharmacokinetics

Blood samples for determining the serum guselkumab concentrations will be drawn from all participants according to the Schedule of Activities in the Protocol.

PK analyses will be performed on the Pharmacokinetics analysis set.

Serum guselkumab concentrations summary and analysis will be based on the observed data; therefore, no imputation of missing data will be performed. All PK data including actual sampling time will be listed. All serum guselkumab concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as such in the concentration database or data presentations. Concentrations below the LLOQ will be imputed as zero in the summary statistics. All participants and samples excluded from the analysis will be clearly documented (eg, unknown or unreliable drug intake information).

Descriptive statistics (N, mean, SD, median, interquartile range, range) will be used to summarize serum guselkumab concentrations at each sampling time point during LTE. Serum guselkumab concentration summarizes will also be presented by the following subgroups:

- Baseline body weight quartiles
- Antibodies to guselkumab status by Subject ADA status who have at least one positive ADA sample or no positive ADA sample during the study

PK data will be displayed graphically by following figures:

- PK concentrations during LTE (in linear and semilog scales) with nominal sampling time
- PK concentrations during LTE (in linear and semilog scales) with nominal sampling time by Subject ADA status who have at least one positive ADA sample or no positive ADA sample

For descriptive statistics of serum concentrations of guselkumab, the following data handling rules will be applied:

- Participants data will be excluded from the PK analyses if their data do not allow for accurate assessment of the PK. In particular, all serum concentration summaries will exclude, from the time of occurrence, data collected for participants who 1) discontinue study intervention, 2) skip an infusion or injection, 3) receive an incomplete infusion or injection, 4) receive an incorrect infusion or injection, 5) receive an additional infusion or injection, and/or 6) receive commercial guselkumab. Exclusion data from PK analysis due to such inadequate administration will be specified by PK analyst.
- Additionally, postinfusion samples that occurred more than 24 hours after infusion and preinfusion samples that were corrected outside of the visit window +/- 7 days will be excluded from the analysis.
- Serum concentrations of guselkumab data will be summarized based on the number of subjects with observed data, including below the lowest quantification (BQL), at each sampling time.
- When more than half (>50%) of the serum concentrations of guselkumab are BQL at each scheduled time point, mean, median, minimum and 25% quartile will be shown as ‘BQL’, and SD and %CV and 75% quartile will be shown as ‘NC’ (not calculated). Maximum observed value will be presented as maximum.
- When all serum concentration data are BQL at each scheduled time point, mean and median will be reported as ‘BQL’; SD and %CV are reported as ‘NC’ (not calculated); IQ range, maximum and minimum will be reported as ‘BQL’.
- When the number of serum concentrations data of guselkumab at each scheduled time point is less than or equal to 2, N, mean and median will be calculated, and SD, %CV, 25% quartile and 75% quartile will be shown as ‘NC’. Minimum and maximum will be shown as ‘NC’ (quantifiable data=1) or will be reported as observed including BQL (quantifiable data =2).
- At the time point where no observation is obtained, ‘NA (not applicable)’ is reported.
- Data of samples with no information about the sampling date and time and/or the drug administration (time and dosage) will be excluded from descriptive statistics.

- Sampling time at Week 0 predose will be substituted with "0" in the figure. The data point at which mean of serum guselkumab concentration is BQL will be treated as LLOQ value (eg, 0.01 μg/mL) in graph.
- Serum guselkumab concentrations below the LLOQ will be imputed as zero in the summary statistics.

The elapsed time from last dosing of next PK sampling point will be described in listing.

4.4.1.1. Population PK Analysis

Population PK modeling may be conducted when appropriate. If population PK analysis is conducted, the results of the modeling analysis will be presented in a separate report.

4.4.2. Immunogenicity

4.4.2.1. Immunogenicity Analysis

Serum samples will be screened for antibodies binding to guselkumab and the titer of confirmed positive samples will be reported. Immunogenicity analysis will be performed based on the immunogenicity analysis set.

The incidence and titers of antibodies to guselkumab will be summarized. The maximum titers of antibodies to guselkumab will be provided for participants who are positive for antibodies to guselkumab. Injection-site reactions by the incidence of antibodies to guselkumab will be summarized.

A listing for antibodies to guselkumab will be provided. The listing will contain visit, serum guselkumab concentration at the visit, baseline immunomodulators use (Yes or No), CDAI score at the visit, SES-CD score at the visit, having at least 1 SB assessment by device-assisted enteroscopy after their first dose of guselkumab,.injection-site reactions/AEs temporarily associated with an infusion, and antibody status (titer and neutralizing antibodies status) for all visits.

The incidence of neutralizing antibodies (NAbs) to guselkumab will be summarized for participants who are positive for antibodies to guselkumab and have samples evaluable for NAbs to guselkumab.

The antibodies to guselkumab summary and analysis will be based on the observed data; therefore no imputation of missing data will be performed.

4.4.3. Pharmacodynamics

C-reactive protein (CRP) and fecal calprotectin will be evaluated using blood and stool samples collected at scheduled visits according to the Schedule of Activities in protocol.

4.4.4. Pharmacokinetic/Pharmacodynamic Relationships

If data permit, the relationship between serum guselkumab concentration (PK data) and efficacy measures for primary and selected key secondary endpoints (PD data) may be analyzed tabularly or graphically (PK/PD analysis). PK/PD analysis will be performed on the PK/PD analysis set.

To explore the relationship between guselkumab serum concentrations and biomarkers and/or efficacy endpoints, the following analyses will be explored:

The relationship between guselkumab serum concentrations (quartiles) and change from baseline in CDAI score, clinical response, clinical remission, endoscopic response and endoscopic remission at Week 96 will be explored tabularly.

The relationship between guselkumab serum concentrations (quartiles) and clinical response, clinical remission, endoscopic response and endoscopic remission at Week 96 will be displayed graphically.

4.4.5. Subgroup Analysis

No subgroup analysis is planned.

4.5. Interim Analysis

There are 2 interim analyses planned at Week 24 DBL as well as Week 48 DBL before the final DBL to review safety and efficacy data. The analyses for Week 24 DBL and Week 48 DBL will be covered under separate SAPs.

4.6. Changes to Protocol-planned Analyses

Not Applicable.

5. SAMPLE SIZE DETERMINATION

As no statistical hypothesis testing based on any endpoint is planned in this study, the sample size was not calculated based on statistical considerations. The objective of the study is to assess the safety of guselkumab in the Japanese patients with moderately to severely active CD together with CNTO1959CRD3001 study, and the sample size was chosen to achieve this objective and provide additional safety information as much as possible.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Participant Dispositions

The number of participants in each analysis set, including the Enrolled Analysis Set, will be summarized.

The number of participants in the following disposition categories will be summarized throughout the study based on the FAS:

- Participants who discontinued guselkumab and reasons for discontinuation, including those due to COVID-19 related events
- Participants who terminated study prematurely and reasons for termination, including those due to COVID-19 related events

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study prematurely
- Participants who were enrolled yet did not receive guselkumab
- Participants who discontinued guselkumab due to COVID-19 (if applicable)
- Participants who terminated study participation prematurely due to COVID-19 (if applicable)

Study Assessment Compliance will be summarized and listed for the FAS. This will include the number of participants who missed at least one scheduled CDAI assessment, or at least one missed study intervention administration due to any reason, due to COVID-19-related events. Other intervention compliance is presented in Appendix 6 if applicable.

6.2. Appendix 2 Baseline Characteristics and Demographics

Table 5 presents a list of the demographic and baseline Crohn's disease characteristics variables that will be summarized for the FAS.

Table 5: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
BMI	
Crohn's disease duration (years)	
CDAI score	
SES-CD score	
mSES-CD score	
PRO-2 score	
CRP	
Fecal Calprotectin	
Categorical Variables	
Sex (male, female)	Frequency distribution with the number and percentage of participants in each category.
Race [a] (Asian, Other)	
Ethnicity (Not Hispanic or Latino)	
Crohn's disease complications	
Involved GI areas	
Involved SB areas	
Endoscopic disease severity per SES-CD score [Mild (<7), Moderate (7-16), Severe (>16)]	
Stool frequency > 3	
Abdominal pain > 1	
Stool frequency > 3 and Abdominal pain >1	
Fecal calprotectin > 250 µg/g	
CRP >3 mg/L	
Fecal calprotectin > 250 µg/g and CRP >3 mg/L	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

6.3. Appendix 3 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to DBL and the participants with major protocol deviations will be summarized by following category based on the FAS.

- Received wrong treatment or incorrect dose
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Developed withdrawal criteria but not withdrawn
- Other
  - COVID-19 related deviations

Participants who did not meet study entry criteria will be further summarized by following category.

- CD disease criteria
- Medication criteria
- Laboratory criteria
- Medical history criteria
- Other

A listing of participants who have study entry criteria not met, along with the category not met, will be provided.

Also, below listings will be provided.

- Participants with major protocol deviations
- Participants with COVID-19 related major protocol deviations
- Participants with COVID-19 related minor protocol deviations
- Participants with study intervention administration irregularities
- Participants who have study entry criteria not met, along with the category not met

6.4. Appendix 4 Medical History

A summary of medical history of interest, as well as a summary of Crohn's disease history and Crohn's disease conditions of interest, and smoking status will be summarized for the FAS.

Participant listing of medical history and medical history of interest will be provided separately.

6.5. Appendix 5 Prior/Concomitant/Follow-up Medications (including dictionary)

Summaries of concomitant medications at baseline and CD medication history for the FAS will be summarized:

- Summary of Concomitant Medications for CD at Baseline
  - Participants with 1 or more concomitant medications for CD (n, %)
  - Immunomodulatory drugs (n, %)
  - Aminosalicylates (n, %)
  - Antibiotics (n, %)
  - Corticosteroids (including budesonide) (n, %)
  - Corticosteroids P.Eq dose (excluding budesonide) (mg/day)
  - Budesonide dose (mg/day)
  - Nutritional therapy [Oral (Enteral), Intravenous] (kcal/day)
- Summary of Crohn's Disease Medication History
  - Corticosteroids (duration of use)
  - Immunomodulators (6-MP/AZA) (duration of use)
  - Biologics (Infliximab, Adalimumab, Vedolizumab, Ustekinumab) (duration of use)
- Summary of TNF Antagonist Therapy History by Number of TNF Antagonists (1 and 2) Received
  - Participants with inadequate initial response (primary nonresponse), loss of response (secondary nonresponse), or intolerance to TNF antagonist
  - Participants with inadequate initial response to TNF antagonist
  - Participants with response followed by loss of response to TNF antagonist
  - Participants with intolerance to TNF antagonist
- Summary of Biologic Therapy History by Biologic (Infliximab, Adalimumab, Vedolizumab)
  - Participants with inadequate initial response (primary nonresponse), loss of response (secondary nonresponse) or intolerance to biologic therapy
  - Participants with inadequate initial response to biologic therapy
  - Participants with response followed by loss of response to biologic therapy
  - Participants with intolerance to biologic therapy
- Summary of CD-related Nonbiologic Medication History (History of Response to or Intolerance of Corticosteroids or 6-MP/AZA)
  - Participants with inadequate response, intolerance, or dependence
  - Participants with inadequate response

  - Participants intolerant
  - Participants dependent
- Summary of CD-related Biologic Medication History
  - Participants without a history of biologic failure
    - Biologic-naïve
    - Biologic experienced but not documented failure
  - Biologic failure
  - Primary nonresponse, secondary nonresponse, or intolerance to
    - At least one anti-TNF
    - ≥ 2 anti-TNFs
    - Anti-TNF only
    - Vedolizumab
    - Vedolizumab only
    - Vedolizumab and at least one anti-TNF

A listing of concomitant medications for COVID-19 infections will be provided.

6.6. Appendix 6 Intervention Compliance

The compliance of treatment will also be summarized during the study within each route of administration (IV and SC). Compliance is calculated as (actual amount of study intervention/ protocol defined amount of study intervention) *100.

The number and percentage of participants who have:

- <60%
- 60 - <80%
- 80 - ≤100%
- >100%

Overall treatment compliance during the study will also be summarized.

6.7. Appendix 7 Adverse Events of Special Interest

AEs of Special Interest and other events of interest are as follows:

- Active Tuberculosis (AESI)
- Malignancies (AESI)
- Opportunistic Infections
- Major Adverse Cardiovascular Events (MACE)
  - Cardiovascular death
  - Nonfatal myocardial infarction (MI)
  - Nonfatal stroke
- Hepatic Disorders
- Venous thromboembolism (VTE)
- Anaphylactic reaction
- Serum-sickness

6.8. Appendix 8 Medications of Special Interest

Prohibited Changes in Crohn's Disease

Participants who had a prohibited change in CD medication described below are considered to have ICE 2:

1. Prohibited medications

Initiation of the following prohibited medications after Week 0:

a. Immunomodulatory agents other than AZA or 6-MP (including, but not limited to, 6-TG, cyclosporine, mycophenolate mofetil, tacrolimus, and sirolimus).

b. Immunomodulatory biologic agents (including, but not limited to, TNF antagonists, natalizumab, ustekinumab, rituximab, vedolizumab).

c. Experimental Crohn's disease medications (including, but not limited to, upadacitinib, filgotinib, ozanimod, etrolizumab, briakinumab, mirikizumab, risankizumab, GS-5745).

d. Thalidomide or related agents.

2. Corticosteroids

The occurrence of the following changes in corticosteroid usage **during induction treatment (ie, before Week 12), OR, during maintenance treatment, between Week 36 and Week 48, including changes initiated before Week 36 that continued after Week 36, unless otherwise specified.**

a. Initiation of oral corticosteroids (including budesonide), parenteral, or rectal corticosteroids due to worsening Crohn's disease.

b. Increase in the dose of oral corticosteroids (including budesonide) above the baseline dose (by the amount specified below for each type of corticosteroid) due to worsening Crohn's disease.

   1) Oral corticosteroids ≥ 5 mg/day (prednisone equivalent)

   2) Oral budesonide ≥ 3 mg/day

c. Initiation of oral corticosteroids (including budesonide) due to reasons other than worsening Crohn's disease for more than 7 days during induction treatment, OR, for more than 28 days during the maintenance time period defined above.

d. Increase in the dose of oral corticosteroids (including budesonide) above the baseline dose (by the amount specified below for each type of corticosteroid) due to reasons other than worsening Crohn's disease for more than 7 days during induction treatment, OR, for more than 28 days during the maintenance time period defined above.

   1) Oral corticosteroids ≥ 5 mg/day (prednisone equivalent)

   2) Oral budesonide ≥ 3 mg/day

3. Immunomodulator agents
    a. Initiation of oral 6-MP/AZA due to worsening Crohn's disease.
    b. Increase in the dose of oral 6-MP/AZA above the baseline dose due to worsening Crohn's disease.

4. 5-ASA

Initiation or increase in the dose of oral 5-ASA compounds due to worsening of Crohn's disease.

5. Antibiotics

Initiation or change of antibiotics due to worsening Crohn's disease.

6. Nutritional therapy

Initiation or change of nutritional therapy due to worsening Crohn's disease.

6.9. Appendix 9 Laboratory Toxicity Grading

Hematology Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
Hemoglobin (g/dL)	Increase	>0 - 2 g/dL above ULN	>2 - 4 g/dL above ULN	>4 g/dL above ULN	
Hemoglobin (g/dL)	Decrease	<LLN - 10.0	<10.0 - 8.0	<8.0	
Lymphocytes (/mm3)	Increase		>4000 - 20,000	>20,000	
Lymphocytes (/mm3)	Decrease	<LLN - 800	<800 - 500	<500 - 200	<200
Neutrophils (/mm3)	Decrease	<LLN - 1500	<1500 - 1000	<1000 - 500	<500
Platelets (/mm3)	Decrease	<LLN - 75,000	<75,000 - 50,000	<50,000 - 25,000	<25,000
Total WBC count (/mm3)	Increase			>100,000	
Total WBC count (/mm3)	Decrease	<LLN - 3000	<3000 - 2000	<2000 - 1000	<1000
Chemistry Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
Albumin (g/L)	Decrease	≥30 - <LLN	≥20 - <30	<20	
Corrected Calcium (mmol/L)	Increase	>ULN - ≤2.9	>2.9 - ≤3.1	>3.1 - ≤3.4	>3.4
Corrected Calcium (mmol/L)	Decrease	≥2.0 - <LLN	<2.0 - ≥1.75	<1.75 - ≥1.5	<1.5
Creatinine	Increase	>ULN - ≤1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Glucose (mmol/L)	Decrease	<LLN - 3.0	<3.0 - 2.2	<2.2 - 1.7	<1.7
Potassium (mmol/L)	Increase	>ULN - ≤5.5	>5.5 - 6.0	>6.0 - 7.0	>7.0
Potassium (mmol/L)	Decrease		<LLN - 3.0	<3.0 - 2.5	<2.5
Sodium (mmol/L)	Increase	>ULN - 150	>150 - 155	>155 - 160	>160
Sodium (mmol/L)	Decrease	<LLN - 130		Sodium <130-120	<120

Note: NCI-CTCAE toxicity grades are based on the laboratory result and do not take into account the clinical component, if applicable

Increases in liver function tests will use the ULN thresholds as follows:

Analyte	**ULN Threshold**
ALT/AST	> 1 x to < 3 x ULN ≥ 3 x to < 5 x ULN ≥ 5 x ULN to < 8 x ULN ≥ 8 x ULN
Total Bilirubin	> 1 to < 2 x ULN ≥ 2 x ULN
Alk Phos	> 1 to < 2 x ULN ≥ 2 to < 4 x ULN ≥ 4 x ULN

7. REFERENCES

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