Statistical Analysis Plan

NCT Number: NCT03279081

Title: A phase 3, randomized, double blind, parallel group, placebo controlled, international, multicenter study to assess efficacy and safety of Cx601, adult allogeneic expanded adipose-derived stem cells (eASC), for the treatment of complex perianal fistula(s) in patients with Crohn's disease over a period of 24 weeks and a follow-up period up to 52 weeks. ADMIRE-CD II study.

Study Number: Cx601-0303

Document Version and Date: Version 6.0, 21-July-2023

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Cx601-0303

A phase 3, randomized, double blind, parallel group, placebo controlled, international, multicenter study to assess efficacy and safety of Cx601, adult allogeneic expanded adipose-derived stem cells (eASC), for the treatment of complex perianal fistula(s) in patients with Crohn's disease over a period of 24 weeks and a follow-up period up to 52 weeks. ADMIRE-CD II study.

PHASE 3

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Version**: Version 6**

Date**:** 21 July 2023

Prepared by:

[redacted], Statistical and Quantitative Sciences, Takeda

Based on:

Protocol Version: Amendment 3

Protocol Date: 28 October 2019

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Version 1.0	12MAR2017	Not Applicable
Version 2.0	20DEC2018	To implement protocol amendment 1
Version 3.0	02SEP2019	To implement protocol amendment 3
Version 4.0	24MAY2022	To improve clarity and completeness and make updates as detailed in section 7.14 and 7.15.
Version 5.0	12JAN2023	To change the timing of Week 24 primary efficacy analysis from Week 24 to end of study
Version 6.0	21JUL2023	To include safety analysis at Week 24 based on the regulatory request, as well as adding multiplicity control for Week 52 efficacy endpoints.

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Approval Signatures

Electronic signature can be found on the last page of this document.

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Approvals:

[redacted], PhD
[redacted], Statistics and Quantitative Sciences

Date

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1.1 Approval Signatures

Approval Signatures:

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2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
anti-TNF	anti-tumor necrosis factor
AR [1]	first order Autoregressive
ASC	Adipose-derived mesenchymal stem cells
AST	Aspartate aminotransferase
CDAI	Crohn's Disease Activity Index
CM	Concomitant medication
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRO	Clinical research organization
CRP	C-reactive protein
CS	Homogenous Compound Symmetry
DSA	Donor-specific antibodies
eASC	expanded adipose-derived mesenchymal stem cells
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
EMA	European Medicine Agency
ePRO	electronic Patient Reported Outcomes
EQ-5D	European Quality of Life-5 Dimensions
ET	Early termination
EUA	Examination under anesthesia
FDA	Food & Drug Administration
HLA	Human leukocyte antigens
HRU	Health Resources Utilization
IA	Interim Analysis
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
IS	Immunosuppressant
ITT	Intention-to-treat
IWRS	Interactive web response system
LMWH	Low-molecular weight heparin
LSmeans	Least-Squared means
mAbs	Monoclonal antibodies
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCS	SF-36 Mental Component Summary

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MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intention to treat
MMRM	Mixed-effect Model for Repeated Measures
MRI	Magnetic resonance imaging
PCS	SF-36 Physical Component Summary
PDAI	Perianal Disease Activity Index
PP	Per protocol
PRO-2	Patient-reported outcomes measure derived from CDAI
R&T	Randomized and Treated
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SES-CD	Simple Endoscopic Score for CD
SF-36	36-Item Short Form Health Survey
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TF	treatment failure
ULN	upper limit of normality
UN	Unstructured Covariance structure
VAS	Visual analogue scale
WHODrug	World Health Organization Drug dictionary
WOCBP	Woman of child-bearing potential
WPAI	Work Productivity and Activity Impairment Questionnaire

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4.0 OBJECTIVES

4.1 Primary Objectives

To evaluate the combined remission of complex perianal fistula(s), defined as the clinical assessment at Week 24 of closure of all treated external openings that were draining at baseline despite gentle finger compression, and absence of collections >2 cm (in at least 2 dimensions) confirmed by blinded central magnetic resonance imaging (MRI) assessment at Week 24.

4.2 Secondary Objectives

- To evaluate the efficacy of Cx601 as compared to placebo in clinical remission at Week 24 and in time to clinical remission (weeks).
- To evaluate the efficacy and safety of Cx601 as compared to placebo in other clinical and time-to-event related endpoints at Weeks 24 and 52.

4.3 Exploratory Objectives

- To evaluate the efficacy of Cx601 as compared to placebo as measured by exploratory endpoints related to patient-reported outcomes, radiological measurements (MRI), cytokine, immune and inflammation-associated markers.
- To characterize microbiome diversity.
- To characterize the immunogenicity of Cx601 (donor-specific antibodies [DSA]) and the impact of immunogenicity on safety and clinical response.

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4.4 Study Design

This is a Phase 3, randomized, double blind, parallel group, placebo controlled, global and multicenter study to assess the efficacy and safety at 24 weeks and with a follow-up period up to 52 weeks after the administration of a new therapy with expanded adipose-derived mesenchymal stem cells (eASCs) (Cx601) for the treatment of complex perianal fistulas in subjects with Crohn's disease (CD).

The outcome of this trial is determined by the results from the primary efficacy analyses at Week 24. In order to evaluate the long term efficacy and safety of Cx601 compared to placebo, the study will continue in a blinded fashion up to Week 52.

The study will follow an add-on design where subjects receiving any ongoing concomitant medical treatment for CD at stable doses at the time of Screening visit will be allowed to continue throughout the study.

A total of 554 subjects are planned to be randomised in a 1:1 ratio to receive either a local injection of Cx601 (120 million cells) or matching placebo.

The study population will consist of subjects whose perianal fistulas were previously treated and have shown an inadequate response, a loss of response, intolerance to immunosuppressant (IS) or monoclonal antibodies (mAbs). In addition, complex perianal fistula(s) must be draining at the

screening period despite previous standard medical treatment, with up to 2 internal openings and a maximum of 3 external openings based on clinical assessment. A central reading of a locally performed contrast enhanced (gadolinium) pelvic MRI will be performed to confirm location of the fistula and potential associated perianal abscess(es).

Subject eligibility criteria with full inclusion/exclusion criteria are listed in the study protocol.

4.4.1 Study Treatment

The ultimate therapeutic goal in perianal CD is a complete and sustained closure of the fistulas without development of abscesses and thereby avoiding the need for surgical interventions and improving the patients' quality of life (Taxonera, 2009). In a high number of patients, complete closure cannot be achieved despite medical treatment (including infliximab) and surgery in accordance with clinical practice.

Cell therapy based on stem cell technologies is rapidly being introduced in a variety of areas of medicine, particularly since the introduction of adult stem cells (De Ugarte, 2003), avoiding ethical concerns, relative to embryonic stem cells. As adult adipose stem cells may be obtained in a technically simple way from subdermal adipose tissue, these cells represent adequate candidates for the treatment of autoimmune and inflammatory pathologies. Human lipoaspirates include a population of stem cells of mesenchymal origin with multilineage capacity: adipose derived mesenchymal stem cells (ASC). ASC obtained from human adipose tissue constitute an easily accessible and abundant source of stem cells for several applications as cell based medicinal products.

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Cell therapy can be a simple, minimally invasive outpatient alternative that, based on the available nonclinical and clinical data, would have significant benefits over current clinical management of patients with CD with previously treated complex perianal fistula(s).

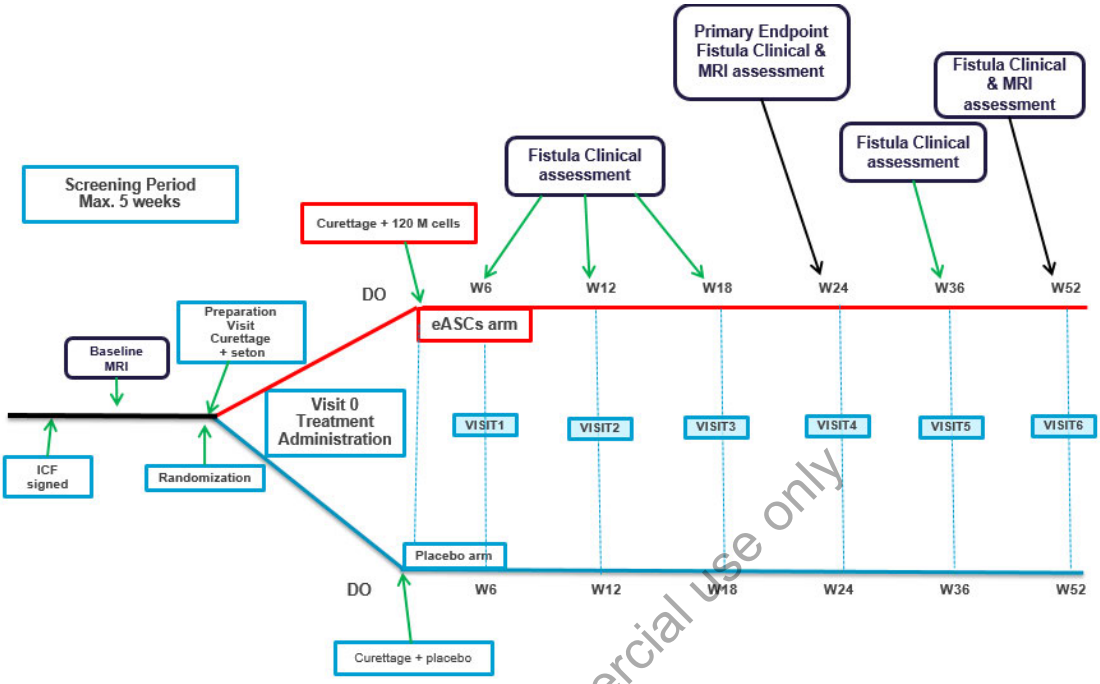
The proposal for a single dose of 120 million cells is based on previous nonclinical and clinical data, published literature, and the feedback received for the previously developed autologous version of Cx601 (Cx401) during the Food & Drug Administration (FDA) meetings (2006, 2008) and the European Medicine Agency (EMA) Scientific Advice (2011).

Main efficacy findings at Week 24 in the phase 1/2 study Cx601-0101 and the phase 3 study Cx601-0302 support the single dose of 120 million cells as outlined in this phase 3 study.

4.4.2 Study Schedule

The planned visit schema is presented below (Figure 4.a). Please refer to the protocol for detailed information pertaining to the schedule of assessments and procedures at each visit.

Figure 4.a Planned Visit Schema



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4.4.3 Withdrawn Subjects

Information pertaining to withdrawal of subjects is detailed in the protocol, including information pertaining to discontinuation of individual subjects, and to discontinuation of the entire study.

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason. Subjects who withdraw their consent are considered withdrawn from the study. The investigator has the right to terminate participation of any subject at any time if it is deemed in the subject's best interest. The reason and circumstances for premature discontinuation will be documented in the subject's case report form (CRF).

Reasons of withdrawal include, but are not limited, to the following:

- Subject's decision; withdrawal of subject consent to participate in the study;
- Physician's decision based on subject's well-being;
- Participation in a new, interventional, clinical trial for CD and/or for perianal disease;
- Death.

For any consenting subject discontinuing the study, the investigator should plan to:

- Ask subject to take part, as far as possible, in the last medical visit in order to examine the subject's health conditions and perform the required blood sampling for the clinical

blood tests, the serum pregnancy test (if it is required), the physical examination including the fistula clinical assessment, the pelvic MRI, the Perianal Disease Activity Index (PDAI) /Patient Reported Outcome 2 (PRO-2) scores, AE assessment and concomitant medication recording.

- Complete the eCRF, indicating in the Study Completion Visit, the date of termination and the unique reason for discontinuing the study, with all data not corresponding to a formal visit filled in the Early Termination visit.
- In consenting subjects who do not come back for the scheduled study visits, documented efforts should be performed to convince them to continue attending study visits and, if unsuccessful, at least the exact reason(s) should be obtained for their discontinuation and any adverse event (AE) associated with it and its date of occurrence (at least month and year) should be recorded.

Randomized subjects who withdraw their consent or discontinued the study should undergo the Early Termination visit (unless some specific, ie, MRI, assessments were conducted within 2 weeks prior to withdrawal and if subject agrees). These data will be registered in the CRF in the Early Termination section and the Study Completion Visit.

No randomized subjects will be replaced, regardless of reason.

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4.4.4 Randomization and Stratification

Treatments will be allocated by central randomization through interactive web randomization system (IWRS) and subjects will be stratified based on the combinations of the concomitant treatment (3 possible levels as defined below) and number of external openings (2 possible levels as defined below)

1. Concomitant treatment:
   - Current use of concomitant IS or mAbs (ie, anti-tumor necrosis factor (anti-TNF) or anti-integrin (ie, vedolizumab) or anti-interleukin (IL)12/23 (ie, ustekinumab) as single agent
   - Current use of concomitant IS or mAbs (ie, anti-TNF or anti-integrin (ie, vedolizumab) or anti-interleukin (IL)12/23 (ie, ustekinumab)) as combination treatment,
   - No ongoing concomitant IS or mAbs treatment at time of randomization.
2. External opening(s):
   - 1 versus >1

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoint of this study is the proportion of subjects who achieve combined remission at Week 24 after investigational medicinal product (IMP) administration where combined remission is defined as:

(a) The closure of all treated external openings that were draining at baseline despite gentle finger compression; and

(b) absence of collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by blinded central MRI assessment.

5.2 Secondary Endpoints

Key Secondary Efficacy Endpoints

- Proportion of subjects who achieve clinical remission at Week 24 after IMP administration where clinical remission is defined as the closure of all treated external openings that were draining at baseline despite gentle finger compression.
- Time to clinical remission (weeks), assessed at Week 24, defined as the time from treatment start to first visit with closure of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed. Subjects who do not achieve clinical remission by Week 24 will be censored at that visit.

Other Secondary Efficacy Endpoints

- Proportion of subjects who achieve clinical response at Week 24 after IMP administration where clinical response is defined as closure of at least 50% of all treated external openings that were draining at baseline, despite gentle finger compression.
- Time to clinical response (weeks), assessed at Week 24, defined as the time from treatment start to first visit with closure of at least 50% of all treated external openings that were draining at baseline, despite gentle finger compression, as clinically assessed. Subjects who do not achieve clinical response by Week 24 will be censored at that visit.
- Proportion of subjects who achieve combined remission at Week 52 after IMP administration where combined remission is defined as:
    a) The closure of all treated external openings that were draining at baseline, despite gentle finger compression;

       and

    b) absence of collection(s) >2cm (in at least 2 dimensions) confirmed by a blinded central MRI assessment.
- Proportion of subjects who achieve clinical remission at Week 52 after IMP administration where clinical remission is defined as closure of all treated external openings that were draining at baseline, despite gentle finger compression.
- Proportion of subjects who achieve clinical response at Week 52 after IMP administration where clinical response defined as closure of at least 50% of all treated external openings that were draining at baseline, despite gentle finger compression.
- Time to clinical remission (weeks), assessed at Week 52, defined as the time from treatment start to first visit with closure of all treated external openings that were draining at baseline,

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despite gentle finger compression, as clinically assessed. Subjects who do not achieve clinical remission by Week 52 will be censored at that visit.

- Time to clinical response (weeks), assessed at Week 52, defined as the time from treatment start to first visit with closure of at least 50% of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed. Subjects who do not achieve clinical response by Week 52 will be censored at that visit.
- Proportion of subjects with a relapse from Week 24 combined remission, where a relapse is defined as:

    a) Reopening of any of the treated external openings with active drainage as clinically assessed in subjects who were in combined remission;

    or

    b) development of a perianal fluid collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by blinded central MRI assessment.

5.3 Exploratory Endpoints

- Change from baseline in total PDAI score at Weeks 6, 12, 18, 24, 36, and 52.
- Change from baseline in PRO-2 score (defined as average daily stool frequency and average daily abdominal pain) at Weeks 6, 12, 18, 24, 36, and 52.
- Change from baseline in blinded central MRI Van Assche score at Weeks 24 and 52.
- Change from baseline in blinded central MRI modified Van Assche score at Weeks 24 and 52.
- Change from baseline in the Magnetic Resonance Novel Index for Fistula Imaging for Crohn's Disease (MAGNIFI-CD) score at Weeks 24 and 52.
- Change from baseline at Weeks 24 and 52 in blinded central MRI analysis of hyperenhancement in T1 sequence, and hyperintensity in T2 sequence.
- Change from baseline in electronic Patient Reported Outcomes (ePRO) listed below at Weeks 12, 24 and 52:
    - Visual Analogue Scale (VAS) from 0 to 10 for perianal pain while standing, sitting, and defecating along last 2 weeks prior to the visit
    - CDAI items scores
    - Number of pads used per day during last 2 weeks prior to each visit
    - Work Productivity and Activity Impairment Questionnaire (WPAI)
    - EQ-5D
    - SF-36

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  - Health Resources Utilization (HRU)

- Immunogenicity responses as measured by DSA generation post-treatment and correlation with safety and efficacy
- Change from baseline in cytokines, immune and other inflammation associated markers at Weeks 6, 12, 24 and 52
- Change from baseline in the microbiome diversity at Week 6

5.4 Safety Endpoints

- Vital signs
- Laboratory parameters
- Incidence of treatment-emergent AEs (TEAEs)
- Incidence of treatment-emergent SAEs (TESAEs)
- Incidence of Adverse Events of Special Interest (AESIs)

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6.0 DETERMINATION OF SAMPLE SIZE

The primary endpoint of the study is the proportion of subjects with combined remission at Week 24. The following assumptions are made in the sample size calculations:

- True combined remission rates at Week 24 of 42.2% and 30% in the Cx601 and placebo groups, respectively (based on estimates from a similar population in the Phase 3 ADMIRE-CD study)
- The family-wise Type-1 error rate will be controlled at 0.05 for the primary and key secondary efficacy endpoints at Week 24.

Based on the above assumptions, a total sample-size of 554 subjects (277 per treatment arm) will provide at least 85% power for the primary efficacy analysis at Week 24.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Baseline values are defined as the last observed value before the administration of study treatment.

All statistical analyses will be performed using SAS® Version 9.1.3 or higher.

Statistical significance for each analysis performed for each endpoint involves conducting a 2-sided hypothesis test at a significance level of 5%. P-values, if applicable, will be presented to 3 decimal places. If the rounded result is a value of 1.000, it will be displayed as >0.999. P-values smaller than 0.001 will be presented as < 0.001.

Quantitative variables will be described showing the number of available and missing observations, as well as the mean, standard deviation, minimum, the first quartile, median, the third quartile and maximum. Frequencies and percentages will be used to describe qualitative variables and will be tabulated by treatment group.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. The minimum and maximum values will be displayed to the same number of decimal places as the raw data. Confidence intervals will be presented using the same number of decimal places as the point estimate. Percentage is presented in brackets and to 1 decimal place. The maximum number of decimal places reported shall be four for any summary statistic. Wherever possible data will be decimal aligned. Body mass index (BMI) should be rounded to 1 decimal place for reporting. Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting. Averaged laboratory and vital sign results eg, diastolic/systolic blood pressure and pulse should be rounded to 1 decimal place for reporting.

Where appropriate, variables will be analyzed and summarized descriptively by study visits, by treatment arms, and overall.

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7.1.1 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their dose of the investigational product. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.2 Definition of Study Visit Windows

Study days will be used to assign the measurements to the study visit:

- For MRI:
  - Week 24 (Target Day: 169): 1 < study day ≤ 266;
  - Week 52 (Target Day: 365): 267 ≤ study day ≤ maximum study days for MRI.
- For clinical assessments, vital signs, PRO-2, and PDAI:
  - Week 6 (Target Day: 43): 1 < study day ≤63;
  - Week 12 (Target Day: 85): 64 ≤ study day ≤105;
  - Week 18 (Target Day: 127): 106 ≤ study day ≤147;
  - Week 24 (Target Day: 169): 148 ≤ study day ≤210;
  - Week 36 (Target Day: 253): 211 ≤ study day ≤308;
  - Week 52 (Target Day: 365): 309 ≤ study day ≤maximum study days.
- For laboratory and ePRO assessments:

- Week 12 (Target Day: 85): 1 < study day ≤126;
- Week 24 (Target Day: 169): 127 ≤ study day ≤266;
- Week 52 (Target Day: 365): 267 ≤ study day ≤maximum study days.

If a subject has more than one non-missing measurement in the same visit window, the measurement closest to the target day will be used. If two non-missing measurements in the same window are of equal distance to the target day, the measurement that occurs later will be used.

7.1.3 Conventions for Missing Dates

The conventions for missing dates (AE, concomitant medication [CM]) are as follows:

For AE/CM start date:

- If completely missing, then start date is imputed with stop date. (ie if stop date ≥ IMP date then the AE will be considered treatment-emergent/CM will be considered as concomitant, if stop date < IMP date it will be considered prior). If AE/CM stop date is also missing, impute the maximum of IMP date or randomization date or informed consent signature date.
- If year and month are present and day is missing then day is imputed as the 1st of the month, except where the IMP treatment start date month is the same as the AE/CM start date month, then AE/CM start date is imputed as IMP treatment start date.
- If year is present and day and month missing, or year and day are present, and month is missing, impute as 1st January, except where IMP treatment start date year equals AE/CM start date year, then AE/CM start date is imputed as IMP treatment start date.

For AE/CM stop date:

- If "ongoing" is checked on CM, no imputation is necessary, CM is considered concomitant.
- If completely missing, then impute maximum of IMP start date or CM start date. If CM start date is also missing, impute the maximum of IMP date or randomization date or informed consent signature date.
- If year and month are present and day is missing, it can be imputed as the last day of the month.
- If year is present and day and month missing,
- If YYYY ≤ the maximum of year of IMP treatment date or year of randomization date, then 31st of December will be imputed.
- If YYYY > the maximum of year of IMP treatment date or year of randomization date, then 1st of January will be imputed.

For AEs, if the start and end dates are both missing, the AE will be considered treatment emergent. For CM, if the start and end dates are both missing, the CM will be considered concomitant.

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If a subject dies during the study and the AE/CM stop date is missing, then the death date will be used for AE/CM stop date. After the imputation, all the imputed stop dates are compared with the start dates to ensure the stop date does not occur before the start date. If the imputed stop date occurs prior to the start date, then the imputed stop date will be the same as the start date.

If the day of the date of diagnosis or the start date for complex perianal fistula(s) is missing, it will be imputed to be 1st of the month; if the month of the date is missing, it will be imputed to be January. If the date is completely missing, it will not be imputed.

Listings should not present imputed date, listing should present partial dates or "." if data entirely missing.

7.2 Analysis Sets

7.2.1 Intention To Treat (ITT) Analysis Set

The Intention to Treat (ITT) Analysis Set: Includes all randomized subjects regardless of being treated or not, regardless of having any post-baseline efficacy measurements or not, presented according to their randomized treatment. This population will be used as the primary analysis set for all endpoints except for the safety endpoints or if specified otherwise.

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7.2.2 Modified Intention To Treat (mITT) Analysis Set

The modified Intention to Treat (mITT) Analysis Set: Includes all randomized subjects who have received the study treatment, presented according to the randomized treatment and for whom at least one post-baseline efficacy value (fistula clinical assessment) is present, independently of the degree of adherence to the protocol.

7.2.3 Per-Protocol Analysis Set

The Per Protocol (PP) Analysis Set: Includes all randomized and treated subjects, presented according to the actual treatment they received and who adhered to the protocol with no major deviations which might impact the assessment of the primary endpoint, and for whom at least one post-baseline efficacy value (fistula clinical assessment) is present.

Before the database lock, protocol deviations will be evaluated and classified as major or minor protocol deviations. The major protocol deviations that lead to exclusion from the per protocol set include:

- Not meeting the entry criteria for complex perianal fistula
- Use of any prohibited concomitant medication
- Received wrong treatment or incorrect dose

The classification of protocol deviations is described in the Protocol Deviation Specification document and each deviation is reviewed by the team prior to unblinding and a category will be assigned in accordance with the specification document.

7.2.4 Safety Analysis Set

The Safety Analysis Set: Includes all randomized subjects who have received the study treatment according to the actual treatment received. All safety analyses will be based on Safety Analysis Set.

7.2.5 All Screened Analysis Set

The All Screened Analysis Set: Includes all subjects who were screened for entry to the study, irrespective of screening outcome.

7.2.6 Randomized and Treated (R&T) Analysis Set

The Randomized and Treated Analysis Set: Include all subjects who were randomized and received the study treatment, presented according to the randomized treatment.

The analysis set will not be presented if it is the same as mITT.

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7.3 Disposition of Subjects

A summary of screen failures will be presented by region and country for the All Screened Patients set.

The number of subjects included in each analysis set will be summarized by treatment group and overall.

The number of subjects randomized and not treated, the number of subjects who received study treatment, who completed or prematurely withdrew from the study, and the reasons for any premature withdrawal, will be presented by treatment group, overall and split by country/region. Summaries of disposition will be performed on the ITT.

Time on the study will be presented by treatment group for Safety Analysis Set. Major protocol deviations will be listed and summarized on the ITT, including protocol deviations leading to exclusion from the per-protocol population. Major protocol deviations leading to the exclusion from the per-protocol population will be summarized at Week 24 only.

Enrollment will be summarized by region, country and site in All Screened analysis set.

7.4 Demographic and Other Baseline Characteristics

Baseline demographic and clinical characteristics including baseline age, race, gender, ethnicity, baseline height, baseline weight, baseline body mass index (BMI), smoking status, colonoscopy status at baseline, concomitant treatment and external openings based on CRF will be summarized by treatment group and overall. These will be presented on the ITT, mITT, Safety, PP, and R&T analysis sets.

Colonoscopy information at screening will be summarized by treatment group and overall on the ITT.

Stratification factors (as recorded in IWRS) will be summarized by treatment group and overall on the ITT.

Crohn's Disease history will be summarized overall and by region, for both treatment groups and overall, which will include time since CD diagnosis, previous surgery related to CD, number of CD-related surgeries, the location of the surgery related to CD, time from CD surgery to screening and type of surgery. Perianal Disease (PD) history will be summarized overall and by region, for both treatment groups and overall. This will include previous surgery related to PD, number of PD related surgeries, location of surgery related to PD, time from PD surgery to screening, type of surgery, and whether the surgery is related to ongoing PD at screening. These two measures will be assessed on the ITT.

Baseline anti-HLA and anti-DSA antibody status will be summarized by treatment group and overall on the ITT.

Baseline ePRO endpoints will be summarized by treatment group and overall on the ITT.

Baseline fistula status based on MRI report at screening/baseline will be provided by treatment group and overall. The description will include location and abscess. Distribution of topography of internal openings and external openings from the fistula preparation CRF will be summarized by treatment arm and overall on the ITT.

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7.5 Medical History and Concurrent Medical Conditions

All baseline conditions should be recorded as part of medical history. If a condition is present at the time of signing the informed consent, it will only be considered an AE if it worsens after this time-point. The coding dictionary to be used is Medical Dictionary for Regulatory Activities (MedDRA).

Prior and ongoing medical history will be summarized by system organ class and preferred term and by treatment group and overall, using Safety Analysis Set. Prior medical history includes all medical conditions with a stop date prior to Visit 0. A concurrent medical condition is a condition which occurs on or after the date of treatment administration (Visit 0), including those started before but are ongoing on the day of Visit 0.

7.6 Prior Medications and Concomitant Medications

The prior medications and concomitant medications are defined as follows:

- Prior medication refers to the medication that the study subjects stopped taking prior to treatment administration visit.
- Concomitant medications are defined as medications taken on or after the date of treatment administration (Visit 0), including those started before but are ongoing on the day of treatment administration.
- Concomitant procedures are defined as procedures performed on or after the date of treatment administration.

Medications will be coded using the WHO DRUG dictionary. Prior, concomitant and rescue medications use will be summarized descriptively using frequency and percentage of subjects by treatment group, drug class and preferred drug name on the ITT. Concomitant medications will also be summarized by indication on the ITT separately. Tables will be sorted in ATC3 alphabetical order and by preferred name within ATC3 in decreasing frequency in Cx601 group.

Prior treatment for CD and fistulas will be summarized as frequency and percentages by treatment group and overall, on the ITT. The subset of prior treatment for CD and fistulas ongoing at screening will be summarized separately.

Concomitant procedures will be summarized by treatment group and overall, system organ class, and preferred term on the ITT, also by indication as well as by modality separately.

7.7 Study Drug Exposure and Compliance

This study contains a single dose administration of randomized study treatment on Study Day 1. The frequency and proportion for subjects treated in each treatment group will be summarized.

7.8 Efficacy Analysis

The analyses of the primary and key secondary endpoints will be performed on ITT, mITT, PP, and R&T, with the ITT as the primary analysis set.

The analyses of the secondary endpoints other than key secondary endpoints, and the exploratory endpoints will be performed on ITT, unless otherwise specified. Analyses of clinical response at Week 24 and Week 52 will be performed on both ITT and mITT. Analyses of combined remission, clinical remission, and time to clinical remission at Week 52, will also be performed on both ITT and mITT.

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7.8.1 Derivation of Endpoints

This section describes the endpoint derivation for the primary analysis.

The efficacy endpoints is defined in section 5.1 and 5.2. For binary endpoints, in order to be classified as a responder, subjects must meet the clinical assessment and MRI criteria as defined in section 5.1.

If a subject received rescue medication or rescue procedure before the clinical assessment date or MRI date, the subject is considered as non-responder (section 7.8.7). Subjects who don't have either the clinical assessment or MRI will be classified as a non-responder (section 7.8.8).

Details of the algorithm will be included in the analysis data specifications.

7.8.2 Multiplicity adjustment for Primary, Key Secondary endpoints and other week 52 secondary endpoints

For multiplicity adjustment of the tested endpoints, the key secondary endpoints and two week 52 secondary endpoints are grouped into the first and second secondary endpoint families SF1 or SF2, respectively, with two null hypotheses in each family. The family-wise Type-1 error rate

will be controlled at 0.05 for the analyses of the primary, key secondary efficacy endpoints at Week 24 and two other secondary endpoints at Week 52 (combined remission at Week 52 and clinical remission at Week 52).

The primary endpoint will be tested first. Once null hypothesis for the primary endpoint is rejected, key secondary endpoints and two week 52 endpoints will be tested via a modified Hochberg based gate-keeping approach, as detailed in the flowchart below.

STEP 1: Conduct the primary efficacy analysis for the primary endpoint (proportion of subjects with combined remission at Week 24). If the 2-tailed p-value is not significant at 5% significance level (p-value > 0.05) then STOP. Otherwise, proceed to STEP 2 where the Hochberg procedure will be used in the testing of the two key secondary endpoints.

STEP 2: The p-values of the two key secondary endpoints will be ordered from largest to smallest. If the largest p-value is less than or equal to 0.05, then both p-values will be declared significant and testing ceases, otherwise the Hochberg procedure testing continues. If the largest p-value is greater than 0.05, then the smallest p-value will be assessed at 0.025. If this p-value is less than or equal to 0.025, then this p-value will be declared significant.

STEP 3: If p-values of both key secondary endpoints are significant in STEP 2, the two other secondary endpoints at Week 52 will be tested in the same fashion as in STEP 2.

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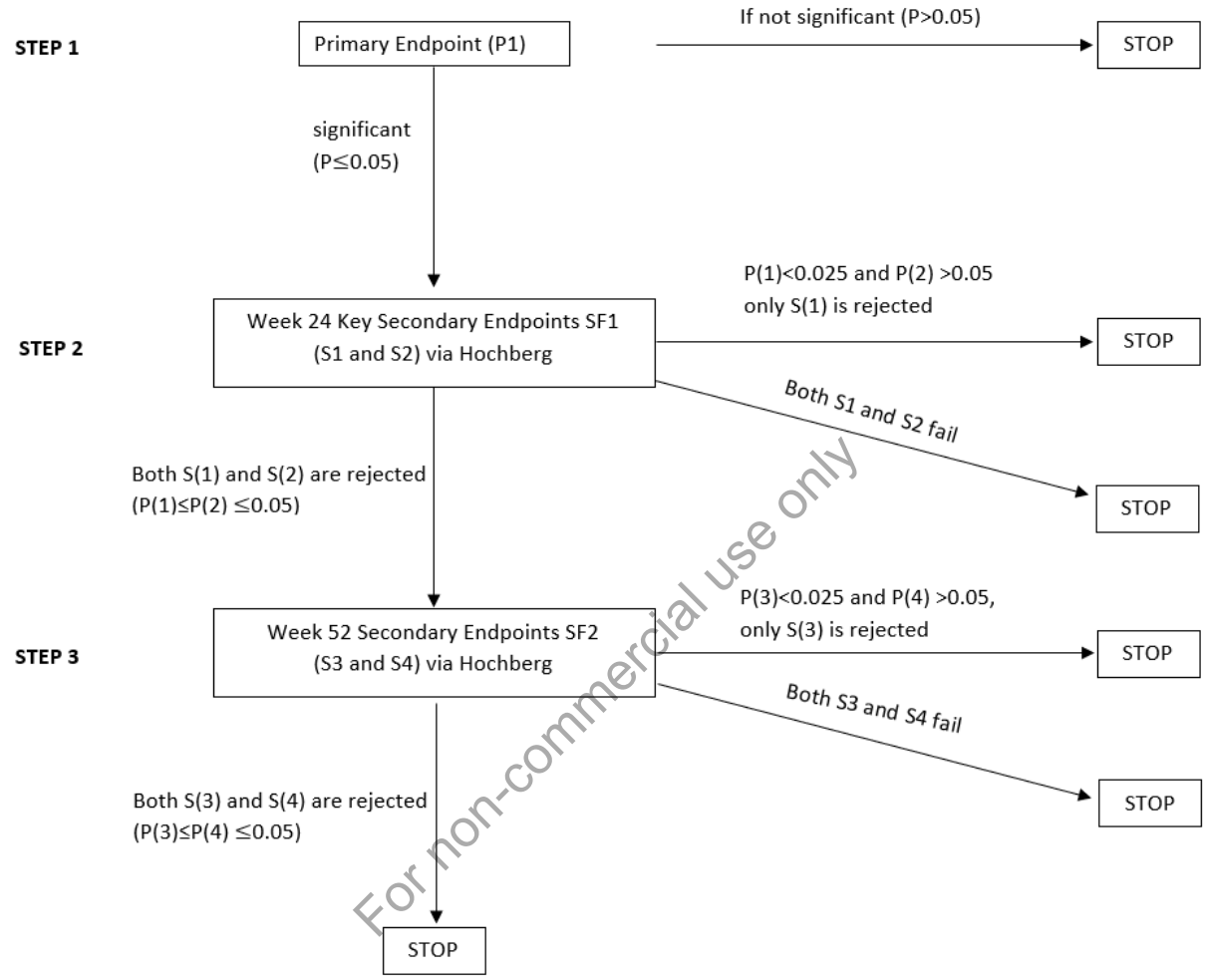
Figure 7.a Multiplicity Test Steps



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Where S1 and S2 are the key secondary endpoints, P(1) and P(2) are the p-values of S1 and S2 ordered as P(1) < P(2). Similarly, S3 and S4 are the two Week 52 secondary endpoints, P(3) and P(4) are the p-values of S3 and S4 ordered as P(3) < P(4).

7.8.3 Primary Efficacy Analysis

The primary efficacy analysis for the primary endpoint of combined remission at Week 24 will test the following statistical hypothesis:

- H_0: $P_{trt} = P_{pbo}$
- H_a: $P_{trt} \neq P_{pbo}$

  where P_{trt} is the combined remission rate at Week 24 for subjects randomized to Cx601 and P_{pbo} is the combined remission rate for subjects randomized to placebo.

The primary efficacy analysis uses a stratified Cochran-Mantel-Haenszel (CMH) method for comparing proportions, adjusting for the IWRS randomization stratification factors.

The above stated hypothesis test will be conducted using an alpha level of 0.05 for the final analysis. Descriptive statistics will be presented by treatment group. Count, percentage and associated 95% CI using the normal approximation will be provided for each treatment group. The p-value and point estimate of treatment difference based on the CMH method adjusted for stratification factors along with 95% confidence interval will be presented. In addition, relative risk will be provided along with the 95% two-sided confidence interval estimate. If the number of remitters or non-remitters in either of treatment arm is too small (ie, ≤5), the exact method (ie, Fisher's Exact test and exact unconditional confidence limits) will be performed instead.

The study is considered positive if the above described primary efficacy analysis yields a 2-tailed p-value that is ≤ 0.05 (combined remission rate of Cx601 is greater than placebo).

The primary efficacy analysis will use non-responder imputation (NRI) for handling of missing data. Details of handling of missing data are provided in Section 7.8.8.

Table 7.a summarizes the primary, sensitivity, and supplemental analyses for the primary and key secondary efficacy endpoints. All analyses listed in Table 7.a, subjects will be treated as "non-response" from the next day that they have rescue medication or rescue surgery.

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Table 7.a Primary, Sensitivity, and Supplemental Analyses for the Primary and Key Secondary Endpoints

Type of Analysis	Analysis Set	Description of Missing Data Handling Method
Primary analysis	ITT	Missing values are imputed as "non-response"
Supplemental analysis	mITT	Missing values are imputed as "non-response"
Supplemental analysis	PP	Missing values are imputed as "non-response"
Supplemental analysis	R&T	Missing values are imputed as "non-response"
Sensitivity analysis	ITT	Missing values will be imputed with multiple imputation[1] Rescue medication or rescue surgery treated as "non-response" after multiple imputation

[1] If percentage of missing values at Week 24 is above 10% overall, then multiple imputation analysis will be performed.

The treatment difference in the proportion of subjects achieving combined remission and corresponding 95% confidence interval will be presented graphically together for all the analyses presented in Table 7.a.

Week 24 primary analysis was planned when all subjects had completed Week 24 visit in order to support a potential initial BLA submission based on data through Week 24. However, in response to the FDA's feedback to the Type B meeting questions in July 2022 that an initial BLA should be submitted after Week 52 data are available, the sponsor has decided not to conduct the Week 24 primary efficacy analysis until the end of the study. The study will continue in a blinded fashion up to Week 52.

7.8.3.1 Subgroup Analyses

Subgroup analyses for the primary, key secondary endpoints will be performed for the following subgroups using the ITT:

- Gender (Male vs Female)
- Race (White vs Black or African American vs Asian vs American Indian or Alaska Native vs Native Hawaiian or Other Pacific Islander vs Not Applicable)
- Age group (<65 years vs ≥65 years)
- Donor
- Region 1 (Europe + Israel, North America)
- Region 2 (USA, Non-USA)
- Smoking status (Former smoker vs Current smoker vs never smoked)
- Colonoscopy status at baseline (Full colonoscopy performed at screening vs colonoscopy performed prior to screening)
- Concomitant treatment based on CRF (3 levels):
  - Concomitant immunosuppressant (IS) or monoclonal antibodies (mAbs) (ie, anti-tumor necrosis factor (anti-TNF) or anti-integrin (ie, vedolizumab) or anti-interleukin (IL)12/23 (ie, ustekinumab) as single agent
  - Concomitant IS or mAbs (ie, anti-TNF or anti-integrin (ie, vedolizumab) or anti-interleukin (IL)12/23 (ie, ustekinumab)) as combination treatment,
  - No ongoing concomitant IS or mAbs treatment at time of randomization
- External opening(s) based on CRF (1 vs > 1)
- Concomitant treatment based on CRF (4 levels):
  - Concomitant immunosuppressant (IS) as single agent
  - Monoclonal antibodies (mAbs) (ie, anti-tumor necrosis factor (anti-TNF) or anti-integrin (ie, vedolizumab) or anti-interleukin (IL)12/23 (ie, ustekinumab) as single agent
  - Concomitant IS or mAbs (ie, anti-TNF or anti-integrin (ie, vedolizumab) or anti-interleukin (IL)12/23 (ie, ustekinumab)) as combination treatment,
  - No ongoing concomitant IS or mAbs treatment at time of randomization
- By level of combination of the following IWRS stratification factor (at randomization):
  - Current concomitant immunosuppressant or biologics as single agent or as a combination or no ongoing concomitant treatment at Screening visit (3 levels)
  - External opening(s) (1 or >1) (2 levels)

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The point estimate of the treatment difference and corresponding 95% confidence interval of the primary, key secondary endpoints and two other secondary endpoints in the multiplicity adjustment will be presented graphically by subgroup using a forest plot.

7.8.4 Secondary Efficacy Analysis

7.8.4.1 Key Secondary Efficacy Analysis

The two key secondary endpoints (Clinical Remission at Week 24, Time to clinical remission) will be tested with adjustment for multiplicity as described in Section 7.8.2.

Clinical Remission at Week 24

The following statistical hypothesis will be tested:

- H_0: $P_{trt} = P_{pbo}$
- H_a: $P_{trt} \neq P_{pbo}$

where P_{trt} is the clinical remission rate at Week 24 for subjects randomized to Cx601 and P_{pbo} is the clinical remission rate for subjects randomized to placebo.

The key secondary endpoint of proportion of subjects with clinical remission at Week 24 will be analyzed using the same methodology that was outlined above for the primary efficacy endpoint, including the handling of missing data and treatment failures.

The p-value and point estimate of treatment difference (Cx601vs placebo) based on the CMH method, adjusted for stratification factors, along with 95% confidence interval will be presented.

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Time to Clinical Remission (weeks)

The following hypothesis will be tested:

- H_0: $s_{trt}(t) = s_{pbo}(t)$, for all $t <= 24$
- H_a: $s_{trt}(t) \neq s_{pbo}(t)$, for all $t <= 24$

Where $s_{trt}(t)$ is the probability of clinical remission at time t in the treatment (Cx601) arm and $s_{pbo}(t)$ is the probability of clinical remission at time t in the placebo arm.

The key secondary endpoint of time to clinical remission will be analyzed using the stratified log-rank test for comparing Cx601 and placebo, adjusting for the randomization stratification factors. The p-value obtained from the stratified log-rank test will be used to assess statistical significance of clinical remission.

The Cox proportional hazards model will be used to obtain estimates of the hazard ratio and the associated CIs. Kaplan-Meier curves will be presented along with median survival times.

Subjects who do not achieve clinical remission by Week 24 will be censored at Week 24 visit. Also, subjects who discontinue without clinical remission before Week 24 will be censored at the date of last visit.

7.8.4.2 Secondary Efficacy Endpoints in the Multiplicity adjustment

The two week 52 secondary endpoints (Combined Remission at Week 52 and Clinical Remission at Week 52) will be tested with adjustment for multiplicity as described in Section 7.8.2.

Combined Remission at Week 52

The following statistical hypothesis will be tested:

- H_0: $P_{trt} = P_{pbo}$
- H_a: $P_{trt} \neq P_{pbo}$

where P_{trt} is the combined remission rate at Week 52 for subjects randomized to Cx601 and P_{pbo} is the combined remission rate for subjects randomized to placebo.

Clinical Remission at Week 52

The following statistical hypothesis will be tested:

- H_0: $P_{trt} = P_{pbo}$
- H_a: $P_{trt} \neq P_{pbo}$

where P_{trt} is the clinical remission rate at Week 52 for subjects randomized to Cx601 and P_{pbo} is the clinical remission rate for subjects randomized to placebo.

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The two secondary endpoints will be analyzed using the same methodology that was outlined above for the primary efficacy endpoint, including the handling of missing data and treatment failures.

The p-values and point estimates of treatment differences (Cx601vs placebo) based on the CMH method, adjusted for stratification factors, along with 95% confidence interval will be presented.

7.8.4.3 Other Secondary Efficacy Endpoints

All the other binary secondary endpoints will be analyzed using the same methodology described above for the primary efficacy endpoint, including the handling of missing data and treatment failures.

Time-to-event endpoints will be analyzed using the same methodology described above for the key secondary endpoint (time to clinical remission).

Proportion of subjects with a relapse at Week 52 from Week 24 combined remission response will be summarized using descriptive statistics and compared between the treatment groups using a stratified Cochran-Mantel-Haenszel (CMH) test, adjusting for the randomization strata. The denominator in the calculation of the percentages is the number of subjects with combined remission at Week 24. The numerator is the number of subjects with combined remission being no at Week 52.

Nominal p-values, point estimates and 95% CI's will be presented for other secondary endpoints. No multiplicity adjustments will be implemented for the other secondary efficacy endpoints.

7.8.5 Exploratory Efficacy Analysis

All continuous endpoints collected at multiple post-treatment visits will be analyzed using a Mixed-effect Model for Repeat Measures (MMRM) model with treatment, randomization strata, visit, and visit-by-treatment interaction as fixed factors. The baseline value will be used as a covariate.

An unstructured covariance structure will be used to model the within-subject errors. If the model fails to converge, the model will be fit using covariance matrices in the following order

- Heterogeneous first order autoregressive (ARH1)
- Homogenous first order autoregressive (AR1)
- Heterogenous Compound Symmetry (CSH)
- Compound Symmetry (CS)

Least square means (LS means) for change from baseline and 95% CI for each treatment group will be presented. Estimated treatment differences for Cx601 versus placebo and corresponding 95% CIs and p-values will be presented at each scheduled time point.

For all variables collected on a daily basis prior to a visit; the data will be averaged over the period of collection prior to the visit when performing the statistical analysis. Details for each endpoint will be included in the section below.

Endpoints which are averaged over the days collected (VAS, Number of Pads and Evening Diary) will use nominal windows as entered in the electronic data capture (EDC) rather than windows based on date of assessment.

For PDAI, PRO-2, ePRO measurements collected from the day after subjects starting rescue medication or rescue procedure will not be included in the analysis.

Perianal disease progression occurred on a treated fistula tract and not on a treated fistula tract will be summarized separately by treatment cumulatively for ITT.

New external openings will be summarized by treatment for ITT.

7.8.5.1 Severity of the perianal Crohn's disease with the Perianal Disease Activity Index (PDAI)

Severity of the perianal Crohn's disease assessed with the Perianal Disease Activity Index (PDAI) will be assessed at Screening, Visit 0 (Study Day 1, before treatment administration), Visit 1 (Week 6), Visit 2 (Week 12), Visit 3 (Week 18), Visit 4 (Week 24), Visit 5 (Week 36), Visit 6 (Week 52) or Early Termination Visit.

The PDAI is a scoring system to evaluate the severity of perianal Crohn's disease (Irvine, 1995). It includes five items: (a) discharge; (b) pain; (c) restriction of sexual activity; (d) type of perianal disease; and (e) degree of induration. Each category is graded on a 5-point Likert scale ranging from no symptoms (score of 0) to severe symptoms (score of 4); a higher score indicates a more severe disease. The total score is calculated as the total of all responses.

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Summary statistics of total PDAI scores and domains at each visit will be presented by treatment group. Change from baseline in total PDAI scores, discharge and pain at each visit will be summarized by treatment group. The difference between treatment groups and associated 95% CI at each visit will be derived based on the repeated mixed model and will be presented graphically. Note that domain scores different from 0, 1, 2, 3, 4 will be treated as missing values.

7.8.5.2 PRO-2

The PRO-2 score will also be assessed at Screening, Visit 0 (Study Day 1, before treatment administration), Visit 1 (Week 6), Visit 2 (Week 12), Visit 3 (Week 18), Visit 4 (Week 24), Visit 5 (Week 36), Visit 6 (Week 52) or Early Termination Visit.

The PRO-2 score is defined as average daily stool frequency and average daily abdominal pain. The PRO-2 score will be derived based on Appendix E. Only subjects with four or more days data in the seven days before the visit will be used. If individual domain scores are not available at baseline, the PRO-2 score calculated by the investigator will be used.

Change from baseline in PRO-2 score will be summarized by treatment group using descriptive statistics for each visit. The difference between treatment groups and associated 95% CI at each visit will be derived based on the repeated mixed model and will be presented graphically.

7.8.5.3 Patient's Reported Outcomes

The following types of analysis for the continuous patient-reported outcome (PRO) endpoints will be performed:

- Descriptive statistics for each subject score, and domain;
- MMRM presented by visit for change from baseline for each score and domain.

The following variables will be assessed at Study Day 1, Weeks 12, 24 and 52:

- Visual Analogue Scale (VAS) from 0 to 10 for perianal pain while standing, sitting, and defecating along last 2 weeks prior to the visit
- Crohn's Disease Activity Index (CDAI) items scores
- Number of pads used per day during last 2 weeks prior to each visit
- Work Productivity and Activity Impairment Questionnaire (WPAI)
- European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L)
- 36-item Short Form Health Survey (SF-36)
- Health Resources Utilization (HRU)

VAS score will be collected for each of three pain scales (perianal pain while standing, perianal pain while sitting, perianal pain while defecating) each day for two weeks prior to the visit; the average scores and change from baseline will be presented. If a subject has less than two weeks' worth of data, the average will be taken over the available data. If a subject has more than two

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weeks' worth of data, the average will be taken for the two weeks closest to the visit. Only subjects with four or more days data in each week will be used.

CDAI items include liquid stools, abdominal pain, general well-being, evening temperature and medicine for diarrhea. Fever (yes/no) is defined as over 37.8 ºC during seven days. Medicine for diarrhea is categorized as 'yes' if any medication was taken during seven days. For liquid stools, abdominal pain and general well-being, the average over seven days will be used, the same data handling method as VAS scores will be followed. For categorical variables fever and medicine for diarrhea, only descriptive statistics will be provided.

The number of pads per day will be collected for the last two weeks prior to visit, and an average per day will be calculated. The same data handling method as VAS scores will be followed.

The WPAI will be collected for the 6 questions, as shown in Appendix B. The sub-domains are to be calculated as follows:

- Percent activity impairment due to problem:
  - (Q6 / 10) x100

The following sub-domains are calculated if the answer to Q1 is 'Yes'.

- Percent work time missed due to problem:
  - [Q2/ (Q2+Q4)] x100
- Percent impairment while working due to problem:
  - (Q5/10) x100
- Percent overall work impairment due to problem:
  a. {(Q2 / (Q2+Q4)) + [(1-(Q2/ (Q2+Q4))) x (Q5/10)]} x100

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The EQ-5D-5L will collect answers on five domains at 5 levels (Anxiety/depression, mobility, pain/discomfort, health today and usual activities) and scores for each domain and the index score will be calculated as per the 2005 EQ-5D User Guide (Reenen & Janssen, 2015). The EQ-5D index scores will be summarized by visit and analyzed using an MMRM model. Shift table will be provided for each domain (from category 4/5 moving to 3 or lower) at each visit of evaluation.

The SF-36 scores will be summarized by visit for each of the 8 sub-domains and 2 component summary measures. Further information for calculating the SF-36 scores can be found in Appendix A. These domains are the Physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue and general health perceptions. The eight domain scores and weights from the 1990 US population will be used to calculate physical (PCS) and mental (MCS) component summary measures per the user manual (Ware, 2000). SF-36 Mental Component Summary (MCS) and Physical Component Summary (PCS) will be calculated based on PRO Core® (version 2, 17-Dec-2020) a software from Quality Metric (Bayliss, 2012) The 8 domains and the 2 component summary measures will be analyzed using an MMRM model.

The HRU will be summarized for each of the 4 categories described below separately for related and not related to perianal fistula/abscess. Results for individual questions within each category will be cumulatively summarized. The questions in the HRU questionnaire fall under one of the four categories as follows:

- Number of times the subject has visited various specialists since Visit 0
- Number of various surgeries the subject has undergone since Visit 0
- Number of visits the subject has made to hospital since Visit 0
- Number of diagnostic tests or assessments the subject has undergone since Visit 0.

7.8.6 Biomarker Analysis

The following analysis will be performed for the biomarker data.

- Frequency of the HLA+ as well as pre-sensitized (DSA+) and naïve subjects at baseline will be provided.
- Frequency and percentage of immunogenicity events (DSA+) for both treatment arms will be summarized by visits. Subgroup analysis will include frequency of immunogenicity events for naïve and pre-sensitized groups.
- Analysis of primary endpoint Combined Remission at Weeks 24 and 52 will be summarized for each treatment arm by subgroups of naïve vs pre-sensitized and for DSA+ and DSA- population within each subgroup.
- TEAE through Week 52 will be summarized for each treatment arm by subgroups of naïve vs pre-sensitized and for DSA+ and DSA- population within each subgroup.

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Analysis related to change from baseline in cytokines, immune and other inflammation associated markers at Weeks 6, 12, 24 and 52, and change from baseline in the microbiome diversity at Week 6 will not be covered in this SAP.

7.8.7 Rescue Medication and Procedure

Subjects who take any rescue medication or go through a rescue surgery at any time during the study, will be considered as non-responders for the analysis of binary endpoints from the next day of “rescue medication” or “rescue surgery” and onwards.

The following situation qualify as “rescue medication” or “rescue surgery”

- Switch to or addition of any new immunosuppressant or mAb, not ongoing at Screening.
- Increase in dose or frequency of any prior ongoing immunosuppressant or mAb.
- Systemic or rectal steroids for CD flare, if given more than once or at any dose in excess of equivalent-to 60 mg of intravenously prednisolone.
- Prolonged use of systemic antibiotics (more than two weeks) to treat perianal disease or any other suspected/documented infection after the treatment administration visit (V0).

- Subjects starting any investigational drugs for CD or any other local investigational treatments in the perianal region while participating in the study.
- Any new surgical procedure required in the perianal region for the fistula(s) or draining of collections or established abscess(es) or any ostomy required due to luminal CD flare.

Listings of rescue medications and rescue procedures taken by subjects during the study will be provided.

7.8.8 Handling of Missing Data

Unless otherwise specified, non-responder imputation (NRI) rule for the analysis of binary endpoints will be applied for each visit as follows: if the value is missing at the visit, then the subject will be classified as non-responder for the endpoint(s) with missing value.

If the percentage of missing data is greater than 10%, multiple imputation will be used in a sensitivity analysis to be conducted to evaluate the impact of missing data in ITT. Multiple imputation replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. The multiply-imputed data sets are then analyzed by using standard procedures for complete data and combining the results from these analyses (Rubin, 1987) (Yuan, 2011), (Berglund, 2014). Assuming an arbitrary (as opposed to a monotone) missing data pattern, with a binary response variable, SAS PROC MI's Fully Conditional Specification (FCS) logistic regression will be used to impute 50 complete datasets. Age, sex, treatment assignment and randomization strata will be included as covariates. A random seed of 17658834 is pre-specified for the imputation. Example SAS code is provided below.

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```
proc mi data=adeff1 out=impds1 seed=17658834 nimpute=50 ;
  class ivrsgr1n trt01pn asexn aval ;
  var   ivrsgr1n trt01pn asexn age aval;
  fcs logistic (aval = ivrsgr1n trt01pn asexn age / descending likelihood=augment);
run;
```

Rescue medication rule will be applied after multiple imputation. Each of the 50 complete datasets will be analyzed using the standard method of a stratified Cochran-Mantel-Haenszel test, and then SAS PROC MIANALYZE will be used to combine those results into a set of results representative of a single analysis.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

{Not applicable}

7.9.1 Pharmacokinetic Analysis

{Not applicable}

7.9.2 Pharmacodynamic Analysis

{Not applicable}

7.10 Other Outcomes

{Not applicable}

7.11 Safety Analysis

For safety analyses, subjects will be grouped according to the actual treatment received, and the Safety Analysis Set will be used for all analyses. Subjects will be evaluated for safety through the Week 52 visit. Summaries will be provided by treatment group. Safety data (including physical examination, vital signs and laboratory tests) will be summarized using descriptive statistics. Missing safety data will generally not be imputed. However, safety assessment values of the form of "<x" (ie, below the lower limit of quantification) or ">x" (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

7.11.1 Adverse Events

AEs will be summarized descriptively with frequency and percentages. AEs are coded using MedDRA dictionary.

Treatment-emergent adverse events (TEAE) will be defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study drug. Partial or fully missing AE dates will be imputed as per Section 7.1.3. If, after imputation, it is unclear whether the AE is treatment-emergent, it will be assumed that it is. AEs which occur before administration of the study treatment are non-TEAEs.

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The number, and percentage of subjects reporting TEAEs will be tabulated by System Organ Class (SOC)/Preferred Term (PT), and maximum severity. Serious TEAEs, TEAEs related to investigational product will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same PT for the same subject, the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product.

Potential AESIs based on Standardized MedDRA Queries (SMQs) are listed in Appendix C. AESI based on CRF will also be presented.

AE summaries will be presented by treatment group, whether concomitant medication was given, relationship to study drug and severity of AE, as well as by system organ class and preferred term.

The following summaries of AEs will be provided:

- Overall Summary including TEAEs, treatment-related TEAEs, serious TEAEs, treatment-related serious TEAEs, TEAEs leading to study discontinuation, Serious TEAEs leading to study discontinuation, fatal SAEs
- TEAEs by SOC and PT
- TEAEs by decreasing frequency of PT in treatment arm

- Treatment-related TEAEs by decreasing frequency of PT in treatment arm
- Serious TEAEs by SOC and PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related Serious TEAEs by SOC and PT
- TEAEs by severity, SOC and PT
- Serious TEAEs by severity, SOC and PT
- TEAEs or TESAEs leading to study withdrawal by SOC and PT
- Serious TEAEs leading to study withdrawal by SOC and PT
- Treatment-emergent AESIs by SOC and PT for each AESI category
- Serious TEAEs related to the IMP administration procedure by SOC and PT
- TEAEs related to the IMP administration procedure by SOC and PT
- TEAEs by relationship, SOC and PT
- Serious TEAEs by relationship, SOC and PT
- Fatal TESAEs by SOC and PT

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These summaries will present frequency and percentages up to Week 24 and up to Week 52. The AE categories above will also be summarized by alphabetical order of system organ class, preferred term and severity. Missing severity or outcome will be classed as unknown.

Related events are defined as events with relationship to study medication of probably related, possibly related, unknown or missing; unrelated events are defined as events with relationship to study medication of unlikely or not related.

Non-treatment emergent events (starting prior to exposure to study treatment) will be included in the subject listings but not included in the above summaries.

All other information collected (eg, action taken) will be listed as appropriate.

7.11.2 Clinical Laboratory Evaluations

The laboratory test will be performed at Screening, Visit 0 (Study Day 1), Visit 2 (Week 12), Visit 4 (Week 24), Visit 6 (Week 52) or Early Termination Visit, and will include the following parameters:

Hematology: Hemoglobin, Hematocrit, Red blood cell, MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), White blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils and basophiles), Platelet count.

Serum biochemistry: CRP, urea, creatinine, glucose, ASAT, ALAT, albumin, total bilirubin (direct bilirubin if total is above the ULN), potassium, sodium, chloride.

National Cancer Institute (NCI) CTCAE grades will be applied for the following lab parameters based on CTCAE V5.0 Grading for Laboratory Values as in Appendix D.

Hematology: hemoglobin, leukocytes, lymphocytes, neutrophils, eosinophils, basophils, and platelet count;

Biochemistry: creatinine, glucose, AST, ALT, albumin, total bilirubin (direct bilirubin if total bilirubin is above the ULN), potassium and sodium.

The worst post baseline NCI CTCAE grade will be presented by treatment arm for each lab test. Subjects with multiple grades will be counted at their highest grade. Subjects with at least 1 on-study measurement for each laboratory parameter will be included, regardless of whether or not a baseline assessment is present. Unscheduled lab values will also be considered for determining the highest CTCAE grade.

The observed value, the change from baseline, and NCI CTCAE grades in hematology and serum biochemistry laboratory data will be summarized descriptively by visit and treatment group.

Laboratory results and NCI CTCAE grades for hematology, and serum chemistry will be presented in data listings. Laboratory data values will be converted to standard units.

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7.11.3 Vital Signs

Vital signs measurements (sitting blood pressure [mmHg], pulse rate [beats/min], and body temperature [ºC]) will be also measured at all study visits except for the Preparation (Week -3) visit and will be assessed as either clinically or non-clinically significant findings defined by the investigator.

The observed value and the change from baseline in vital signs measurements will be summarized descriptively by visit and treatment group.

7.11.4 12-Lead ECGs

{Not applicable}

7.11.5 Other Observations Related to Safety

{Not applicable}

7.12 Interim Analysis

No interim analysis is planned for this study.

7.13 Additional Analysis Related to COVID-19

Depending on the prevalence of coronavirus disease (COVID-19) infections and illness in regions where the study is conducted, additional analysis may be performed to evaluate the

impact of COVID-19 on the safety of all participating subjects. This analysis will be agreed prior to database lock and may include but not limited to the following:

- COVID-19 related discontinuation, including discontinuation due to AEs in light of COVID-19 infection and discontinuation due to COVID-19 related reasons other than COVID-19 infection (eg, travel limitation, reduced site staff, etc.).
- COVID-19 related AEs, including preferred term of "COVID-19 infection".
- All SAEs in COVID-19 infected subjects.
- All major protocol deviations related to COVID-19.
- Data listing of all subjects affected by COVID-19 related study disruption, including subject ID, site ID, and description of how individual's participation was altered.

7.14 Changes from Protocol

Randomized and treated analysis set is added for supplemental analysis.

Subgroup analysis of Prior treatment with either immunosuppressants or biologics or both is not performed due to limitations of collection of prior treatment data. Prior treatments are collected only for the past two years immediately prior to enrollment.

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7.15 Changes in the Statistical Analysis Plan

This SAP amendment is based on the protocol amendment 3 (dated 28 October 2019). Changes made to the analysis methods are summarized in Table 7.b below. In addition, there were other minor changes made to improve organization, flow, clarity and completeness. As these changes were primarily editorial in nature, they are not summarized here.

Table 7.b Revision History

Version	Section	Change	Rationale
4.0	**7.2 Analysis Sets**	Addition of Randomized and Treated Analysis set.	As supplemental analysis for the primary and key secondary endpoints.
	7.8.3 Primary Efficacy Analysis	- Supplemental analysis using Randomized and Treated analysis set added - Relative risk and it's 95% confidence interval added	As supplemental analysis for the primary and key secondary endpoints.
	7.8.4 Secondary Efficacy Analysis	- Supplemental analysis using Randomized and Treated analysis set added - Relative risk and it's 95% confidence interval added	As supplemental analysis for the primary and key secondary endpoints.

Table 7.b Revision History

Version	Section	Change	Rationale
	7.8.5 Exploratory Efficacy Analysis	- Text on MMRM analysis of continuous endpoints revised - Editorial changes to the PRO instruments - Clarification to the PRO endpoints - MRI exploratory analysis are removed	- Text revised for purposes of improved clarity, completeness, and transparency - MRI exploratory analysis will be in a separate report.
	7.8.6 Biomarker Analysis	Analysis updated	Added to detail the exploratory biomarker efficacy analysis.
	7.11.1 Adverse Events	Analysis for AESI added	To be consistent with updates in protocol amendment 3, dated 28-Oct2019.
5.0	7.1.3	Clarification of AE/CM stop date imputation	
	7.5, 7.8, 7.11	Update the timing of the Week 24 analysis to the end of the study.	
	Appendix C	Updated the SMQ search criteria	
6.0	7.8.2	Two Week 52 endpoints are added to multiplicity test after communication with the regulatory agency.	
	7.8.8	The covariates used in multiple imputation were added.	
	7.11.1	AE by Week 24 was added based on FDA's response on safety analysis.	

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9.0 APPENDIX A

The 36-Item Short Form Health Survey (SF-36) derivations are detailed in this section. There are 8 subscales derived from the SF-36 shown in Table 9.a. The items which have prefix as "I" are the individual questions, and the number which follows is the question number that item is referring to. The items which are prefixed by "GH" and "BP" are derived in later tables.

Table 9.a Derivation of the SF-36 Subscales

Sub-Scale	Items (I, BP, GH)	Formula
Physical Functioning	I3a, …, I3j	100*(I3a+…+I3j-10)/(30-10)
Role-Physical	I4a…, I4d	100*(I4a+...+I4d-4)/(20-4)
Bodily Pain (BP)	BP1, BP2	100*(BP1+BP2-2)/(12-2)
General Health (GH)	GH1, I11a,…, I11d	100*(GH1+I11a+6-I11b+I11c+6-I11d-5)/(25-5)
Vitality (energy/fatigue)	I9a, I9e, I9g, I9i	100*(6-I9a+6-I9e+I9g+I9i-4)/(20-4)
Social Functioning	I6, I10	100*(6-I6+I10-2)/(10-2)
Role-Emotional	I5a, I5b, I5c	100*(I5a+I5b+I5c-3)/(15-3)
Mental Health (Emotional Well-being)	I9b, I9c, I9d, I9f, I9h	100*(I9b+I9c+6-I9d+I9f+6-I9h-5)/(25-5)

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For the Bodily Pain (BP) Index and the General Health (GH) Index, new items are derived from the original SF-36 items as shown in Table 9.b and Table 9.c.

Table 9.b Calculation of Derived Items BP1 and BP2

SF-36 Item 7	BP1	SF-36 Item 8	BP2
1	6	1	6
2	5.4	1	5
3	4.2	2	4
4	3.1	3	3
5	2.2	4	2
6	1	5	1

SF-36 Bodily Pain Index is calculated by transforming SF-36 items 7 and 8, with new scores (BP1 and BP2) being derived as shown in Table 9.b. For example, item 7=1 corresponds to BP1=6 and item 7=2 corresponds to BP1=5.4. Note that BP2=6 if item 7 and item 8 equal 1, and BP2=5 if item 8 = 1 and item 7 ≥ 2.

The SF-36 General Health Index is derived from SF-36 items 1 and 11a-11d. A new item (GH1) is derived from item 1 as described in Table 9.c.

Table 9.c Derived Item GH1 from SF-36 Item 1

SF-36 Item 1	Derived GH1
1	5
2	4.4
3	3.4
4	2
5	1

The rules for imputing missing items when calculating the indices derived from SF-36 are found in Table 9.d. For all the indices, apart from Bodily Pain, missing items are imputed as the mean of the remaining items contributing to the subscale.

Table 9.d Rules for Imputation in the SF-36 Subscales

SF-36 Sub-Scale	Smallest number of non-missing items leading to imputation	Items (I, BP, GH)
Physical Functioning	5	I3a, …, I3j
Role-Physical	2	I4a…, I4d
Bodily Pain	1	See Table 9.e
General Health	3	GH1, I11a,…, I11d
Vitality	2	I9a, I9e, I9g, I9i
Social Functioning	1	I6, I10
Role-Emotional	2	I5a, I5b, I5c
Mental Health	3	I9b, I9c, I9d, I9f, I9h

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In the case of either SF-36 item 7 or item 8 missing then the derived items BP1 and BP2 are calculated as shown in Table 9.e.

Table 9.e Calculation of Derived Items for Bodily Pain in Case of Missing Item 7 or 8

SF-36 Item 7 observed and Item 8 missing		SF-36 Item 8 observed and Item 7 missing	
SF-36 Item 7	BP1=BP2	SF-36 Item 8	BP1=BP2
1	6	1	6
2	5.4	2	4.75
3	4.2	3	3.5
4	3.1	4	2.25
5	2.2	5	1
6	1		

10.0 APPENDIX B

The questions collected in the WPAI are presented in this Appendix, to aid full understanding of the derivations of the subdomains.

1. Are you currently employed (working for pay)?
    a. Yes
    b. No

    if 'No' to question 1 then skip to question 6.
2. During the past seven days, how many hours did you miss from work because of problems associated with your Crohn's Disease?

    Include hours you missed on sick days, times you went in late, left early, etc. because of your Crohn's Disease. Do not include time you missed to participate in this study.
3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
4. During the past seven days, how many hours did you actually work?
5. During the past seven days, how much did your Crohn's Disease affect your productivity while you were working?

0	1	2	3	4	5	6	7	8	9	10
Crohn's Disease had no effect on my work										Crohn's Disease completely prevented me from working

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6. During the past seven days, how much did your Crohn's Disease affect your ability to do your regular daily activities, other than work at a job?

0	1	2	3	4	5	6	7	8	9	10
Crohn's Disease had no effect on my daily activities										Crohn's Disease completely prevented me from doing my daily activities

11.0 APPENDIX C

The following AEs are considered AESI.

- Tumorigenicity
  - SOC 'Neoplasms benign, malignant and unspecified (including cysts and polyps)'.
  - SMQ 'Malignancies' (Broad and Narrow).
- Ectopic tissue formation
  - HLGT 'Benign neoplasms gastrointestinal'.
- Hypersensitivity reactions
  - SMQ 'Hypersensitivity" (Broad and Narrow)
  - SMQ 'Anaphylactic reactions' (Broad and Narrow).
- Transmission of infectious agents
  - PT 'Transmission of an infectious agent via product'.
- Immunogenicity/allo-immunoreactions
  - SMQ ('Immune-mediated/autoimmune disorders' (Broad and Narrow).
- Medication errors
  - SMQ 'Medication errors' (Broad) *This should be kept as broad only due to Takeda convention*

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12.0 APPENDIX D

Table 12.a CTCAE Grade for the Safety Labs

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
Creatinine increased	>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	-
Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-

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Table 12.a CTCAE Grade for the Safety Labs

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukocytes decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Potassium increased	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Sodium increased	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Albumin decreased	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Potassium decreased	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

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13.0 APPENDIX E

Patient Reported Outcome 2 (PRO-2) scoring adapted from (Khanna R, 2015)

(b) Patient Reported Outcome 2 (PRO2)

VARIABLE	DAY							7 DAY AVERAGE	WEIGHTING FACTOR	TOTAL
	1	2	3	4	5	6	7			
Number of liquid or very soft stools									x 2 =	
Abdominal pain 0=none, 1=mild, 2=moderate, 3=severe									x 5 =	
									PRO2 TOTAL=	

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