Statistical Analysis Plan

NCT Number: NCT03706456

Title: A Phase 3, Multicenter, Open-Label, Uncontrolled Study to Evaluate the Efficacy and Safety of Cx601 in the Treatment of Complex Perianal Fistulas in Adult Patients with Crohn's Disease

Study Number: Darvadstrocel-3002

Document Version and Date
Analysis using Data up to Week 24: Version 2 / 02-Sep-2020
Analysis using Data up to Week 52: Version 2 / 05-Mar-2021
Analysis using Data up to Week 156: Version 1 / 09-May-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

[Analysis using Data up to Week 24]

STUDY NUMBER: Darvadstrocel-3002

A Phase 3, Multicenter, Open-Label, Uncontrolled Study to Evaluate the Efficacy and Safety of Cx601 in the Treatment of Complex Perianal Fistulas in Adult Patients with Crohn's Disease

PHASE 3

Version: 2nd

Date: 2 September 2020

Prepared by:

[redacted]

Based on:

Protocol Version: Amendment 3

Protocol Date: 9 October 2019

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDAI	Crohn's Disease Activity Index
DMEM	Dulbecco Modified Eagle's Medium
eASC	expanded allogeneic adipose-derived stem cells
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EO	External Opening
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HSA	human serum albumin
ICH	International Conference on Harmonisation
IL	interleukin
INR	international normalized ratio
IO	Internal Opening
IRB	institutional review board
ITT	intention to treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intention to treat
MRI	magnetic resonance imaging
PCR	polymerase chain reaction
PDAI	Perianal Disease Activity Index
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per protocol set
PTE	Pretreatment event
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent AE
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell

4.0 OBJECTIVES

4.1 Primary Objectives

- To evaluate the efficacy of Cx601 for the treatment of complex perianal fistulas in adult patients with Crohn's disease over 24 weeks.

4.2 Secondary Objectives

- To evaluate the efficacy of Cx601 for the treatment of complex perianal fistulas in adult patients with Crohn's disease over 52 weeks.
- To evaluate the safety of Cx601 for the treatment of perianal fistulas in adult patients with Crohn's disease over minimum 156 weeks.

4.3 Additional Objectives

- To evaluate the absence of clinically relevant alloreactivity.
- To evaluate the effects of Cx601 on Crohn's disease activity and quality of life.

4.4 Study Design

This is Phase 3, a multicenter, open-label, uncontrolled study to evaluate the efficacy and safety of Cx601 in the treatment of complex perianal fistulas in adult patients with Crohn's disease.

Subjects with Crohn's disease whose complex perianal fistulas were previously treated and refractory (inadequate response, loss of response or intolerance) to at least one of the following treatments: antibiotics, immunosuppressants or biologics (anti-TNFs, anti-integrin or anti-IL-12/23) will be included in the study. Note that those subjects who are refractory to antibiotics only will be must be less than 25% of all subjects enrolled.

The study will permit continuation of baseline treatments for Crohn's disease in an add-on design (ie, biologics, immunosuppressants, etc.) . A total of 20 subjects are planned to be enrolled, and study product, cell suspension containing 120×10^6 cells of eASCs, will be intralesionally injected to all participants. Since this is the first study of Cx601 in Japanese subjects, the enrollment of at least the first 3 subjects will be adjusted not to be administered the study product at the same day.

This study consists of the screening period (approximately 5 weeks prior to study product administration, including the screening visit and the preparation visit), the treatment period (the day of study product administration) , the follow-up period (approximately 52 weeks after study product administration) , and the long-term follow-up period (from Week 52 to Week 156 or later; for a minimum of 104 weeks) . Cx601 will be administrated once on Day 1, and the efficacy and safety of Cx601 will be mainly evaluated in the subsequent 52-week follow-up period. The primary endpoint will be evaluated at Week 24. Additionally, in the long-term follow-up period after Week 52, a safety follow-up evaluation will be performed for all subjects every 26 weeks (6 months) until Week 156 or later.

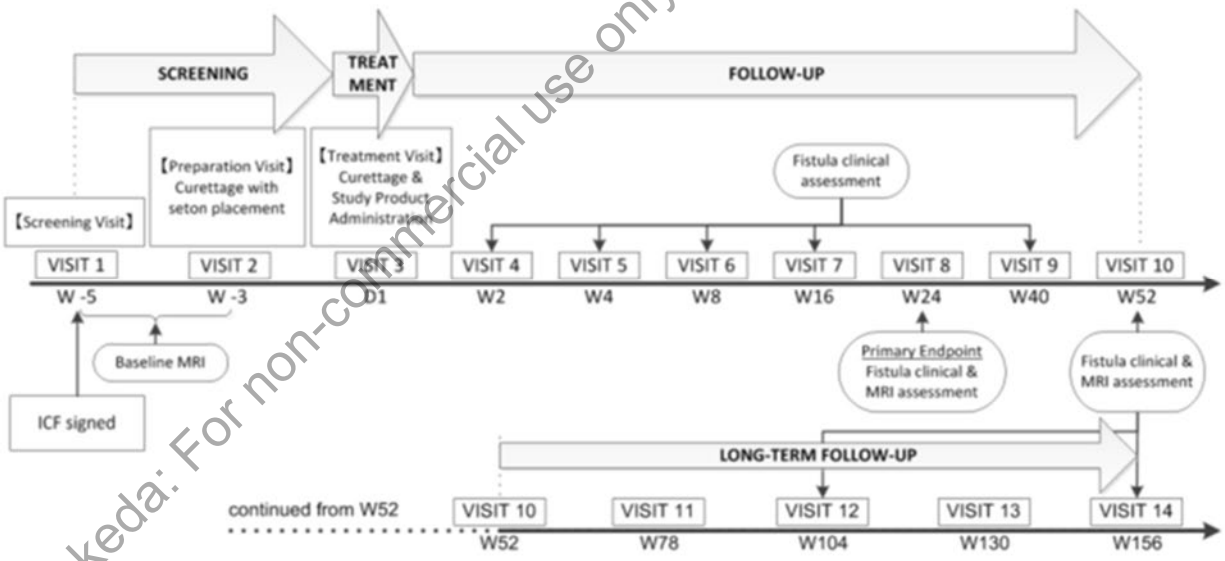
In the screening period, a screening visit (Visit 1) to determine a subject's eligibility is scheduled during the period from Day -39 to the day before preparation. All the subjects eligible by the screening will receive fistula curettage and seton placement under anesthesia at the preparation visit (Visit 2: Day -21, done no later than Day -14). Seton(s) placed will be removed on the day of study product administration (Visit 3: Day 1), just before the administration of the study product. Appropriate training for the preparation and the administration will be implemented to standardize the procedures between study sites.

The subjects who meet all the eligibility criteria will visit the study site on Day 1, and receive fistula curettage under anesthesia and an intralesional injection of cell suspension containing 120×10^6 cells of eASCs (Cx601). Thereafter, in follow-up period, the subjects will visit the study site for the clinical assessments including fistula closure at Weeks 2, 4, 8, 16, 24, 40 and 52. Radiological assessments (MRI) of fistula closure will also be performed at Weeks 24 and 52.

Additionally, in the long-term follow-up period, the safety follow-up will be performed on all the subjects (where possible) every 26 weeks (6 months) from a visit in Week 52 through Week 156. This study will be switched to a post-marketing clinical study if Cx601 is approved before the study completion.

A schematic study design is shown in Figure 4.a.

Figure 4.a Schematic Study Design



5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

- Proportion of subjects with combined remission at Week 24.

5.2 Secondary Endpoints

Efficacy analysis using data up to Week 24:

- Proportion of subjects with clinical remission at Week 24.
- Proportion of subjects with response at Week 24.
- Time to clinical remission by Week 24.
- Time to response by Week 24.
- Proportion of subjects with relapse at Week 24 in subjects with clinical remission at previous visit.
- Time to relapse by Week 24 in subjects with clinical remission at previous visit.
- PDAI score (including total score, discharge sub-score and pain sub-score) up to Week 24.
- CDAI score up to Week 24.
- Van Assche score up to Week 24.

Efficacy analysis using data up to Week 52:

- Proportion of subjects with combined remission at Week 52.
- Proportion of subjects with clinical remission at Week 52.
- Proportion of subjects with response at Week 52.
- Time to combined remission by Week 52.
- Time to clinical remission by Week 52.
- Time to response by Week 52.
- Proportion of subjects with relapse at Week 52 in subjects with combined remission at Week 24.
- Time to relapse by Week 52 in subjects with combined remission at Week 24.
- PDAI score (including total score, discharge sub-score and pain sub-score) up to Week 52.
- CDAI score up to Week 52.
- Van Assche score up to Week 52.

5.3 Safety Endpoints

- Adverse events (AEs) including serious adverse events (SAEs) and AEs of special interest.
- Product malfunctions.
- Physical examination findings.
- Vital signs (heart rate, blood pressure, body temperature).
- Clinical laboratory test results (serum chemistry, hematology and urinalysis).

5.4 Additional Endpoints

- Presence/absence of anti-donor antibody.

6.0 DETERMINATION OF SAMPLE SIZE

The planned sample size is 20 based on feasibility. However, this study has at least 94% probability to show a proportion of subjects with combined remission of 35% or more given an expected proportion of subjects with combined remission of 50% based on Week 24 results in the Cx601-0302 study.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after receiving study treatment.
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to study treatment administration.
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Duration of study after baseline (days): Date of last visit/contact - date of study treatment administration + 1.
  If subject is ongoing, date of last visit/contact will be imputed by date of data cut off.
- Duration of follow-up after baseline by Week 24 (weeks): (Date of the latest fistula clinical assessment or the latest visit by Day 198 – date of study treatment administration + 1)/7.
- Duration of Crohn's Disease (years): Date of informed consent - date of Crohn's disease diagnosis.
  (If month of diagnosis is missing, month will be replaced with January. If day of diagnosis is missing, day will be replaced with 1st.)
- Combined remission: Defined as the clinically confirmed closure of all treated external openings that were draining at the screening despite gentle finger compression, and absence of collections >2 cm in the treated fistulas which is confirmed by the central MRI assessment (a collection >2 cm is considered as present if at least two out of the 3 dimensions centrally assessed are >2 cm in any of fistula tract).
- Clinical remission: Defined as the clinically confirmed closure of all treated external openings that were draining at the screening despite gentle finger compression.
- Response: Defined as the clinically confirmed closure of at least 50% of all treated external openings that were draining at the screening despite gentle finger compression. Note : Clinically confirmed closure of at least 50% is defined as 1 closure for subjects with 1 baseline external opening, 1 or 2 closures for subjects with 2 baseline external openings, and 2 or 3 closures for subjects with 3 baseline external openings.
- Relapse: Defined as the clinically confirmed reopening of any of the treated external openings with active drainage, or the development of a collection >2 cm in the treated fistulas confirmed by central MRI assessment

(a collection >2 cm is considered as present if at least two out of the 3 dimensions centrally assessed are >2 cm in any of fistula tract).

- Time to combined remission/clinical remission/response (days): The time from the study treatment administration to the first visit by which combined remission/clinical remission/response is observed.
  For combined remission, date is the latest of fistula MRI assessment and fistula clinical assessment.
- Time to relapse (days): The time from the first visit which clinical remission is observed to the first visit by which relapse is observed.
  (Time to relapse by Week 52 in subjects who achieved combined remission at Week 24 is defined as "the time from the combined remission at Week 24 to the first visit by which relapse is observed.)
- Presence/Absence of donor specific antibody: Results for each post-baseline visit will be presence when at least one of donor specific antibody tests (Class I and/or Class II) is presence, otherwise results will be absence. A result at baseline will represent presence/absence of anti-HLA Class I and Class II antibody.
- CDAI total score: CDAI total score and body weight will be cut-off by -10, i.e. score below -10 will be treated as -10.

7.1.2 Definition of Study Days

The following definitions and calculation formulas will be used.

- Study Day: The day before study treatment administration will be defined as Study Day -1 and the day of the study treatment administration will be defined as Study Day 1. If the date of the observation is on the same date or after the day of the study treatment administration, Study Day will be calculated relative to Study Day 1. Otherwise, Study Day will be calculated relative to Study Day -1.

7.1.3 Definition of Study Visit Windows

When calculating Study Day relative to a reference date (ie, study treatment administration [Day 1]) , if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

7.1.3.1 Fistula Assessment

All evaluable data (ie, non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the largest Study Day will be used.

Table 7.a Visit Window of Fistula MRI Assessment

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	Day Before Preparation	- Day Before Preparation
Week 24	Study Day:	169	2 - 198
Week 52	Study Day:	365	199 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -
Week 24(LOCF)	Study Day:		2 - 198
Week 52(LOCF)	Study Day:		2 - 448
Week 104(LOCF)	Study Day:		2 - 812
Week 156(LOCF)	Study Day:		2 -

Table 7.b Visit Window of Fistula Clinical Assessment

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	Day Before Preparation	- Day Before Preparation
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -
Week 2(LOCF)	Study Day:		2 - 22
Week 4(LOCF)	Study Day:		2 - 43
Week 8(LOCF)	Study Day:		2 - 85
Week 16(LOCF)	Study Day:		2 - 141
Week 24(LOCF)	Study Day:		2 - 198
Week 40(LOCF)	Study Day:		2 - 323
Week 52(LOCF)	Study Day:		2 - 448
Week 104(LOCF)	Study Day:		2 - 812
Week 156(LOCF)	Study Day:		2 -

7.1.3.2 Endpoints Other Than Fistula Assessment

All evaluable data (ie, non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day for others, the later observation will be used.

Table 7.c Visit Window of PDAI Score

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -

Table 7.d Visit Window of CDAI Score

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 24	Study Day:	169	2 - 198
Week 52	Study Day:	365	199 - 448
Week 156	Study Day:	1093	449 -

Table 7.e Visit Window of Van Assche Score

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	-35	-39 - -1
Week 24	Study Day:	169	1 - 198
Week 52	Study Day:	365	199 - 448
Week 156	Study Day:	1093	449 -

Table 7.f Visit Window of Vital Signs

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 78	Study Day:	547	449 - 638
Week 104	Study Day:	729	639 - 812
Week 130	Study Day:	911	813 - 1002
Week 156	Study Day:	1093	1003 -

Table 7.g Visit Window of Clinical Laboratory Tests

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 52	Study Day:	365	199 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -

Table 7.h Visit Window of Anti-donor Antibody Test

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 52	Study Day:	365	199 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -

7.1.4 Significance Level and Confidence Coefficient

- Confidence coefficient: 90% (two-sided), 95% (two-sided).

7.1.5 Calculation of Combined Remission, Clinical Remission, Response

- Combined Remission at Week 24(Primary endpoint)
  Fistula MRI assessment at Week 24(LOCF) and fistula clinical assessment at Week 24(LOCF) will be used when combined remission at Week 24 is calculated based on the definition of section 7.1.1.
  If either of the two is missing, non-remission will be imputed.
  If a subject received rescue therapy which is not allowed in section 7.4 of the protocol or

medications which could affect fistula closure directly prior to visit 8(Week 24) will be handled as non-remission.

- Clinical Remission, Response at Week 24(Secondary endpoint).
  Fistula clinical assessment at Week 24(LOCF) will be used when clinical remission or response at Week 24 is calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, non-remission(non-response) will be imputed.
  If a subject received rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly prior to visit 8(Week 24) will be handled as non-remission.
- Combined Remission at Week 52(Secondary endpoint).
  Fistula MRI assessment at Week 52(LOCF) and fistula clinical assessment at Week 52(LOCF) will be used when combined remission at Week 52 is calculated based on the definition of section 7.1.1.
  If either of the two is missing, non-remission will be imputed.
- Clinical Remission, Response at Week 52(Secondary endpoint).
  Fistula clinical assessment at Week 52(LOCF) will be used when clinical remission or response at Week 52 is calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, non-remission(non-response) will be imputed.
- Combined Remission at Week 104/Week 156(Additional endpoint).
  Fistula MRI assessment at Week 104(LOCF)/Week 156(LOCF) and fistula clinical assessment at Week 104(LOCF)/156(LOCF) will be used when combined remission at Week 104/Week 156 are calculated based on the definition of section 7.1.1.
  If either of the two is missing, non-remission will be imputed.
- Clinical Remission, Response at Week 104/Week 156(Additional endpoint).
  Fistula clinical assessment at Week 104(LOCF)/Week 156(LOCF) will be used when clinical remission or response at Week 104/Week 156 are calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, non-remission(non-response) will be imputed.
- Clinical Remission, Response for Time Point Analysis(Additional endpoint).
  Fistula clinical assessment at each analysis visit after baseline in Table 7.b other than LOCF will be used when clinical remission or response for each time point analysis is calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, it will be handled as missing.

7.1.6 Calculation of Relapse in Subjects with Clinical/Combined Remission

- Relapse at Week 24 in subjects with clinical remission at previous visit.

The first clinical remission date before Day 198 will be identified. Per subject with clinical remission above, subject will be defined as relapsed if there is a fistula MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the first

clinical remission and by Day 198 based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 52 in subjects with combined remission at Week 24.

The combined remission date at Week 24(latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 198, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the combined remission date and by Day 448 based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 104 in subjects with combined remission at Week 52.

The combined remission date at Week 52(latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 448, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the combined remission date and by Day 812 based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 156 in subjects with combined remission at Week 104.

The combined remission date at Week 104(latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 812, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the combined remission date based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

7.2 Analysis Sets

- Intention to treat (ITT):
  All subjects who have enrolled into treatment period.
- Modified intention to treat (mITT):
  All subjects who have received the study treatment and whose primary efficacy endpoint is evaluable.
- Per protocol set (PPS):
  All subjects who have completed the minimum protocol-specified procedures without any major protocol deviations (ie, subjects who met the following criteria will be excluded from the PPS).
  - Subjects who did not meet inclusion criteria #3, #5, #6, or #7.
  - Subjects who met exclusion criteria #1, #2, #3, #4, #5, #6, #7, #8, #9, #10, #11, #21, #23, #24, #25, or #27.

- Subjects who have violated the rules for medications and treatments specified in section 7.3 of the protocol prior to visit 8(Week 24).
- Subjects who have violated the rules for rescue therapy specified in section 7.4 of the protocol prior to visit 8(Week 24).
- Subjects who received less than 24 mL of the study treatment.
- Subjects who did not have either fistula MRI assessment or fistula clinical assessment 45 days prior to or post Study Day 169.

- Safety analysis set:
  All subjects who have received the study treatment.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date First Subject Signed Informed Consent Form

Date of Last Subject's Last Visit/Contact

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variables:

Age (years)

Gender [Male, Female]

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Eligibility Status

[Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]

Primary Reason for Subject Not Being Eligible

[Death, Adverse Event, Screen Failure, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical Methods:

(1) Eligibility for Entrance into the Treatment Period

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Status of Entrance into the Treatment Period [Entered]

Stratum:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Who Entered the Treatment Period by Site

Frequency distributions will be provided for each stratum.

7.3.5 Disposition of Subjects for Follow-up Period

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Study Treatment Administration Status

[Eligible but Not Treated]

Reason for Not Being Treated

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Completion Status for Follow-up Period

[Completed/Ongoing, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

(2) Completion Status for Follow-up Period

Frequency distributions will be provided for Completion Status for Follow-up Period(categories of Completed, Ongoing and Prematurely Discontinued).

7.3.6 Completion Status for Follow-up Period

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Completion Status for Follow-up Period

[Completed/Ongoing, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Categories:

Duration of Study after Baseline (days)

[Min - 57, 58 - 169, 170-281, 282 - Max]

Analytical Methods:

(1) Completion Status for Follow-up Period by Duration of Study after Baseline

Frequency distributions will be provided for each category of duration of study after baseline.

7.3.7 Disposition of Subjects for Long-Term Follow-up Period

Analysis Set:

All Subjects Who Completed the Follow-up period

Analysis Variables:

Completion Status for Long-Term Follow-up Period

[Completed/Ongoing, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

(2) Completion Status for Long-Term Follow-up Period

Frequency distributions will be provided for Completion Status for Long-Term Follow-up Period (categories of Completed, Ongoing and Prematurely Discontinued).

7.3.8 Completion Status for Long-Term Follow-up Period

Analysis Set:

All Subjects Who Completed the Follow-up Period

Analysis Variables:

Completion Status for Long-Term Follow-up Period

[Completed/Ongoing, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Categories:

Duration of Study after Baseline (days)

[Min - 547, 548 - 729, 730-911, 912 - Max]

Analytical Methods:

(1) Completion Status for Long-Term Follow-up Period

Frequency distributions will be provided for each category of duration of study after baseline.

7.3.9 Protocol Deviations and Analysis Sets

7.3.9.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria]

Analytical Methods:

(1) Protocol Deviations

Frequency distributions will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.9.2 Analysis Sets

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Handling of Subjects

[Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

Intention to Treat	[Included]
Modified Intention to Treat	[Included]
Per Protocol Set	[Included]
Safety Analysis Set	[Included]

Analytical Methods:

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:

Intention to Treat

Analysis Variables:

Age (years) [Min<= - <=65, 65< - <=Max]

Gender [Male, Female]

Height (cm)

Weight (kg)

BMI (kg/m^2)

Smoking Classification [Never, Current, Former]

Previous use of Antibiotics [Yes, No]

Previous use of Immunosuppressants [Yes, No]

Previous use of Biologics [Yes, No]

Concomitant Medications [Biologics only, Immunosuppressants only, Biologics+Immunosuppressants, None of 2 types of concomitant drugs]

Duration of Crohn's Disease (years)

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 IO + 1 EO, 1 IO + 2 EOs, 1 IO + 3 EOs, 2 IOs + 1 EO, 2 IOs + 2 EOs, 2 IOs + 3 EOs]

Topography of Draining EOs at Screening

[0 EO, 1 EO, 2 EOs, 3EOs]

CDAI Total Score at Baseline [Min<= - <150, 150<= - <=220, 220< - <=Max]

Analytical Methods:

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.5 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Concomitant medications whose start date occurred on or before Week 24 visit, i.e. the latest fistula clinical assessment or the latest visit by Day 198, will be summarized.

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medication History

Concomitant Medications

Analytical Methods:

(1) Medication History by Preferred Medication Name

(2) Concomitant Medications That Started and Stopped Prior to Baseline by Preferred Medication Name

(3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline by Preferred Medication Name

(4) Concomitant Medications That Started After Baseline by Preferred Medication Name

(5) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variables:

Total Exposure (mL)

Total Exposure per IOs (mL)

Total Exposure per EOs (mL)

Duration of follow-up after baseline by Week 24 (weeks)

Analytical Methods:

(1) Summary of Total Exposure

Descriptive statistics will be provided.

7.8 Efficacy Analysis

The intention to treat will be the main analysis set used. The modified intention to treat and the per protocol set will be used for the primary and secondary endpoints in order to examine the robustness of the results.

7.8.1 Primary Endpoint

7.8.1.1 Proportion of Subjects with Combined Remission at Week 24

Analysis Set:

Intention to Treat

Modified Intention to Treat

Per Protocol Set

Analysis Variables:

Combined Remission at Week 24

Analytical Methods:

(1) Primary Analysis
Frequency distributions will be provided with proportion and the two-sided 90% and 95% confidence intervals(Wald's method) for the intention to treat.

(2) Secondary Analysis
Frequency distributions will be provided with proportion and the two-sided 90% and 95% confidence intervals(Wald's method) for the modified intention to treat and the per protocol set.

7.8.2 Secondary Endpoints

Efficacy analysis using data up to Week 24

7.8.2.1 Proportion of Subjects with Clinical Remission and Response at Week 24

Analysis Set:

Intention to Treat

Modified Intention to Treat

Per Protocol Set

Analysis Variables:

Clinical Remission at Week 24

Response at Week 24

Analytical Methods:

The same analysis for the primary endpoint will be performed.

7.8.2.2 Proportion of Subjects with Relapse at Week 24

Analysis Set:

Intention to Treat

Analysis Variables:

Relapse at Week 24

Analytical Methods:

(1) Number and Percentage of Subjects with Relapse at Week 24
Within the subjects with clinical remission at previous visit, frequency distributions will be provided with proportion and the two-sided 90% and 95% confidence intervals(Wald's method).

7.8.2.3 Time to Clinical Remission and Response by Week 24

Analysis Set:

Intention to Treat

Analysis Variables:

Time to Clinical Remission by Week 24

Time to Response by Week 24

Analytical Methods:

For the following time to event analyses, subjects without event will be handled as censor at the date of last fistula clinical assessment.

(1) Summary of Time to Event by Week 24
Frequency distribution of subjects who experienced event and who were censored will be provided. Quartiles of time to event will be estimated using the Kaplan-Meier method.

(2) Kaplan-Meier Plot
Kaplan-Meier plot of time to clinical remission/response by Week 24 will be provided.

7.8.2.4 Time to Relapse by Week 24

Analysis Set:

Intention to Treat

Analysis Variables:

Time to Relapse by Week 24

Analytical Methods:

Within the subjects with clinical remission at previous visit, the following analyses will be performed. For the following time to event analyses, subjects without event will be handled as censor at the date of last fistula clinical assessment or last fistula MRI assessment.

(1) Summary of Time to Event by Week 24
Frequency distribution of subjects who experienced event and who were censored will be provided. Quartiles of time to event will be estimated using the Kaplan-Meier method.

(2) Kaplan-Meier Plot
Kaplan-Meier plot of time to relapse by Week 24 will be provided.

7.8.2.5 PDAI Score

Analysis Set:

Intention to Treat

Analysis Variables:

PDAI Total Score

PDAI Domain Scores(Discharge, Pain/restriction of activities, Restriction of Sexual Activity, Type of Perianal Disease, Degree of Induration)

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24

Analytical Methods:

(1) Summary of PDAI Scores and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline for each visit will be provided.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted for each visit with standard deviation bars.

7.8.2.6 CDAI Score

Analysis Set:

Intention to Treat

Analysis Variables:

CDAI Total Score [Min<= - <150, 150<= - <=220, 220< - <=450, 450< - <=Max]

CDAI Sub Scores

Visit:

Baseline, Week 24

Analytical Methods:

(1) Summary of CDAI Scores and Change from Baseline by Visit
Frequency distribution for categorical variables and descriptive statistics of observed values and changes from baseline for each visit will be provided.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted for each visit with standard deviation bars.

7.8.2.7 Van Assche Score

Analysis Set:

Intention to Treat

Analysis Variables:

Van Assche Total Score

Van Assche Domain Scores

Visit:

Baseline, Week 24

Analytical Methods:

(1) Summary of Van Assche Scores and Change from Baseline by Visit
Frequency distribution for categorical variables and descriptive statistics of observed values and changes from baseline for each visit for continuous variables will be provided.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted for each visit with standard deviation bars for continuous variables.

7.8.3 Additional Endpoints

Efficacy analysis using data up to Week 24

7.8.3.1 Timepoint Analysis of Clinical Remission and Response

Analysis Set:

Intention to Treat

Analysis Variables:

Clinical Remission

Response

Visit:

Week 2, Week 4, Week 8, Week 16, Week 24

Analytical Methods:

The same analysis for the primary endpoint will be performed by visit.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

Values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values above the upper limit of quantification will be treated as the upper limit of quantification when calculating the descriptive statistics.

For combined remission, clinical remission, response

For the primary and secondary analyses of the primary endpoint, the last observation carried forward (LOCF) from the latest earlier post-baseline visit (including an Early Termination Visit prior to Week 24, if applicable) will apply in case of missing clinical assessment at Week 24. In case of missing MRI data at Week 24, LOCF from an Early Termination Visit prior to Week 24 will apply if applicable. In case of no MRI data by Week 24 or no post-baseline clinical assessment, non-response will be imputed. If rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly occur prior to visit 8(Week 24) , non-response will be imputed overriding all other imputation conventions.

The handling above for the primary endpoint will also be applied to proportion of subjects with clinical remission at Week 24, proportion of subjects with response at Week 24 and proportion of subjects with combined remission at Week 52.

7.8.4.3 Multicenter Studies

Although this study is a multicenter study, treatment-by-center interaction will not be explored since the number of subjects for each center is not sufficient for such exploration.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

In addition to analyses on the primary endpoint using the intention to treat, a secondary analysis will also be performed using the modified intention to treat and the per protocol set to confirm the robustness of the results.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.4.7 Examination of Subgroups

Efficacy analysis using data up to Week 24

Analysis Set:

Intention to treat

Analysis Variables:

Combined Remission at Week 24

Clinical Remission at Week 24

Response at Week 24

Subgroups:

Age [Min<= - <=65, 65< - <=Max]

Gender [Male, Female]

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 IO + 1 EO, 1 IO + (2<= EOs), 2 IOs + (1<= EOs)]

Previous use of Antibiotics [Yes, No]

Previous use of Immunosuppressants [Yes, No]

Previous use of Biologics [Yes, No]

Concomitant Medications [Biologics only, Immunosuppressants only, Biologics+Immunosuppressants, None of 2 types of concomitant drugs]

Analytical Methods:

(1) Descriptive Statistics

Frequency distributions will be provided for above each subgroups.

7.9 Other Outcomes

Not applicable.

7.10 Safety Analysis

Safety analysis using data up to Week 24

7.10.1 Adverse Events

TEAEs whose date of onset occurred on or before Week 24 visit, i.e. the latest fistula clinical assessment or the latest visit by Day 198, will be summarized.

7.10.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Relationship to Study Treatment [Related, Not Related]

Intensity [Mild, Moderate, Severe]

Analytical Methods:

The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
2) Relationship of Treatment-Emergent Adverse Events to study treatment (number of events, number and percentage of subjects).
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
4) Treatment-Emergent Adverse Events leading to study discontinuation (number of events, number and percentage of subjects).
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
6) Relationship of serious Treatment-Emergent Adverse Events to study treatment (number of events, number and percentage of subjects).
7) Serious Treatment-Emergent Adverse Events leading to study discontinuation (number of events, number and percentage of subjects).
8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects).

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- Summaries other than 2), 3), and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

7.10.1.2 Displays of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Intensity	[Mild, Moderate, Severe]
Time of Onset (day)	[1 - 57, 58 - 169, 170-281, 282 - Max]

Analytical Methods:

The following summaries will be provided using frequency distribution.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Study Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Study Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(10) Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term

(11) Product Malfunction-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distributions will be provided according to the rules below.

Number of subjects

- Summary tables other than (5), (6) and (9)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

- Summary table for (9)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. Percentages will be based on the number of subjects in the safety analysis set.

7.10.1.3 Subgroup Analysis of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Subgroups:

Age [Min<= - <=65, 65< - <=Max]

Gender [Male, Female]

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 EO, 2 <= EOs]

Previous use of Antibiotics [Yes, No]

Previous use of Immunosuppressants [Yes, No]

Previous use of Biologics [Yes, No]

Concomitant Medications [Biologics only, Immunosuppressants only, Biologics+Immunosuppressants, None of 2 types of concomitant drugs]

Analytical Methods:

The following summaries will be provided for each subgroup using frequency distribution. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set for each subgroup.

7.10.1.4 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

PTE

Analytical Methods:

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term.

(2) Serious Pretreatment Events by System Organ Class and Preferred Term.

The frequency distributions will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.10.2 Clinical Laboratory Evaluations

7.10.2.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Hemoglobin, Hematocrit, Red blood cells count, Mean Cprpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, White blood cells count, differential WBC (Neutrophils, Basophils, Eosinophils, Lymphocytes, Monocytes), Platelet count

Serum Chemistry

C-reactive protein, ALT, AST, Alkaline phosphatase, Gamma-glutamyl transpeptidase, Total bilirubin, Total protein, Glucose, Creatinine, Creatine phosphokinase, Blood urea nitrogen, Potassium, Sodium, Chloride

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24

Analytical Methods:

For each variable, summaries (1) to (3) will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each laboratory test, the laboratory values will be classified as “Low”, “Normal”

or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

7.10.2.2 Urinalysis

Analysis Set:

Safety Analysis Set

Analysis Variables:

Specific Gravity	
pH	
Glucose	[-, +-, +, 2+, 3+]
Protein	[-, +-, +, 2+, 3+]
Occult blood	[-, +, 2+, 3+]
Ketone body	[-, +-, +, 2+, 3+]
Bilirubin	[-, +, 2+, 3+]
Urobilinogen	[+-, +, 2+, 3+]

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24

Analytical Methods:

For specific gravity, summaries (1), (2) and (4) will be provided.

For pH, summary (4) will be provided.

For each variable other than specific gravity or pH, summaries (3) and (4) will be provided.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

(4) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

For each urine laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

7.10.3 Vital Signs

Analysis Set:

Safety Analysis Set

Analysis Variables:

Temperature

Systolic Blood Pressure

Diastolic Blood Pressure

Heart Rate

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24

Analytical Methods:

For each variable, summaries (1) and (2) will be provided

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

7.10.4 Other Observations Related to Safety

7.10.4.1 Donor Specific Antibody

Analysis Set:

Safety Analysis Set

Analysis Variables:

Donor Specific Antibody

[Presence, Absence]
(Categories used in analytical methods (1) and (2))

[Presence at baseline and Presence during post-baseline,
Presence at baseline and Absence during post-baseline,
Absence at baseline and Presence during post-baseline,

Absence at baseline and Absence during post-baseline]
(Categories used in analytical methods (3) and (4))

[Presence during post-baseline, Absence during post-baseline]
(Categories used in analytical method (4))

(Presence/Absence at baseline is results of anti-HLA antibody.)

(Presence/Absence during post-baseline is results of donor specific antibody during post-baseline by Week 24, i.e. Presence if any positive results during post-baseline by Week 24, Absence if no positive results during post-baseline by Week 24.)

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24

Analytical Methods:

(1) Summary of Donor Specific Antibody by Visit

Frequency distributions for each visit will be provided.

(2) Summary of Shifts of Donor Specific Antibody

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

(3) Number of Subjects in Categories of Donor Specific Antibody

Frequency distributions of results at baseline and during post-baseline will be provided.

(4) Subgroup Analysis of Efficacy and Safety Endpoints by Donor Specific Antibody

The same analyses of Section 7.8.4.7 and 7.10.1.3 will be conducted for each subgroup of Donor Specific Antibody.

7.10.4.2 Displays of Treatment-Emergent Adverse Events (Japanese)

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Analytical Methods:

TEAEs will be summarized in the same way as in section 7.10.1.2 and 7.10.1.3. All summaries will be presented in Japanese.

7.11 Interim Analysis

There will not be any interim analysis. Note, the analysis using data up to Week 24 is the primary analysis for marketing application. Additionally, separate analyses using data up to Week 52 and overall data will be performed after all subjects complete Week 52 and Week 156 respectively.

7.12 Changes in the Statistical Analysis Plan

The analyses in the statistical analysis plan do not differ from the analyses specified in the protocol.

Changes from the previous version are listed below.

Page 11, Section 7.1.1

Existing Text

(new)

- Response: Defined as the clinically confirmed closure of at least 50% of all treated external openings that were draining at the screening despite gentle finger compression.

Revised Text

- Duration of follow-up after baseline by Week 24 (weeks): (Date of the latest fistula clinical assessment or the latest visit by Day 198 – date of study treatment administration + 1)/7.
- Response: Defined as the clinically confirmed closure of at least 50% of all treated external openings that were draining at the screening despite gentle finger compression. Note : Clinically confirmed closure of at least 50% is defined as 1 closure for subjects with 1 baseline external opening, 1 or 2 closures for subjects with 2 baseline external openings, and 2 or 3 closures for subjects with 3 baseline external openings.

Rationale for Amendment

Added the definition of duration of follow-up after baseline by Week 24 and clarification of the definition of clinically confirmed closure of at least 50% in each case.

Page 12, Section 7.1.1

Existing Text

(new)

Revised Text

- Presence/Absence of donor specific antibody: Results for each post-baseline visit will be presence when at least one of donor specific antibody tests (Class I and/or Class II) is presence, otherwise results will be absence. A result at baseline will represent presence/absence of anti-HLA Class I and Class II antibody.

- CDAI total score: CDAI total score and body weight will be cut-off by -10, i.e. score below -10 will be treated as -10.

Rationale for Amendment

Clarification of the definition of Presence/Absence of donor specific antibody and to add cut-off of CDAI score.

Page 13, Section 7.1.3.1

Existing Text

Table 7.i Visit Window of Fistula MRI Assessment

Visit	Time Interval (days) Study Day
Baseline	-39 - Day Before Preparation
Week 24	1 - 198
Week 52	199 - 448
Week 104	449 - 812
Week 156	813 -
Week 24(LOCF)	1 - 198
Week 52(LOCF)	1 - 448
Week 104(LOCF)	1 - 812
Week 156(LOCF)	1 -

Table 7.j Visit Window of Fistula Clinical Assessment

Visit	Time Interval (days) Study Day
Baseline	-39 - Day Before Preparation
Week 2	1 - 22
Week 4	23 - 43
Week 8	44 - 85
Week 16	86 - 141
Week 24	142 - 198
Week 40	199 - 323
Week 52	324 - 448
Week 104	449 - 812
Week 156	813 -
Week 2(LOCF)	1 - 22
Week 4(LOCF)	1 - 43
Week 8(LOCF)	1 - 85
Week 16(LOCF)	1 - 141
Week 24(LOCF)	1 - 198
Week 40(LOCF)	1 - 323
Week 52(LOCF)	1 - 448
Week 104(LOCF)	1 - 812
Week 156(LOCF)	1 -

Revised Text

Table 7.k Visit Window of Fistula MRI Assessment

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	Day Before Preparation	- Day Before Preparation
Week 24	Study Day:	169	2 – 198
Week 52	Study Day:	365	199 – 448
Week 104	Study Day:	729	449 – 812
Week 156	Study Day:	1093	813 -
Week 24(LOCF)	Study Day:		2 - 198
Week 52(LOCF)	Study Day:		2 - 448
Week 104(LOCF)	Study Day:		2 - 812
Week 156(LOCF)	Study Day:		2 -

Table 7.1 Visit Window of Fistula Clinical Assessment

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	Day Before Preparation	- Day Before Preparation
Week 2	Study Day:	15	2 – 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -
Week 2(LOCF)	Study Day:		2 – 22
Week 4(LOCF)	Study Day:		2 – 43
Week 8(LOCF)	Study Day:		2 – 85
Week 16(LOCF)	Study Day:		2 – 141
Week 24(LOCF)	Study Day:		2 – 198
Week 40(LOCF)	Study Day:		2 – 323
Week 52(LOCF)	Study Day:		2 – 448
Week 104(LOCF)	Study Day:		2 – 812
Week 156(LOCF)	Study Day:		2 -

Rationale for Amendment

To address scheduled study day of visit window for fistula assessment as well as other endpoints. Lower limit of time interval of baseline was removed to include all screening assessment. A subject performed fistula clinical assessment on Day 1 prior to study treatment administration. Modification to exclude Day 1 assessment prior to study treatment administration from post-baseline.

Page 17, Section 7.1.5

Existing Text

If a subject received rescue therapy which is not allowed in section 7.4 of the protocol prior to visit 8(Week 24) will be handled as non-remission.

Revised Text

If a subject received rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly prior to visit 8(Week 24) will be handled as non-remission.

Rationale for Amendment

To align with revised text in the protocol amendment 3 section 13.1.3.3.

Page 22, Section 7.3.6

Existing Text

Duration of Study after Baseline (days)

[0 - 57, 58 - 169, 170-281, 282 - Max]

Revised Text

Duration of Study after Baseline (days)

[Min - 57, 58 - 169, 170-281, 282 - Max]

Rationale for Amendment

To correct typo.

Page 24, Section 7.4

Existing Text

Previous use of Immunosupressants [Yes, No]

Topography of Internal IOs and EOs at Baseline

[1 IO, 2 IOs]

[2 EOs, 3 EOs]

[1 IO + 2 EOs, 1 IO + 3 EOs, 2IOs + 2 EOs, 2IOs + 3 EOs]

Revised Text

Previous use of Immunosuppressants [Yes, No]

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 IO + 1 EO, 1 IO + 2 EOs, 1 IO + 3 EOs, 2 IOs + 1 EO, 2 IOs + 2 EOs, 2 IOs + 3 EOs]

Rationale for Amendment

To correct typo and categories of topography of IOs and EOs at Baseline.

Page 25, Section 7.6

Existing Text

(new)

Revised Text

Concomitant medications whose start date occurred on or before Week 24 visit, i.e. the latest fistula clinical assessment or the latest visit by Day 198, will be summarized.

Rationale for Amendment

Clarification of targeted concomitant medications analyzed using data up to Week 24.

Page 26, Section 7.7

Existing Text

Analysis Variables:

(new)

Revised Text

Analysis Variables:

Duration of follow-up after baseline by Week 24 (weeks)

Rationale for Amendment

To add summary of duration of follow-up after baseline by Week 24.

Page 28, Section 7.8.2.4

Existing Text

Within the subjects with clinical remission at previous visit, the following analyses will be performed. For the following time to event analyses, subjects without event will be handled as censor at the date of last fistula clinical assessment.

Revised Text

Within the subjects with clinical remission at previous visit, the following analyses will be performed. For the following time to event analyses, subjects without event will be handled as censor at the date of last fistula clinical assessment or last fistula MRI assessment.

Rationale for Amendment

To correct appropriate text.

Page 31, Section 7.8.4.2

Existing Text

In case of no MRI data by Week 24 or no post-baseline clinical assessment, non-response will be imputed. If rescue therapy which is not allowed in section 7.4 of the protocol occur prior to visit 8(Week 24), non-response will be imputed overriding all other imputation conventions.

Revised Text

In case of no MRI data by Week 24 or no post-baseline clinical assessment, non-response will be imputed. If rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly occur prior to visit 8(Week 24), non-response will be imputed overriding all other imputation conventions.

Rationale for Amendment

To align with revised text in the protocol amendment 3 section 13.1.3.3.

Page 32, Section 7.8.4.7

Existing Text

Analysis Variables:

Combined Remission at Week 24

Subgroups:

Previous use of Immunosupressants [Yes, No]

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[2 EOs, 3 EOs]

Revised Text

Analysis Variables:

Combined Remission at Week 24

Clinical Remission at Week 24

Response at Week 24

Subgroups:

Previous use of Immunosuppressants [Yes, No]

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 IO + 1 EO, 1 IO + (2<= EOs) , 2 IOs + (1<= EOs)]

Rationale for Amendment

To add analysis variables and subgroup category, and to correct typo and category of subgroups in topography of EOs at Baseline.

Page 32, Section 7.10.1

Existing Text

(new)

Revised Text

TEAEs whose date of onset occurred on or before Week 24 visit, i.e. the latest fistula clinical assessment or the latest visit by Day 198, will be summarized.

Rationale for Amendment

Clarification of targeted TEAEs analyzed using data up to Week 24.

Page 34, Section 7.10.1.2

Existing Text

Displays of Treatment-Emergent Adverse events

Revised Text

Displays of Treatment-Emergent Adverse Events

Rationale for Amendment

To correct typo.

Page 35, Section 7.10.1.2

Existing Text

(new)

Revised Text

7.10.1.3 Subgroup Analysis of Treatment-Emergent Adverse Events

Rationale for Amendment

To add subgroup analysis of TEAEs.

Page 35, Section 7.10.1.2

Existing Text

(new)

Revised Text

7.10.1.3 Subgroup Analysis of Treatment-Emergent Adverse Events

Rationale for Amendment

To add subgroup analysis of TEAEs.

Page 39, Section 7.10.3

Existing Text

Pulse Rate

Revised Text

Heart Rate

Rationale for Amendment

To correct typo.

Page 39-40, Section 7.10.4.1

Existing Text

Analysis Variables:

Anti-donor Antibody [Presence, Absence]

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24

Analytical Methods:

Frequency distributions will be provided.

Revised Text

Analysis Variables:

Donor Specific Antibody

[Presence, Absence]
(Categories used in analytical methods (1) and (2))

[Presence at baseline and Presence during post-baseline,
Presence at baseline and Absence during post-baseline,
Absence at baseline and Presence during post-baseline,
Absence at baseline and Absence during post-baseline]
(Categories used in analytical methods (3) and (4))

[Presence during post-baseline, Absence during post-baseline]
(Categories used in analytical method (4))

(Presence/Absence at baseline is results of anti-HLA antibody.)

(Presence/Absence during post-baseline is results of donor specific antibody during post-baseline by Week 24, i.e. Presence if any positive results during post-baseline by Week 24, Absence if no positive results during post-baseline by Week 24.)

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24

Analytical Methods:

(5) Summary of Donor Specific Antibody by Visit

Frequency distributions for each visit will be provided.

(6) Summary of Shifts of Donor Specific Antibody

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

(7) Number of Subjects in Categories of Donor Specific Antibody

Frequency distributions of results at baseline and during post-baseline will be provided.

(8) Subgroup Analysis of Efficacy and Safety Endpoints by Donor Specific Antibody

The same analyses of Section 7.8.4.7 and 7.10.1.3 will be conducted for each subgroup of Donor Specific Antibody.

Rationale for Amendment

Detailed categories and analytical methods of donor specific antibody as well as subgroup analysis of efficacy and safety by donor specific antibody was added.

Page 40, Section 7.10.4.2

Existing Text

TEAEs will be summarized in the same way as in section 7.10.1.2. All summaries will be presented in Japanese.

Revised Text

TEAEs will be summarized in the same way as in section 7.10.1.2 and 7.10.1.3. All summaries will be presented in Japanese.

Rationale for Amendment

To add Japanese summary of 7.10.1.3.

8.0 REFERENCES

Not applicable.

9.0 APPENDIX

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	16-Sep-2020 02:07 UTC

STATISTICAL ANALYSIS PLAN

[Analysis using Data up to Week 52]

STUDY NUMBER: Darvadstrocel-3002

A Phase 3, Multicenter, Open-Label, Uncontrolled Study to Evaluate the Efficacy and Safety of Cx601 in the Treatment of Complex Perianal Fistulas in Adult Patients with Crohn's Disease

PHASE 3

Version: 2nd

Date: 05 March 2021

Prepared by:

[redacted]

Based on:

Protocol Version: Amendment 4

Protocol Date: 6 October 2020

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDAI	Crohn's Disease Activity Index
DMEM	Dulbecco Modified Eagle's Medium
eASC	expanded allogeneic adipose-derived stem cells
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EO	External Opening
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HSA	human serum albumin
ICH	International Conference on Harmonisation
IL	interleukin
INR	international normalized ratio
IO	Internal Opening
IRB	institutional review board
ITT	intention to treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intention to treat
MRI	magnetic resonance imaging
PCR	polymerase chain reaction
PDAI	Perianal Disease Activity Index
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per protocol set
PTE	Pretreatment event
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction

TEAE	treatment-emergent AE
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell

4.0 OBJECTIVES

4.1 Primary Objectives

- To evaluate the efficacy of Cx601 for the treatment of complex perianal fistulas in adult patients with Crohn's disease over 24 weeks.

4.2 Secondary Objectives

- To evaluate the efficacy of Cx601 for the treatment of complex perianal fistulas in adult patients with Crohn's disease over 52 weeks.
- To evaluate the safety of Cx601 for the treatment of perianal fistulas in adult patients with Crohn's disease over minimum 156 weeks.

4.3 Additional Objectives

- To evaluate the absence of clinically relevant alloreactivity.
- To evaluate the effects of Cx601 on Crohn's disease activity and quality of life.

4.4 Study Design

This is Phase 3, a multicenter, open-label, uncontrolled study to evaluate the efficacy and safety of Cx601 in the treatment of complex perianal fistulas in adult patients with Crohn's disease.

Subjects with Crohn's disease whose complex perianal fistulas were previously treated and refractory (inadequate response, loss of response or intolerance) to at least one of the following treatments: antibiotics, immunosuppressants or biologics (anti-TNFs, anti-integrin or anti-IL-12/23) will be included in the study. Note that those subjects who are refractory to antibiotics only will be must be less than 25% of all subjects enrolled.

The study will permit continuation of baseline treatments for Crohn's disease in an add-on design (ie, biologics, immunosuppressants, etc.) . A total of 20 subjects are planned to be enrolled, and study product, cell suspension containing 120×10^6 cells of eASCs, will be intralesionally injected to all participants. Since this is the first study of Cx601 in Japanese subjects, the enrollment of at least the first 3 subjects will be adjusted not to be administered the study product at the same day.

This study consists of the screening period (approximately 5 weeks prior to study product administration, including the screening visit and the preparation visit), the treatment period (the day of study product administration) , the follow-up period (approximately 52 weeks after study product administration), a nd the long-term follow-up period (from Week 52 to Week 156 or later; for a minimum of 104 weeks) . Cx601 will be administrated once on Day 1, and the efficacy and safety of Cx601 will be mainly evaluated in the subsequent 52-week follow-up period. The primary endpoint will be evaluated at Week 24. Additionally, in the long-term follow-up period after Week 52, a safety follow-up evaluation will be performed for all subjects every 26 weeks (6 months) until Week 156 or later.

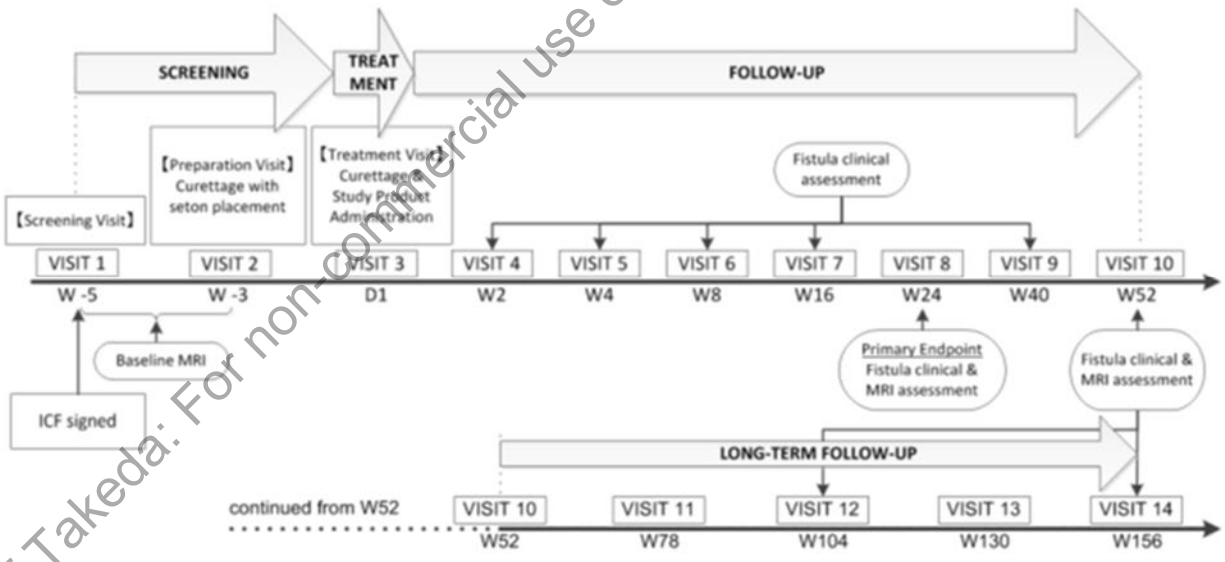
In the screening period, a screening visit (Visit 1) to determine a subject's eligibility is scheduled during the period from Day -39 to the day before preparation. All the subjects eligible by the screening will receive fistula curettage and seton placement under anesthesia at the preparation visit (Visit 2: Day -21, done no later than Day -14). Seton(s) placed will be removed on the day of study product administration (Visit 3: Day 1), just before the administration of the study product. Appropriate training for the preparation and the administration will be implemented to standardize the procedures between study sites.

The subjects who meet all the eligibility criteria will visit the study site on Day 1, and receive fistula curettage under anesthesia and an intralesional injection of cell suspension containing 120×10^6 cells of eASCs (Cx601). Thereafter, in follow-up period, the subjects will visit the study site for the clinical assessments including fistula closure at Weeks 2, 4, 8, 16, 24, 40 and 52. Radiological assessments (MRI) of fistula closure will also be performed at Weeks 24 and 52.

Additionally, in the long-term follow-up period, the safety follow-up will be performed on all the subjects (where possible) every 26 weeks (6 months) from a visit in Week 52 through Week 156. This study will be switched to a post-marketing clinical study if Cx601 is approved before the study completion.

A schematic study design is shown in Figure 4.a.

Figure 4.a Schematic Study Design



5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

- Proportion of subjects with combined remission at Week 24.

5.2 Secondary Endpoints

Efficacy analysis using data up to Week 24:

- Proportion of subjects with clinical remission at Week 24.
- Proportion of subjects with response at Week 24.
- Time to clinical remission by Week 24.
- Time to response by Week 24.
- Proportion of subjects with relapse at Week 24 in subjects with clinical remission at previous visit.
- Time to relapse by Week 24 in subjects with clinical remission at previous visit.
- PDAI score (including total score, discharge sub-score and pain sub-score) up to Week 24.
- CDAI score up to Week 24.
- Van Assche score up to Week 24.

Efficacy analysis using data up to Week 52:

- Proportion of subjects with combined remission at Week 52.
- Proportion of subjects with clinical remission at Week 52.
- Proportion of subjects with response at Week 52.
- Time to combined remission by Week 52.
- Time to clinical remission by Week 52.
- Time to response by Week 52.
- Proportion of subjects with relapse at Week 52 in subjects with combined remission at Week 24.
- Time to relapse by Week 52 in subjects with combined remission at Week 24.
- PDAI score (including total score, discharge sub-score and pain sub-score) up to Week 52.
- CDAI score up to Week 52.
- Van Assche score up to Week 52.

5.3 Safety Endpoints

- Adverse events (AEs) including serious adverse events (SAEs) and AEs of special interest.
- Product malfunctions.
- Physical examination findings.

- Vital signs (heart rate, blood pressure, body temperature).
- Clinical laboratory test results (serum chemistry, hematology and urinalysis).

5.4 Additional Endpoints

- Presence/absence of anti-donor antibody.

6.0 DETERMINATION OF SAMPLE SIZE

The planned sample size is 20 based on feasibility. However, this study has at least 94% probability to show a proportion of subjects with combined remission of 35% or more given an expected proportion of subjects with combined remission of 50% based on Week 24 results in the Cx601-0302 study.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after receiving study treatment.
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to study treatment administration.
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Duration of study after baseline (days): Date of last visit/contact - date of study treatment administration + 1.
  If subject is ongoing, date of last visit/contact will be imputed by date of data cut off.
- Duration of follow-up after baseline by Week 52 (weeks): (Date of the latest fistula clinical assessment or the latest visit by Day 448 – date of study treatment administration + 1)/7.
- Duration of Crohn's Disease (years): (Date of informed consent - date of Crohn's disease diagnosis)/365.25.
  (If month of diagnosis is missing, month will be replaced with January. If day of diagnosis is missing, day will be replaced with 1st.)
- Combined remission: Defined as the clinically confirmed closure of all treated external openings that were draining at the screening despite gentle finger compression, and absence of collections >2 cm in the treated fistulas which is confirmed by the central MRI assessment

(a collection >2 cm is considered as present if at least two out of the 3 dimensions centrally assessed are >2 cm in any of fistula tract).

- Clinical remission: Defined as the clinically confirmed closure of all treated external openings that were draining at the screening despite gentle finger compression.
- Response: Defined as the clinically confirmed closure of at least 50% of all treated external openings that were draining at the screening despite gentle finger compression. Note: Clinically confirmed closure of at least 50% is defined as 1 closure for subjects with 1 baseline external opening, 1 or 2 closures for subjects with 2 baseline external openings, and 2 or 3 closures for subjects with 3 baseline external openings.
- Relapse: Defined as the clinically confirmed reopening of any of the treated external openings with active drainage, or the development of a collection >2 cm in the treated fistulas confirmed by central MRI assessment
  (a collection >2 cm is considered as present if at least two out of the 3 dimensions centrally assessed are >2 cm in any of fistula tract).
- Time to combined remission/clinical remission/response (days): The time from the study treatment administration to the first visit by which combined remission/clinical remission/response is observed.
  For combined remission, date is the latest of fistula MRI assessment and fistula clinical assessment.
- Time to relapse (days): The time from the first visit which clinical remission is observed to the first visit by which relapse is observed.
  (Time to relapse by Week 52 in subjects who achieved combined remission at Week 24 is defined as "the time from the combined remission at Week 24 to the first visit by which relapse is observed.)
- Presence/Absence of donor specific antibody: Results for each post-baseline visit will be presence when at least one of donor specific antibody tests (Class I and/or Class II) is presence, otherwise results will be absence. A result at baseline will represent presence/absence of anti-HLA Class I and Class II antibody.
- CDAI total score: CDAI total score and body weight will be cut-off by -10, ie, score below -10 will be treated as -10.

7.1.2 Definition of Study Days

The following definitions and calculation formulas will be used.

- Study Day: The day before study treatment administration will be defined as Study Day -1 and the day of the study treatment administration will be defined as Study Day 1. If the date of the observation is on the same date or after the day of the study treatment administration, Study Day will be calculated relative to Study Day 1. Otherwise, Study Day will be calculated relative to Study Day -1.

7.1.3 Definition of Study Visit Windows

When calculating Study Day relative to a reference date (ie, study treatment administration [Day 1]), if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

7.1.3.1 Fistula Assessment

All evaluable data (ie, non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the largest Study Day will be used.

Table 7.a Visit Window of Fistula MRI Assessment

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	Day Before Preparation	- Day Before Preparation
Week 24	Study Day:	169	2 - 198
Week 52	Study Day:	365	199 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -
Week 24(LOCF)	Study Day:		2 - 198
Week 52(LOCF)	Study Day:		2 - 448
Week 104(LOCF)	Study Day:		2 - 812
Week 156(LOCF)	Study Day:		2 -

Table 7.b Visit Window of Fistula Clinical Assessment

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	Day Before Preparation	- Day Before Preparation
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -
Week 2(LOCF)	Study Day:		2 - 22
Week 4(LOCF)	Study Day:		2 - 43
Week 8(LOCF)	Study Day:		2 - 85
Week 16(LOCF)	Study Day:		2 - 141
Week 24(LOCF)	Study Day:		2 - 198
Week 40(LOCF)	Study Day:		2 - 323
Week 52(LOCF)	Study Day:		2 - 448
Week 104(LOCF)	Study Day:		2 - 812
Week 156(LOCF)	Study Day:		2 -

7.1.3.2 Endpoints Other Than Fistula Assessment

All evaluable data (ie, non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day for others, the later observation will be used.

Table 7.c Visit Window of PDAI Score

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -

Table 7.d Visit Window of CDAI Score

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 24	Study Day:	169	2 - 198
Week 52	Study Day:	365	199 - 448
Week 156	Study Day:	1093	449 -

Table 7.e Visit Window of Van Assche Score

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	-35	-39 - -1
Week 24	Study Day:	169	1 - 198
Week 52	Study Day:	365	199 - 448
Week 156	Study Day:	1093	449 -

Table 7.f Visit Window of Vital Signs

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 78	Study Day:	547	449 - 638
Week 104	Study Day:	729	639 - 812
Week 130	Study Day:	911	813 - 1002
Week 156	Study Day:	1093	1003 -

Table 7.g Visit Window of Clinical Laboratory Tests

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 52	Study Day:	365	199 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -

Table 7.h Visit Window of Anti-donor Antibody Test

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 52	Study Day:	365	199 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -

7.1.4 Significance Level and Confidence Coefficient

- Confidence coefficient: 90% (two-sided), 95% (two-sided).

7.1.5 Calculation of Combined Remission, Clinical Remission, Response

- Combined Remission at Week 24(Primary endpoint)
  Fistula MRI assessment at Week 24(LOCF) and fistula clinical assessment at Week 24(LOCF) will be used when combined remission at Week 24 is calculated based on the definition of section 7.1.1.
  If either of the two is missing, non-remission will be imputed.
  If a subject received rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly prior to visit 8(Week 24) will be handled as non-remission.

- Clinical Remission, Response at Week 24(Secondary endpoint).
  Fistula clinical assessment at Week 24(LOCF) will be used when clinical remission or response at Week 24 is calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, non-remission(non-response) will be imputed.
  If a subject received rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly prior to visit 8(Week 24) will be handled as non-remission.

- Combined Remission at Week 52(Secondary endpoint).
  Fistula MRI assessment at Week 52(LOCF) and fistula clinical assessment at Week 52(LOCF) will be used when combined remission at Week 52 is calculated based on the definition of section 7.1.1.
  If either of the two is missing, non-remission will be imputed.

- Clinical Remission, Response at Week 52(Secondary endpoint).
  Fistula clinical assessment at Week 52(LOCF) will be used when clinical remission or response at Week 52 is calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, non-remission(non-response) will be imputed.
- Combined Remission at Week 104/Week 156(Additional endpoint).
  Fistula MRI assessment at Week 104(LOCF)/Week 156(LOCF) and fistula clinical assessment at Week 104(LOCF)/156(LOCF) will be used when combined remission at Week 104/Week 156 are calculated based on the definition of section 7.1.1.
  If either of the two is missing, non-remission will be imputed.
- Clinical Remission, Response at Week 104/Week 156(Additional endpoint).
  Fistula clinical assessment at Week 104(LOCF)/Week 156(LOCF) will be used when clinical remission or response at Week 104/Week 156 are calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, non-remission(non-response) will be imputed.
- Clinical Remission, Response for Time Point Analysis(Additional endpoint).
  Fistula clinical assessment at each analysis visit after baseline in Table 7.b other than LOCF will be used when clinical remission or response for each time point analysis is calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, it will be handled as missing.

7.1.6 Calculation of Relapse in Subjects with Clinical/Combined Remission

- Relapse at Week 24 in subjects with clinical remission at previous visit.

The first clinical remission date before Day 198 will be identified. Per subject with clinical remission above, subject will be defined as relapsed if there is a fistula MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the first clinical remission and by Day 198 based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 52 in subjects with combined remission at Week 24.

The combined remission date at Week 24(latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 198, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the combined remission date and by Day 448 based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 104 in subjects with combined remission at Week 52.

The combined remission date at Week 52(latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 448, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings

with active drainage after the combined remission date and by Day 812 based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 156 in subjects with combined remission at Week 104.

The combined remission date at Week 104(latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 812, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the combined remission date based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

7.2 Analysis Sets

- Intention to treat (ITT):
  All subjects who have enrolled into treatment period.
- Modified intention to treat (mITT):
  All subjects who have received the study treatment and whose primary efficacy endpoint is evaluable.
- Per protocol set (PPS):
  All subjects who have completed the minimum protocol-specified procedures without any major protocol deviations (ie, subjects who met the following criteria will be excluded from the PPS).
  - Subjects who did not meet inclusion criteria #3, #5, #6, or #7.
  - Subjects who met exclusion criteria #1, #2, #3, #4, #5, #6, #7, #8, #9, #10, #11, #21, #23, #24, #25, or #27.
  - Subjects who have violated the rules for medications and treatments specified in section 7.3 of the protocol prior to visit 8 (Week 24).
  - Subjects who have violated the rules for rescue therapy specified in section 7.4 of the protocol prior to visit 8 (Week 24).
  - Subjects who received less than 24 mL of the study treatment.
  - Subjects who did not have either fistula MRI assessment or fistula clinical assessment 45 days prior to or post Study Day 169.
- Safety analysis set:
  All subjects who have received the study treatment.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date First Subject Signed Informed Consent Form

Date of Last Subject's Last Visit/Contact

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variables:

Age (years)

Gender [Male, Female]

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Eligibility Status

[Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]

Primary Reason for Subject Not Being Eligible

[Death, Adverse Event, Screen Failure, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical Methods:

(1) Eligibility for Entrance into the Treatment Period

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Status of Entrance into the Treatment Period [Entered]

Stratum:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Who Entered the Treatment Period by Site

Frequency distributions will be provided for each stratum.

7.3.5 Disposition of Subjects for Follow-up Period

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Study Treatment Administration Status

[Eligible but Not Treated]

Reason for Not Being Treated

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Completion Status for Follow-up Period

[Completed, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

(2) Completion Status for Follow-up Period

Frequency distributions will be provided for Completion Status for Follow-up Period(categories of Completed, Ongoing and Prematurely Discontinued).

7.3.6 Completion Status for Follow-up Period

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Completion Status for Follow-up Period

[Completed, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Categories:

Duration of Study after Baseline (days)

[Min - 57, 58 - 169, 170-281, 282 - Max]

Analytical Methods:

(1) Completion Status for Follow-up Period by Duration of Study after Baseline

Frequency distributions will be provided for each category of duration of study after baseline.

7.3.7 Disposition of Subjects for Long-Term Follow-up Period

Analysis Set:

All Subjects Who Completed the Follow-up period

Analysis Variables:

Completion Status for Long-Term Follow-up Period

[Completed/Ongoing, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

(2) Completion Status for Long-Term Follow-up Period

Frequency distributions will be provided for Completion Status for Long-Term Follow-up Period (categories of Completed, Ongoing and Prematurely Discontinued).

7.3.8 Completion Status for Long-Term Follow-up Period

Analysis Set:

All Subjects Who Completed the Follow-up Period

Analysis Variables:

Completion Status for Long-Term Follow-up Period

[Completed/Ongoing, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Categories:

Duration of Study after Baseline (days)

[Min - 547, 548 - 729, 730-911, 912 - Max]

Analytical Methods:

(1) Completion Status for Long-Term Follow-up Period

Frequency distributions will be provided for each category of duration of study after baseline.

7.3.9 Protocol Deviations and Analysis Sets

7.3.9.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria]

Analytical Methods:

(1) Protocol Deviations

Frequency distributions will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.9.2 Analysis Sets

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Handling of Subjects

[Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

Intention to Treat	[Included]
Modified Intention to Treat	[Included]
Per Protocol Set	[Included]
Safety Analysis Set	[Included]

Analytical Methods:

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:

Intention to Treat

Analysis Variables:

Age (years) [Min<= - <=65, 65< - <=Max]

Gender [Male, Female]

Height (cm)

Weight (kg)

BMI (kg/m^2)

Smoking Classification [Never, Current, Former]

Previous use of Antibiotics [Yes, No]

Previous use of Immunosuppressants [Yes, No]

Previous use of Biologics [Yes, No]

Concomitant Medications [Biologics only, Immunosuppressants only, Biologics+Immunosuppressants, None of 2 types of concomitant drugs]

Duration of Crohn's Disease (years)

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 IO + 1 EO, 1 IO + 2 EOs, 1 IO + 3 EOs, 2 IOs + 1 EO, 2 IOs + 2 EOs, 2 IOs + 3 EOs]

Topography of Draining EOs at Screening

[0 EO, 1 EO, 2 EOs, 3EOs]

CDAI Total Score at Baseline [Min<= - <150, 150<= - <=220, 220< - <=Max]

Analytical Methods:

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.5 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Concomitant medications whose start date occurred on or before Week 52 visit, ie, the latest fistula clinical assessment or the latest visit by Day 448, will be summarized.

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medication History

Concomitant Medications

Analytical Methods:

(1) Medication History by Preferred Medication Name.

(2) Concomitant Medications That Started and Stopped Prior to Baseline by Preferred Medication Name.

(3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline by Preferred Medication Name.

(4) Concomitant Medications That Started After Baseline by Preferred Medication Name.

(5) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name.

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variables:

Total Exposure (mL)

Total Exposure per IOs (mL)

Total Exposure per EOs (mL)

Duration of follow-up after baseline by Week 52 (weeks)

Analytical Methods:

(1) Summary of Total Exposure

Descriptive statistics will be provided.

7.8 Efficacy Analysis

7.8.1 Secondary Endpoints

Efficacy analysis using data up to Week 52

7.8.1.1 Proportion of Subjects with Combined Remission, Clinical Remission and Response at Week 52

Analysis Set:

Intention to Treat

Analysis Variables:

Combined Remission at Week 52

Clinical Remission at Week 52

Response at Week 52

Analytical Methods:

Frequency distributions will be provided with proportion and the two-sided 90% and 95% confidence intervals(Wald's method).

7.8.1.2 Proportion of Subjects with Relapse at Week 52 in subjects with combined remission at Week 24

Analysis Set:

Intention to Treat

Analysis Variables:

Relapse at Week 52

Analytical Methods:

(1) Number and Percentage of Subjects with Relapse at Week 52
Within the subjects with combined remission at Week 24, frequency distributions will be provided with proportion and the two-sided 90% and 95% confidence intervals(Wald's method).

7.8.1.3 Proportion of Subjects with Combined Remission at Week 52 and combined remission at Week 24

Analysis Set:

Intention to Treat

Analysis Variables:

Combined Remission at Week 24 and Week 52

Analytical Methods:

(1) Number and Percentage of Subjects with Combined Remission at Week 24 and Week 52
For the number and percentage of subjects with combined remission at Week 24 and Week 52 as well as the number and percentage of subjects with combined remission at Week 24 and without combined remission at Week 52, frequency distributions will be provided with proportion and the two-sided 90% and 95% confidence intervals(Wald's method).

7.8.1.4 Time to Combined Remission, Clinical Remission and Response by Week 52

Analysis Set:

Intention to Treat

Analysis Variables:

Time to Combined Remission by Week 52

Time to Clinical Remission by Week 52

Time to Response by Week 52

Analytical Methods:

For the following time to event analyses, subjects without event will be handled as censor at the date of last fistula clinical assessment.

(1) Summary of Time to Event by Week 52
Frequency distribution of subjects who experienced event and who were censored will be provided. Quartiles of time to event will be estimated using the Kaplan-Meier method.

(2) Kaplan-Meier Plot
Kaplan-Meier plot of time to combined remission, clinical remission, and response by Week 52 will be provided.

7.8.1.5 Time to Relapse by Week 52

Analysis Set:

Intention to Treat

Analysis Variables:

Time to Relapse by Week 52

Analytical Methods:

Within the subjects with combined remission at Week 24, the following analyses will be performed. For the following time to event analyses, subjects without event will be handled as censor at the date of last fistula clinical assessment or last fistula MRI assessment.

(1) Summary of Time to Event by Week 52
Frequency distribution of subjects who experienced event and who were censored will be provided. Quartiles of time to event will be estimated using the Kaplan-Meier method.

(2) Kaplan-Meier Plot
Kaplan-Meier plot of time to relapse by Week 52 will be provided.

7.8.1.6 PDAI Score

Analysis Set:

Intention to Treat

Analysis Variables:

PDAI Total Score

PDAI Domain Scores(Discharge, Pain/restriction of activities, Restriction of Sexual Activity, Type of Perianal Disease, Degree of Induration)

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 40, Week 52

Analytical Methods:

(1) Summary of PDAI Scores and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline for each visit will be provided.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted for each visit with standard deviation bars.

7.8.1.7 CDAI Score

Analysis Set:

Intention to Treat

Analysis Variables:

CDAI Total Score [Min<= - <150, 150<= - <=220, 220< - <=450, 450< - <=Max]

CDAI Sub Scores

Visit:

Baseline, Week 24, Week 52

Analytical Methods:

(1) Summary of CDAI Scores and Change from Baseline by Visit
Frequency distribution for categorical variables and descriptive statistics of observed values and changes from baseline for each visit will be provided.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted for each visit with standard deviation bars.

7.8.1.8 Van Assche Score

Analysis Set:

Intention to Treat

Analysis Variables:

Van Assche Total Score

Van Assche Domain Scores

Visit:

Baseline, Week 24, Week 52

Analytical Methods:

(1) Summary of Van Assche Scores and Change from Baseline by Visit
Frequency distribution for categorical variables and descriptive statistics of observed values and changes from baseline for each visit for continuous variables will be provided.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted for each visit with standard deviation bars for continuous variables.

7.8.2 Additional Endpoints

Efficacy analysis using data up to Week 52

7.8.2.1 Timepoint Analysis of Clinical Remission and Response

Analysis Set:

Intention to Treat

Analysis Variables:

Clinical Remission

Response

Visit:

Week 2, Week 4, Week 8, Week 16, Week 24, Week 40, Week 52

Analytical Methods:

The same analysis for the primary endpoint will be performed by visit.

7.8.3 Statistical/Analytical Issues

7.8.3.1 Adjustments for Covariates

Not applicable.

7.8.3.2 Handling of Dropouts or Missing Data

Values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values above the upper limit of quantification will be treated as the upper limit of quantification when calculating the descriptive statistics.

For combined remission, clinical remission, response

For the primary and secondary analyses of the primary endpoint, the last observation carried forward (LOCF) from the latest earlier post-baseline visit (including an Early Termination Visit prior to Week 24, if applicable) will apply in case of missing clinical assessment at Week 24. In case of missing MRI data at Week 24, LOCF from an Early Termination Visit prior to Week 24 will apply if applicable. In case of no MRI data by Week 24 or no post-baseline clinical assessment, non-response will be imputed. If rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly occur prior to visit 8(Week 24) , non-response will be imputed overriding all other imputation conventions.

The handling above for the primary endpoint will also be applied to proportion of subjects with clinical remission at Week 24, proportion of subjects with response at Week 24, proportion of subjects with combined remission at Week 52, proportion of subjects with clinical remission at Week 52 and proportion of subjects with response at Week 52 (but handling of rescue therapy will not be applied for Week 52) .

7.8.3.3 Multicenter Studies

Although this study is a multicenter study, treatment-by-center interaction will not be explored since the number of subjects for each center is not sufficient for such exploration.

7.8.3.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.3.5 Use of an "Efficacy Subset" of Subjects

In addition to analyses on the primary endpoint using the intention to treat, a secondary analysis will also be performed using the modified intention to treat and the per protocol set to confirm the robustness of the results.

7.8.3.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.3.7 Examination of Subgroups

Efficacy analysis using data up to Week 52

Analysis Set:

Intention to treat

Analysis Variables:

Combined Remission at Week 52

Clinical Remission at Week 52

Response at Week 52

Subgroups:

Age [Min<= - <=65, 65< - <=Max]

Gender [Male, Female]

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 IO + 1 EO, 1 IO + (2<= EOs), 2 IOs + (1<= EOs)]

Previous use of Antibiotics [Yes, No]

Previous use of Immunosuppressants [Yes, No]

Previous use of Biologics [Yes, No]

Concomitant Medications [Biologics only, Immunosuppressants only, Biologics+Immunosuppressants, None of 2 types of concomitant drugs]

Analytical Methods:

(1) Descriptive Statistics

Frequency distributions will be provided for above each subgroups.

7.9 Other Outcomes

Not applicable.

7.10 Safety Analysis

Safety analysis using data up to Week 52

7.10.1 Adverse Events

TEAEs whose date of onset occurred on or before Week 52 visit, ie, the latest fistula clinical assessment or the latest visit by Day 448, will be summarized.

7.10.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Relationship to Study Treatment [Related, Not Related]

Intensity [Mild, Moderate, Severe]

Analytical Methods:

The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
2) Relationship of Treatment-Emergent Adverse Events to study treatment (number of events, number and percentage of subjects).
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).

4) Treatment-Emergent Adverse Events leading to study discontinuation (number of events, number and percentage of subjects).
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
6) Relationship of serious Treatment-Emergent Adverse Events to study treatment (number of events, number and percentage of subjects).
7) Serious Treatment-Emergent Adverse Events leading to study discontinuation (number of events, number and percentage of subjects).
8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects).

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- Summaries other than 2), 3), and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

7.10.1.2 Displays of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Intensity	[Mild, Moderate, Severe]
Time of Onset (day)	[1 - 57, 58 - 169, 170-281, 282 - Max]

Analytical Methods:

The following summaries will be provided using frequency distribution.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Study Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Study Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(10) Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term

(11) Product Malfunction-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distributions will be provided according to the rules below.

Number of subjects

- Summary tables other than (5), (6) and (9)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

- Summary table for (9)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. Percentages will be based on the number of subjects in the safety analysis set.

7.10.1.3 Subgroup Analysis of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Subgroups:

Age [Min<= - <=65, 65< - <=Max]

Gender [Male, Female]

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 EO, 2 <= EOs]

Previous use of Antibiotics [Yes, No]

Previous use of Immunosuppressants [Yes, No]

Previous use of Biologics [Yes, No]

Concomitant Medications [Biologics only, Immunosuppressants only, Biologics+Immunosuppressants, None of 2 types of concomitant drugs]

Analytical Methods:

The following summaries will be provided for each subgroup using frequency distribution. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set for each subgroup.

7.10.1.4 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

PTE

Analytical Methods:

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term.

(2) Serious Pretreatment Events by System Organ Class and Preferred Term.

The frequency distributions will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.10.2 Clinical Laboratory Evaluations

7.10.2.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Hemoglobin, Hematocrit, Red blood cells count, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, White blood cells count, differential WBC (Neutrophils, Basophils, Eosinophils, Lymphocytes, Monocytes), Platelet count

Serum Chemistry

C-reactive protein, ALT, AST, Alkaline phosphatase, Gamma-glutamyl transpeptidase, Total bilirubin, Total protein, Glucose, Creatinine, Creatine phosphokinase, Blood urea nitrogen, Potassium, Sodium, Chloride

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 52

Analytical Methods:

For each variable, summaries (1) to (3) will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

7.10.2.2 Urinalysis

Analysis Set:

Safety Analysis Set

Analysis Variables:

Specific Gravity

pH

Glucose	[-, +-, +, 2+, 3+]
Protein	[-, +-, +, 2+, 3+]
Occult blood	[-, +-, +, 2+, 3+]
Ketone body	[-, +-, +, 2+, 3+]
Bilirubin	[-, +-, +, 2+, 3+]
Urobilinogen	[+-, +, 2+, 3+]

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 52

Analytical Methods:

For specific gravity, summaries (1), (2) and (4) will be provided.

For pH, summary (4) will be provided.

For each variable other than specific gravity or pH, summaries (3) and (4) will be provided.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

(4) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each urine laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" for specific gravity and pH, classified as "Normal" or "Abnormal" for others relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

7.10.3 Vital Signs

Analysis Set:

Safety Analysis Set

Analysis Variables:

Temperature

Systolic Blood Pressure

Diastolic Blood Pressure

Heart Rate

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 40, Week 52

Analytical Methods:

For each variable, summaries (1) and (2) will be provided

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

7.10.4 Other Observations Related to Safety

7.10.4.1 Donor Specific Antibody

Analysis Set:

Safety Analysis Set

Analysis Variables:

Donor Specific Antibody

[Presence, Absence]
(Categories used in analytical methods (1) and (2))

[Presence at baseline and Presence during post-baseline by Week 24,
Presence at baseline and Absence during post-baseline by Week 24,
Absence at baseline and Presence during post-baseline by Week 24,
Absence at baseline and Absence during post-baseline by Week 24]

[Presence at baseline and Presence during post-baseline by Week 52,
Presence at baseline and Absence during post-baseline by Week 52,
Absence at baseline and Presence during post-baseline by Week 52,
Absence at baseline and Absence during post-baseline by Week 52]

(Categories used in analytical methods (3) and (4))

[Presence at baseline and Presence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52,
Presence at baseline and Presence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52,
Presence at baseline and Absence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52,
Presence at baseline and Absence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52,
Absence at baseline and Presence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52,
Absence at baseline and Presence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52,
Absence at baseline and Absence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52,
Absence at baseline and Absence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52]
(Categories used in analytical methods (3))

[Presence during post-baseline by Week 24, Absence during post-baseline by Week 24]

[Presence during post-baseline by Week 52, Absence during post-baseline by Week 52]
(Categories used in analytical method (4))

(Presence/Absence at baseline is results of anti-HLA antibody.)

(Presence/Absence during post-baseline is results of donor specific antibody during post-baseline by Week 24/52, ie, Presence if any positive results during post-baseline by Week 24/52, Absence if no positive results during post-baseline by Week 24/52.)

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 52

Analytical Methods:

(1) Summary of Donor Specific Antibody by Visit

Frequency distributions for each visit will be provided.

(2) Summary of Shifts of Donor Specific Antibody

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

(3) Number of Subjects in Categories of Donor Specific Antibody

Frequency distributions of results at baseline and during post-baseline by Week 24/52 as well as baseline, during post-baseline by Week 24 and during post-baseline after Week 24 by Week 52 will be provided.

(4) Subgroup Analysis of Efficacy and Safety Endpoints by Donor Specific Antibody

The same analyses of Section 7.8.3.7 and 7.10.1.3 will be conducted for each subgroup of Donor Specific Antibody based on results during post-baseline by Week 52. For the same analyses of Section 7.8.3.7, combined remission at Week 24, clinical remission at Week 24, response at Week 24 will be also analyzed for each subgroup of Donor Specific Antibody based on results during post-baseline by Week 24.

7.10.4.2 Displays of Treatment-Emergent Adverse Events (Japanese)

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Analytical Methods:

TEAEs will be summarized in the same way as in section 7.10.1.2 and 7.10.1.3. All summaries will be presented in Japanese.

7.11 Interim Analysis

There will not be any interim analysis. Note, the analysis using data up to Week 24 is the primary analysis for marketing application. Additionally, separate analyses using data up to Week 52 and overall data will be performed after all subjects complete Week 52 and Week 156 respectively.

7.12 Changes in the Statistical Analysis Plan

The analyses in the statistical analysis plan do not differ from the analyses specified in the protocol.

Changes from the previous version are listed below.

Page 38, Section 7.10.2.2

Existing Text

Occult blood	[-, +, 2+, 3+]
Bilirubin	[-, +, 2+, 3+]

Revised Text

Occult blood	[-, +-, +, 2+, 3+]
Bilirubin	[-, +-, +, 2+, 3+]

Rationale for Amendment

Modified category of occult blood.

Page 38, Section 7.10.2.2

Existing Text

(4) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each urine laboratory test, the laboratory values will be classified as “Low”, “Normal” or “High” relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

Revised Text

(4) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each urine laboratory test, the laboratory values will be classified as “Low”, “Normal” or “High” for specific gravity and pH, classified as “Normal” or

"Abnormal" for others relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

Rationale for Amendment

Further clarified category of abnormality classification.

8.0 REFERENCES

Not applicable.

9.0 APPENDIX

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	12-Mar-2021 13:31 UTC

STATISTICAL ANALYSIS PLAN

[Analysis using Data up to Week 156]

STUDY NUMBER: Darvadstrocel-3002

A Phase 3, Multicenter, Open-Label, Uncontrolled Study to Evaluate the Efficacy and Safety of Cx601 in the Treatment of Complex Perianal Fistulas in Adult Patients with Crohn's Disease

PHASE 3

Version: 1st

Date: 9 May 2022

Prepared by:

[redacted]

Based on:

Protocol Version: Amendment 5

Protocol Date: 13 April 2021

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDAI	Crohn's Disease Activity Index
DMEM	Dulbecco Modified Eagle's Medium
eASC	expanded allogeneic adipose-derived stem cells
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EO	External Opening
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HSA	human serum albumin
ICH	International Conference on Harmonisation
IL	interleukin
INR	international normalized ratio
IO	Internal Opening
IRB	institutional review board
ITT	intention to treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intention to treat
MRI	magnetic resonance imaging
PCR	polymerase chain reaction
PDAI	Perianal Disease Activity Index
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per protocol set
PTE	Pretreatment event
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent AE
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell

4.0 OBJECTIVES

4.1 Primary Objectives

- To evaluate the efficacy of Cx601 for the treatment of complex perianal fistulas in adult patients with Crohn's disease over 24 weeks.

4.2 Secondary Objectives

- To evaluate the efficacy of Cx601 for the treatment of complex perianal fistulas in adult patients with Crohn's disease over 52 weeks.
- To evaluate the safety of Cx601 for the treatment of perianal fistulas in adult patients with Crohn's disease over minimum 156 weeks.

4.3 Additional Objectives

- To evaluate the absence of clinically relevant alloreactivity.
- To evaluate the effects of Cx601 on Crohn's disease activity and quality of life.

4.4 Study Design

This is Phase 3, a multicenter, open-label, uncontrolled study to evaluate the efficacy and safety of Cx601 in the treatment of complex perianal fistulas in adult patients with Crohn's disease.

Subjects with Crohn's disease whose complex perianal fistulas were previously treated and refractory (inadequate response, loss of response or intolerance) to at least one of the following treatments: antibiotics, immunosuppressants or biologics (anti-TNFs, anti-integrin or anti-IL-12/23) will be included in the study. Note that those subjects who are refractory to antibiotics only will be must be less than 25% of all subjects enrolled.

The study will permit continuation of baseline treatments for Crohn's disease in an add-on design (ie, biologics, immunosuppressants, etc.) . A total of 20 subjects are planned to be enrolled, and study product, cell suspension containing 120×10^6 cells of eASCs, will be intralesionally injected to all participants. Since this is the first study of Cx601 in Japanese subjects, the enrollment of at least the first 3 subjects will be adjusted not to be administered the study product at the same day.

This study consists of the screening period (approximately 5 weeks prior to study product administration, including the screening visit and the preparation visit), the treatment period (the day of study product administration) , the follow-up period (approximately 52 weeks after study product administration) , and the long-term follow-up period (from Week 52 to Week 156 or later; for a minimum of 104 weeks) . Cx601 will be administrated once on Day 1, and the efficacy and safety of Cx601 will be mainly evaluated in the subsequent 52-week follow-up period. The primary endpoint will be evaluated at Week 24. Additionally, in the long-term

follow-up period after Week 52, a safety follow-up evaluation will be performed for all subjects every 26 weeks (6 months) until Week 156 or later.

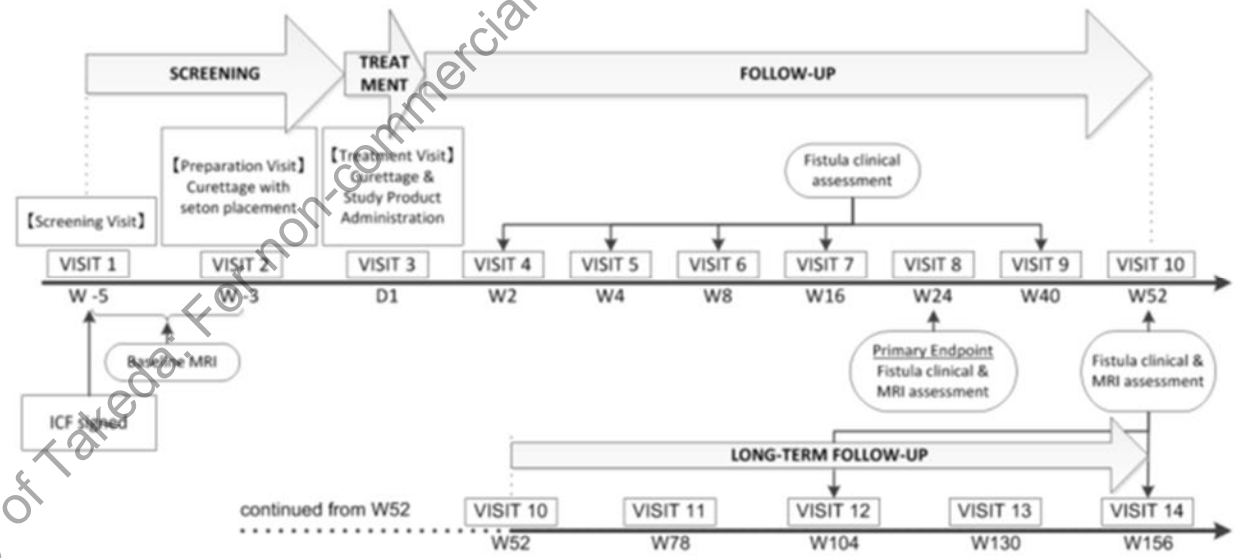
In the screening period, a screening visit (Visit 1) to determine a subject's eligibility is scheduled during the period from Day -39 to the day before preparation. All the subjects eligible by the screening will receive fistula curettage and seton placement under anesthesia at the preparation visit (Visit 2: Day -21, done no later than Day -14). Seton(s) placed will be removed on the day of study product administration (Visit 3: Day 1), just before the administration of the study product. Appropriate training for the preparation and the administration will be implemented to standardize the procedures between study sites.

The subjects who meet all the eligibility criteria will visit the study site on Day 1, and receive fistula curettage under anesthesia and an intralesional injection of cell suspension containing 120×10^6 cells of eASCs (Cx601). Thereafter, in follow-up period, the subjects will visit the study site for the clinical assessments including fistula closure at Weeks 2, 4, 8, 16, 24, 40 and 52. Radiological assessments (MRI) of fistula closure will also be performed at Weeks 24 and 52.

Additionally, in the long-term follow-up period, the safety follow-up will be performed on all the subjects (where possible) every 26 weeks (6 months) from a visit in Week 52 through Week 156. This study will be switched to a post-marketing clinical study if Cx601 is approved before the study completion.

A schematic study design is shown in Figure 4.a.

Figure 4.a Schematic Study Design



5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

- Proportion of subjects with combined remission at Week 24.

5.2 Secondary Endpoints

Efficacy analysis using data up to Week 24:

- Proportion of subjects with clinical remission at Week 24.
- Proportion of subjects with response at Week 24.
- Time to clinical remission by Week 24.
- Time to response by Week 24.
- Proportion of subjects with relapse at Week 24 in subjects with clinical remission at previous visit.
- Time to relapse by Week 24 in subjects with clinical remission at previous visit.
- PDAI score (including total score, discharge sub-score and pain sub-score) up to Week 24.
- CDAI score up to Week 24.
- Van Assche score up to Week 24.

Efficacy analysis using data up to Week 52:

- Proportion of subjects with combined remission at Week 52.
- Proportion of subjects with clinical remission at Week 52.
- Proportion of subjects with response at Week 52.
- Time to combined remission by Week 52.
- Time to clinical remission by Week 52.
- Time to response by Week 52.
- Proportion of subjects with relapse at Week 52 in subjects with combined remission at Week 24.
- Time to relapse by Week 52 in subjects with combined remission at Week 24.
- PDAI score (including total score, discharge sub-score and pain sub-score) up to Week 52.
- CDAI score up to Week 52.
- Van Assche score up to Week 52.

5.3 Safety Endpoints

- Adverse events (AEs) including serious adverse events (SAEs) and AEs of special interest.
- Product malfunctions.
- Physical examination findings.

- Vital signs (heart rate, blood pressure, body temperature).
- Clinical laboratory test results (serum chemistry, hematology and urinalysis).

5.4 Additional Endpoints

- Presence/absence of anti-donor antibody.

6.0 DETERMINATION OF SAMPLE SIZE

The planned sample size is 20 based on feasibility. However, this study has at least 94% probability to show a proportion of subjects with combined remission of 35% or more given an expected proportion of subjects with combined remission of 50% based on Week 24 results in the Cx601-0302 study.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after receiving study treatment.
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to study treatment administration.
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Duration of study after baseline (days): Date of last visit/contact - date of study treatment administration + 1.
  If subject is ongoing, date of last visit/contact will be imputed by date of data cut off.
- Duration of follow-up after baseline by Week 156 (weeks): (Date of the latest fistula clinical assessment or the latest visit – date of study treatment administration + 1)/7.
- Duration of Crohn's Disease (years): (Date of informed consent - date of Crohn's disease diagnosis)/365.25.
  (If month of diagnosis is missing, month will be replaced with January. If day of diagnosis is missing, day will be replaced with 1st.)
- Combined remission: Defined as the clinically confirmed closure of all treated external openings that were draining at the screening despite gentle finger compression, and absence of collections >2 cm in the treated fistulas which is confirmed by the central MRI assessment

(a collection >2 cm is considered as present if at least two out of the 3 dimensions centrally assessed are >2 cm in any of fistula tract).

- Clinical remission: Defined as the clinically confirmed closure of all treated external openings that were draining at the screening despite gentle finger compression.
- Response: Defined as the clinically confirmed closure of at least 50% of all treated external openings that were draining at the screening despite gentle finger compression. Note: Clinically confirmed closure of at least 50% is defined as 1 closure for subjects with 1 baseline external opening, 1 or 2 closures for subjects with 2 baseline external openings, and 2 or 3 closures for subjects with 3 baseline external openings.
- Relapse: Defined as the clinically confirmed reopening of any of the treated external openings with active drainage, or the development of a collection >2 cm in the treated fistulas confirmed by central MRI assessment
  (a collection >2 cm is considered as present if at least two out of the 3 dimensions centrally assessed are >2 cm in any of fistula tract).
- Time to combined remission/clinical remission/response (days): The time from the study treatment administration to the first visit by which combined remission/clinical remission/response is observed.
  For combined remission, date is the latest of fistula MRI assessment and fistula clinical assessment.
- Time to relapse (days): The time from the first visit which clinical remission is observed to the first visit by which relapse is observed.
  (Time to relapse by Week 104/Week 156 in subjects who achieved combined remission at Week 52/Week 104 is defined as "the time from the combined remission at Week 52/Week 104 to the first visit by which relapse is observed.)
- Presence/Absence of donor specific antibody: Results for each post-baseline visit will be presence when at least one of donor specific antibody tests (Class I and/or Class II) is presence, otherwise results will be absence. A result at baseline will represent presence/absence of anti-HLA Class I and Class II antibody.
- CDAI total score: CDAI total score and body weight will be cut-off by -10, i.e. score below -10 will be treated as -10.

7.1.2 Definition of Study Days

The following definitions and calculation formulas will be used.

- Study Day: The day before study treatment administration will be defined as Study Day -1 and the day of the study treatment administration will be defined as Study Day 1. If the date of the observation is on the same date or after the day of the study treatment administration, Study Day will be calculated relative to Study Day 1. Otherwise, Study Day will be calculated relative to Study Day -1.

7.1.3 Definition of Study Visit Windows

When calculating Study Day relative to a reference date (ie, study treatment administration [Day 1]), if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

7.1.3.1 Fistula Assessment

All evaluable data (ie, non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the largest Study Day will be used.

Table 7.a Visit Window of Fistula MRI Assessment

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	Day Before Preparation	- Day Before Preparation
Week 24	Study Day:	169	2 - 198
Week 52	Study Day:	365	199 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -
Week 24(LOCF)	Study Day:		2 - 198
Week 52(LOCF)	Study Day:		2 - 448
Week 104(LOCF)	Study Day:		2 - 812
Week 156(LOCF)	Study Day:		2 -

Table 7.b Visit Window of Fistula Clinical Assessment

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	Day Before Preparation	- Day Before Preparation
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -
Week 2(LOCF)	Study Day:		2 - 22
Week 4(LOCF)	Study Day:		2 - 43
Week 8(LOCF)	Study Day:		2 - 85
Week 16(LOCF)	Study Day:		2 - 141
Week 24(LOCF)	Study Day:		2 - 198
Week 40(LOCF)	Study Day:		2 - 323
Week 52(LOCF)	Study Day:		2 - 448
Week 104(LOCF)	Study Day:		2 - 812
Week 156(LOCF)	Study Day:		2 -

7.1.3.2 Endpoints Other Than Fistula Assessment

All evaluable data (ie, non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day for others, the later observation will be used.

Table 7.c Visit Window of PDAI Score

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -

Table 7.d Visit Window of CDAI Score

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 24	Study Day:	169	2 - 198
Week 52	Study Day:	365	199 - 448
Week 156	Study Day:	1093	449 -

Table 7.e Visit Window of Van Assche Score

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	-35	-39 - -1
Week 24	Study Day:	169	1 - 198
Week 52	Study Day:	365	199 - 448
Week 156	Study Day:	1093	449 -

Table 7.f Visit Window of Vital Signs

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 40	Study Day:	281	199 - 323
Week 52	Study Day:	365	324 - 448
Week 78	Study Day:	547	449 - 638
Week 104	Study Day:	729	639 - 812
Week 130	Study Day:	911	813 - 1002
Week 156	Study Day:	1093	1003 -

Table 7.g Visit Window of Clinical Laboratory Tests

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 52	Study Day:	365	199 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -

Table 7.h Visit Window of Anti-donor Antibody Test

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Baseline	Study Day:	1	-39 - 1
Week 2	Study Day:	15	2 - 22
Week 4	Study Day:	29	23 - 43
Week 8	Study Day:	57	44 - 85
Week 16	Study Day:	113	86 - 141
Week 24	Study Day:	169	142 - 198
Week 52	Study Day:	365	199 - 448
Week 104	Study Day:	729	449 - 812
Week 156	Study Day:	1093	813 -

7.1.4 Significance Level and Confidence Coefficient

- Confidence coefficient: 90% (two-sided), 95% (two-sided).

7.1.5 Calculation of Combined Remission, Clinical Remission, Response

- Combined Remission at Week 24(Primary endpoint)
  Fistula MRI assessment at Week 24(LOCF) and fistula clinical assessment at Week 24(LOCF) will be used when combined remission at Week 24 is calculated based on the definition of section 7.1.1.
  If either of the two is missing, non-remission will be imputed.
  If a subject received rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly prior to visit 8(Week 24) will be handled as non-remission.

- Clinical Remission, Response at Week 24(Secondary endpoint).
  Fistula clinical assessment at Week 24(LOCF) will be used when clinical remission or response at Week 24 is calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, non-remission(non-response) will be imputed.
  If a subject received rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly prior to visit 8(Week 24) will be handled as non-remission.

- Combined Remission at Week 52(Secondary endpoint).
  Fistula MRI assessment at Week 52(LOCF) and fistula clinical assessment at Week 52(LOCF) will be used when combined remission at Week 52 is calculated based on the definition of section 7.1.1.
  If either of the two is missing, non-remission will be imputed.

- Clinical Remission, Response at Week 52(Secondary endpoint).
  Fistula clinical assessment at Week 52(LOCF) will be used when clinical remission or response at Week 52 is calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, non-remission(non-response) will be imputed.
- Combined Remission at Week 104/Week 156(Additional endpoint).
  Fistula MRI assessment at Week 104(LOCF)/Week 156(LOCF) and fistula clinical assessment at Week 104(LOCF)/156(LOCF) will be used when combined remission at Week 104/Week 156 are calculated based on the definition of section 7.1.1.
  If either of the two is missing, non-remission will be imputed.
- Clinical Remission, Response at Week 104/Week 156(Additional endpoint).
  Fistula clinical assessment at Week 104(LOCF)/Week 156(LOCF) will be used when clinical remission or response at Week 104/Week 156 are calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, non-remission(non-response) will be imputed.
- Clinical Remission, Response for Time Point Analysis(Additional endpoint).
  Fistula clinical assessment at each analysis visit after baseline in Table 7.b other than LOCF will be used when clinical remission or response for each time point analysis is calculated based on the definition of section 7.1.1.
  If fistula clinical assessment is missing, it will be handled as missing.

7.1.6 Calculation of Relapse in Subjects with Clinical/Combined Remission

- Relapse at Week 24 in subjects with clinical remission at previous visit.

The first clinical remission date before Day 198 will be identified. Per subject with clinical remission above, subject will be defined as relapsed if there is a fistula MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the first clinical remission and by Day 198 based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 52 in subjects with combined remission at Week 24.

The combined remission date at Week 24(latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 198, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the combined remission date and by Day 448 based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 104 in subjects with combined remission at Week 52.

The combined remission date at Week 52(latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 448, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings

with active drainage after the combined remission date and by Day 812 based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 156 in subjects with combined remission at Week 104.

The combined remission date at Week 104(latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 812, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the combined remission date based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 156 in subjects with combined remission at Week 24.

The combined remission date at Week 24 (latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 198, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the combined remission date based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

- Relapse at Week 156 in subjects with combined remission at Week 52.

The combined remission date at Week 52 (latest date of MRI and clinical assessment, LOCF) will be identified. Per subject with combined remission above and who have at least one fistula MRI assessment or fistula clinical assessment after Day 448, the subject will be defined as relapsed if there is a MRI assessment of >2 cm or a clinical assessment of reopening of external openings with active drainage after the combined remission date based on the definition of section 7.1.1. Otherwise the subject will be defined as non-relapsed.

7.2 Analysis Sets

- Intention to treat (ITT):
  All subjects who have enrolled into treatment period.
- Modified intention to treat (mITT):
  All subjects who have received the study treatment and whose primary efficacy endpoint is evaluable.
- Per protocol set (PPS):
  All subjects who have completed the minimum protocol-specified procedures without any major protocol deviations (ie, subjects who met the following criteria will be excluded from the PPS).
  - Subjects who did not meet inclusion criteria #3, #5, #6, or #7.
  - Subjects who met exclusion criteria #1, #2, #3, #4, #5, #6, #7, #8, #9, #10, #11, #21, #23, #24, #25, or #27.

- Subjects who have violated the rules for medications and treatments specified in section 7.3 of the protocol prior to visit 8(Week 24).
- Subjects who have violated the rules for rescue therapy specified in section 7.4 of the protocol prior to visit 8(Week 24).
- Subjects who received less than 24 mL of the study treatment.
- Subjects who did not have either fistula MRI assessment or fistula clinical assessment 45 days prior to or post Study Day 169.

- Safety analysis set:
  All subjects who have received the study treatment.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date First Subject Signed Informed Consent Form

Date of Last Subject's Last Visit/Contact

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variables:

Age (years)

Gender [Male, Female]

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Eligibility Status

[Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]

Primary Reason for Subject Not Being Eligible

[Death, Adverse Event, Screen Failure, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical Methods:

(1) Eligibility for Entrance into the Treatment Period

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Status of Entrance into the Treatment Period [Entered]

Stratum:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Who Entered the Treatment Period by Site

Frequency distributions will be provided for each stratum.

7.3.5 Disposition of Subjects for Follow-up Period

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Study Treatment Administration Status

[Eligible but Not Treated]

Reason for Not Being Treated

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Completion Status for Follow-up Period

[Completed, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

(2) Completion Status for Follow-up Period

Frequency distributions will be provided for Completion Status for Follow-up Period (categories of Completed, Ongoing and Prematurely Discontinued).

7.3.6 Completion Status for Follow-up Period

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Completion Status for Follow-up Period

[Completed, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Categories:

Duration of Study after Baseline (days)

[Min - 57, 58 - 169, 170-281, 282 - Max]

Analytical Methods:

(1) Completion Status for Follow-up Period by Duration of Study after Baseline

Frequency distributions will be provided for each category of duration of study after baseline.

7.3.7 Disposition of Subjects for Long-Term Follow-up Period

Analysis Set:

All Subjects Who Completed the Follow-up period

Analysis Variables:

Completion Status for Long-Term Follow-up Period

[Completed, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

(2) Completion Status for Long-Term Follow-up Period

Frequency distributions will be provided for Completion Status for Long-Term Follow-up Period (categories of Completed and Prematurely Discontinued).

7.3.8 Completion Status for Long-Term Follow-up Period

Analysis Set:

All Subjects Who Completed the Follow-up Period

Analysis Variables:

Completion Status for Long-Term Follow-up Period

[Completed, Prematurely Discontinued]

Reason for Discontinuation

[Death, Adverse Event, Lack of Efficacy, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Other]

Categories:

Duration of Study after Baseline (days)

[Min - 547, 548 - 729, 730-911, 912 - Max]

Analytical Methods:

(1) Completion Status for Long-Term Follow-up Period

Frequency distributions will be provided for each category of duration of study after baseline.

7.3.9 Protocol Deviations and Analysis Sets

7.3.9.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria]

Analytical Methods:

(1) Protocol Deviations

Frequency distributions will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.9.2 Analysis Sets

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Handling of Subjects

[Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

Intention to Treat	[Included]
Modified Intention to Treat	[Included]
Per Protocol Set	[Included]
Safety Analysis Set	[Included]

Analytical Methods:

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:

Intention to Treat

Analysis Variables:

Age (years) [Min<= - <=65, 65<= - <=Max]

Gender [Male, Female]

Height (cm)

Weight (kg)

BMI (kg/m^2)

Smoking Classification [Never, Current, Former]

Previous use of Antibiotics [Yes, No]

Previous use of Immunosuppressants [Yes, No]

Previous use of Biologics [Yes, No]

Concomitant Medications [Biologics only, Immunosuppressants only, Biologics+Immunosuppressants, None of 2 types of concomitant drugs]

Duration of Crohn's Disease (years)

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 IO + 1 EO, 1 IO + 2 EOs, 1 IO + 3 EOs, 2 IOs + 1 EO, 2 IOs + 2 EOs, 2 IOs + 3 EOs]

Topography of Draining EOs at Screening

[0 EO, 1 EO, 2 EOs, 3EOs]

CDAI Total Score at Baseline [Min<= - <150, 150<= - <=220, 220< - <=Max]

Analytical Methods:

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.5 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medication History

Concomitant Medications

Analytical Methods:

(1) Medication History by Preferred Medication Name

(2) Concomitant Medications That Started and Stopped Prior to Baseline by Preferred Medication Name

(3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline by Preferred Medication Name

(4) Concomitant Medications That Started After Baseline by Preferred Medication Name

(5) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variables:

Total Exposure (mL)

Total Exposure per IOs (mL)

Total Exposure per EOs (mL)

Duration of follow-up after baseline by Week 156 (weeks)

Analytical Methods:

(1) Summary of Total Exposure

Descriptive statistics will be provided.

7.8 Efficacy Analysis

7.8.1 Additional Endpoints

Efficacy analysis using data up to Week 156

7.8.1.1 Proportion of Subjects with Combined Remission, Clinical Remission and Response at Week 104/Week 156

Analysis Set:

Intention to Treat

Analysis Variables:

Combined Remission at Week 104/Week 156

Clinical Remission at Week 104/Week 156

Response at Week 104/Week 156

Analytical Methods:

Frequency distributions will be provided with proportion and the two-sided 90% and 95% confidence intervals(Wald's method).

7.8.1.2 Proportion of Subjects with Relapse at Week 104/Week 156 in subjects with combined remission at Week 52/Week 104

Analysis Set:

Intention to Treat

Analysis Variables:

Relapse at Week 104/Week 156

Analytical Methods:

(1) Number and Percentage of Subjects with Relapse at Week 104/Week 156
Within the subjects with combined remission at Week 52/Week 104, frequency distributions will be provided with proportion and the two-sided 90% and 95% confidence intervals(Wald's method).

7.8.1.3 Proportion of Subjects with Combined Remission at Multiple Timepoints

Analysis Set:

Intention to Treat

Analysis Variables:

Combined Remission at Week 24, Week 52 and Week 104
Combined Remission at Week 24, Week 52, Week 104 and Week 156
Combined Remission at Week 52 and Week 104
Combined Remission at Week 52, Week 104 and Week 156

Analytical Methods:

(1) Number and Percentage of Subjects with Combined Remission at Multiple Timepoints
For the number and percentage of subjects with combined remission at multiple timepoints, frequency distributions will be provided with proportion and the two-sided 90% and 95% confidence intervals(Wald's method) . Denominator of the percentage will be the number of subjects who have assessment in Week 104 or Week 156 time window range(i.e. Day 449 - or Day 813 -) .

7.8.1.4 Time to Combined Remission, Clinical Remission and Response by Week 104/Week 156

Analysis Set:

Intention to Treat

Analysis Variables:

Time to Combined Remission by Week 104/Week 156

Time to Clinical Remission by Week 104/Week 156

Time to Response by Week 104/Week 156

Analytical Methods:

For the following time to event analyses, subjects without event will be handled as censor at the date of last fistula clinical assessment.

(1) Summary of Time to Event by Week 104/Week 156
Frequency distribution of subjects who experienced event and who were censored will be provided. Quartiles of time to event will be estimated using the Kaplan-Meier method.

(2) Kaplan-Meier Plot
Kaplan-Meier plot of time to combined remission, clinical remission, and response by Week 104/Week 156 will be provided.

7.8.1.5 Time to Relapse by Week 104/Week 156

Analysis Set:

Intention to Treat

Analysis Variables:

Time to Relapse by Week 104/Week 156

Analytical Methods:

Within the subjects with combined remission at Week 52/Week 104, the following analyses will be performed. For the following time to event analyses, subjects without event will be handled as censor at the date of last fistula clinical assessment or last fistula MRI assessment.

(1) Summary of Time to Event by Week 104/Week 156
Frequency distribution of subjects who experienced event and who were censored will be provided. Quartiles of time to event will be estimated using the Kaplan-Meier method.

(2) Kaplan-Meier Plot
Kaplan-Meier plot of time to relapse by Week 104/Week 156 will be provided.

7.8.1.6 PDAI Score

Analysis Set:

Intention to Treat

Analysis Variables:

PDAI Total Score

PDAI Domain Scores(Discharge, Pain/restriction of activities, Restriction of Sexual Activity, Type of Perianal Disease, Degree of Induration)

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 40, Week 52, Week 104, Week 156

Analytical Methods:

(1) Summary of PDAI Scores and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline for each visit will be provided.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted for each visit with standard deviation bars.

7.8.1.7 CDAI Score

Analysis Set:

Intention to Treat

Analysis Variables:

CDAI Total Score [Min<= - <150, 150<= - <=220, 220< - <=450, 450< - <=Max]

CDAI Sub Scores

Visit:

Baseline, Week 24, Week 52, Week 156

Analytical Methods:

(1) Summary of CDAI Scores and Change from Baseline by Visit
Frequency distribution for categorical variables and descriptive statistics of observed values and changes from baseline for each visit will be provided.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted for each visit with standard deviation bars.

7.8.1.8 Van Assche Score

Analysis Set:

Intention to Treat

Analysis Variables:

Van Assche Total Score

Van Assche Domain Scores

Visit:

Baseline, Week 24, Week 52, Week 156

Analytical Methods:

(1) Summary of Van Assche Scores and Change from Baseline by Visit
Frequency distribution for categorical variables and descriptive statistics of observed values and changes from baseline for each visit for continuous variables will be provided.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted for each visit with standard deviation bars for continuous variables.

7.8.1.9 Timepoint Analysis of Clinical Remission and Response

Analysis Set:

Intention to Treat

Analysis Variables:

Clinical Remission

Response

Visit:

Week 2, Week 4, Week 8, Week 16, Week 24, Week 40, Week 52, Week 104, Week 156

Analytical Methods:

The same analysis for the primary endpoint will be performed by visit.

7.8.2 Statistical/Analytical Issues

7.8.2.1 Adjustments for Covariates

Not applicable.

7.8.2.2 Handling of Dropouts or Missing Data

Values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values above the upper limit of quantification will be treated as the upper limit of quantification when calculating the descriptive statistics.

For combined remission, clinical remission, response

For the primary and secondary analyses of the primary endpoint, the last observation carried forward (LOCF) from the latest earlier post-baseline visit (including an Early Termination Visit prior to Week 24, if applicable) will apply in case of missing clinical assessment at Week 24. In case of missing MRI data at Week 24, LOCF from an Early Termination Visit prior to Week 24 will apply if applicable. In case of no MRI data by Week 24 or no post-baseline clinical assessment, non-response will be imputed. If rescue therapy which is not allowed in section 7.4 of the protocol or medications which could affect fistula closure directly occur prior to visit 8(Week 24) , non-response will be imputed overriding all other imputation conventions.

The handling above for the primary endpoint will also be applied to proportion of subjects with clinical remission at Week 24, proportion of subjects with response at Week 24, proportion of subjects with combined remission at Week 52, proportion of subjects with clinical remission at Week 52, proportion of subjects with response at Week 52, proportion of subjects with combined remission at Week 104, proportion of subjects with clinical remission at Week 104, proportion of subjects with response at Week 104, proportion of subjects with combined remission at Week 156, proportion of subjects with clinical remission at Week 156 and proportion of subjects with response at Week 156 (but handling of rescue therapy will not be applied for Week 52, Week 104, or Week 156) .

7.8.2.3 Multicenter Studies

Although this study is a multicenter study, treatment-by-center interaction will not be explored since the number of subjects for each center is not sufficient for such exploration.

7.8.2.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.2.5 Use of an "Efficacy Subset" of Subjects

In addition to analyses on the primary endpoint using the intention to treat, a secondary analysis will also be performed using the modified intention to treat and the per protocol set to confirm the robustness of the results.

7.8.2.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.2.7 Examination of Subgroups

Efficacy analysis using data up to Week 104/Week 156

Analysis Set:

Intention to treat

Analysis Variables:

Combined Remission at Week 104/Week 156

Clinical Remission at Week 104/Week 156

Response at Week 104/Week 156

Subgroups:

Age [Min<= - <=65, 65< - <=Max]

Gender [Male, Female]

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 IO + 1 EO, 1 IO + (2<= EOs), 2 IOs + (1<= EOs)]

Previous use of Antibiotics [Yes, No]

Previous use of Immunosuppressants [Yes, No]

Previous use of Biologics [Yes, No]

Concomitant Medications [Biologics only, Immunosuppressants only, Biologics+Immunosuppressants, None of 2 types of concomitant drugs]

Analytical Methods:

(1) Descriptive Statistics

Frequency distributions will be provided for above each subgroups.

7.9 Other Outcomes

Not applicable.

7.10 Safety Analysis

Safety analysis using data up to Week 156

7.10.1 Adverse Events

7.10.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Relationship to Study Treatment [Related, Not Related]

Intensity [Mild, Moderate, Severe]

Analytical Methods:

The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
2) Relationship of Treatment-Emergent Adverse Events to study treatment (number of events, number and percentage of subjects).
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
4) Treatment-Emergent Adverse Events leading to study discontinuation (number of events, number and percentage of subjects).
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
6) Relationship of serious Treatment-Emergent Adverse Events to study treatment (number of events, number and percentage of subjects).
7) Serious Treatment-Emergent Adverse Events leading to study discontinuation (number of events, number and percentage of subjects).
8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects).

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- Summaries other than 2), 3), and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

7.10.1.2 Displays of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Intensity [Mild, Moderate, Severe]

Time of Onset (day) [1 - 57, 58 - 169, 170 - 281, 282 - 729, 730 - Max]

Analytical Methods:

The following summaries will be provided using frequency distribution.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Study Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Study Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(10) Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term

(11) Product Malfunction-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distributions will be provided according to the rules below.

Number of subjects

- Summary tables other than (5), (6) and (9)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

- Summary table for (9)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. Percentages will be based on the number of subjects in the safety analysis set.

7.10.1.3 Subgroup Analysis of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Subgroups:

Age [Min<= - <=65, 65< - <=Max]

Gender [Male, Female]

Topography of IOs and EOs at Baseline

[1 IO, 2 IOs]

[1 EO, 2 EOs, 3 EOs]

[1 EO, 2 <= EOs]

Previous use of Antibiotics [Yes, No]

Previous use of Immunosuppressants [Yes, No]

Previous use of Biologics [Yes, No]

Concomitant Medications [Biologics only, Immunosuppressants only, Biologics+Immunosuppressants, None of 2 types of concomitant drugs]

Analytical Methods:

The following summaries will be provided for each subgroup using frequency distribution. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set for each subgroup.

7.10.1.4 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

PTE

Analytical Methods:

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term.

(2) Serious Pretreatment Events by System Organ Class and Preferred Term.

The frequency distributions will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.10.2 Clinical Laboratory Evaluations

7.10.2.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Hemoglobin, Hematocrit, Red blood cells count, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, White blood cells count, differential WBC (Neutrophils, Basophils, Eosinophils, Lymphocytes, Monocytes), Platelet count

Serum Chemistry

C-reactive protein, ALT, AST, Alkaline phosphatase, Gamma-glutamyl transpeptidase, Total bilirubin, Total protein, Glucose, Creatinine, Creatine phosphokinase, Blood urea nitrogen, Potassium, Sodium, Chloride

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 52, Week 104, Week 156

Analytical Methods:

For each variable, summaries (1) to (3) will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each laboratory test, the laboratory values will be classified as "Low", "Normal"

or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

7.10.2.2 Urinalysis

Analysis Set:

Safety Analysis Set

Analysis Variables:

Specific Gravity

pH

Glucose	[-, +-, +, 2+, 3+]
Protein	[-, +-, +, 2+, 3+]
Occult blood	[-, +-, +, 2+, 3+]
Ketone body	[-, +-, +, 2+, 3+]
Bilirubin	[-, +-, +, 2+, 3+]
Urobilinogen	[+-, +, 2+, 3+]

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 52, Week 104, Week 156

Analytical Methods:

For specific gravity, summaries (1), (2) and (4) will be provided.

For pH, summary (4) will be provided.

For each variable other than specific gravity or pH, summaries (3) and (4) will be provided.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

(4) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

For each urine laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" for specific gravity and pH, classified as "Normal" or "Abnormal" for others relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

7.10.3 Vital Signs

Analysis Set:

Safety Analysis Set

Analysis Variables:

Temperature

Systolic Blood Pressure

Diastolic Blood Pressure

Heart Rate

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 40, Week 52, Week 78, Week 104, Week 130, Week 156

Analytical Methods:

For each variable, summaries (1) and (2) will be provided

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

7.10.4 Other Observations Related to Safety

7.10.4.1 Donor Specific Antibody

Analysis Set:

Safety Analysis Set

Analysis Variables:

Donor Specific Antibody

[Presence, Absence]
(Categories used in analytical methods (1) and (2))

[Presence at baseline and Presence during post-baseline by Week

24,
Presence at baseline and Absence during post-baseline by Week 24,
Absence at baseline and Presence during post-baseline by Week 24,
Absence at baseline and Absence during post-baseline by Week 24]

[Presence at baseline and Presence during post-baseline by Week 52,
Presence at baseline and Absence during post-baseline by Week 52,
Absence at baseline and Presence during post-baseline by Week 52,
Absence at baseline and Absence during post-baseline by Week 52]

[Presence at baseline and Presence during post-baseline by Week 156,
Presence at baseline and Absence during post-baseline by Week 156,
Absence at baseline and Presence during post-baseline by Week 156,
Absence at baseline and Absence during post-baseline by Week 156]

(Categories used in analytical methods (3) and (4))

[Presence at baseline and Presence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52 and Presence during post-baseline after Week 52 by Week 156,
Presence at baseline and Presence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52 and Absence during post-baseline after Week 52 by Week 156,
Presence at baseline and Presence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52 and Presence during post-baseline after Week 52 by Week 156,
Presence at baseline and Presence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52 and Absence during post-baseline after Week 52 by Week 156
Presence at baseline and Absence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52 and Presence during post-baseline after Week 52 by Week 156,
Presence at baseline and Absence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52 and

Absence during post-baseline after Week 52 by Week 156
Presence at baseline and Absence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52 and Presence during post-baseline after Week 52 by Week 156,
Presence at baseline and Absence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52 and Absence during post-baseline after Week 52 by Week 156
Absence at baseline and Presence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52 and Presence during post-baseline after Week 52 by Week 156,
Absence at baseline and Presence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52 and Absence during post-baseline after Week 52 by Week 156
Absence at baseline and Presence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52 and Presence during post-baseline after Week 52 by Week 156,
Absence at baseline and Presence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52 and Absence during post-baseline after Week 52 by Week 156
Absence at baseline and Absence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52 and Presence during post-baseline after Week 52 by Week 156,
Absence at baseline and Absence during post-baseline by Week 24 and Presence during post-baseline after Week 24 by Week 52 and Absence during post-baseline after Week 52 by Week 156
Absence at baseline and Absence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52 and Presence during post-baseline after Week 52 by Week 156,
Absence at baseline and Absence during post-baseline by Week 24 and Absence during post-baseline after Week 24 by Week 52 and Absence during post-baseline after Week 52 by Week 156]
(Categories used in analytical methods (3))

[Presence during post-baseline by Week 24, Absence during post-baseline by Week 24]

[Presence during post-baseline by Week 52, Absence during post-baseline by Week 52]

[Presence during post-baseline by Week 156, Absence during post-baseline by Week 156]
(Categories used in analytical method (4))

[Clearance, non-Clearance]
[Presence at baseline and Clearance, Presence at baseline and non-

Clearance, Absence at baseline and Clearance, Absence at baseline and non-Clearance]
(Categories used in analytical method (5))

(Presence/Absence at baseline is results of anti-HLA antibody.)

(Presence/Absence during post-baseline is results of donor specific antibody during post-baseline by Week 24/52/156, ie, Presence if any positive results during post-baseline by Week 24/52/156, Absence if no positive results during post-baseline by Week 24/52/156.)

Visit:

Baseline, Week 2, Week 4, Week 8, Week 16, Week 24, Week 52, Week 104, Week 156

Analytical Methods:

(1) Summary of Donor Specific Antibody by Visit

Frequency distributions for each visit will be provided.

(2) Summary of Shifts of Donor Specific Antibody

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

(3) Number of Subjects in Categories of Donor Specific Antibody

Frequency distributions of results at baseline and during post-baseline by Week 24/52/156 as well as baseline, during post-baseline by Week 24, during post-baseline after Week 24 by Week 52 and during post-baseline after Week 52 by Week 156 will be provided.

(4) Subgroup Analysis of Efficacy and Safety Endpoints by Donor Specific Antibody

The same analyses of Section 7.8.2.7 and 7.10.1.3 will be conducted for each subgroup of Donor Specific Antibody based on results during post-baseline by Week 156. For the same analyses of Section 7.8.2.7, combined remission at Week 24/52, clinical remission at Week 24/52, response at Week 24/52 will be also analyzed for each subgroup of Donor Specific Antibody based on results during post-baseline by Week 24/52.

(5) Number of Subjects of Clearance

Frequency distributions of results of clearance at Week 156 will be provided for subjects who have presence at any post-baseline visits by Week 104 and have assessment at Week 156. Clearance is defined as the status that subjects have presence at any post-baseline visits by Week 104 with absence at Week 156.

7.10.4.2 Displays of Treatment-Emergent Adverse Events (Japanese)

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Analytical Methods:

TEAEs will be summarized in the same way as in section 7.10.1.2 and 7.10.1.3. All summaries will be presented in Japanese.

7.11 Interim Analysis

There will not be any interim analysis. Note, the analysis using data up to Week 24 is the primary analysis for marketing application. Additionally, separate analyses using data up to Week 52 and overall data will be performed after all subjects complete Week 52 and Week 156 respectively.

7.12 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

Not applicable.

9.0 APPENDIX

Not applicable.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	12-May-2022 01:17 UTC