Statistical Analysis Plan

NCT Number: NCT04118088

Title: Postauthorization Safety Study of the Long-Term Safety and Efficacy of Repeat Administration of Darvadstrocel in Patients With Crohn's Disease and Complex Perianal Fistula

Study Number: Alofisel-4001

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Alofisel-4001

Postauthorization Safety Study of the Long-Term Safety and Efficacy of Repeat Administration of Darvadstrocel in Patients With Crohn's Disease and Complex Perianal Fistula PHASE IV

Version: Final 2.0

Date: 25 February 2025

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Based on:

Protocol Version: Amendment 4

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Approval Signatures

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

Sponsor signatures are collected in separate document Alofisel-4001 PXL 244727 SAP 2.0 Sign-Off.

Study Title: Postauthorization Safety Study of the Long-Term Safety and Efficacy of Repeat Administration of Darvadstrocel in Patients With Crohn's Disease and Complex Perianal Fistula

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft 0.1	25 Oct 2019	New document
Draft 0.2	20 Nov 2019	Comments implementation
Draft 0.3	06 Oct 2020	Implementation of protocol amendment 1
Draft 0.4	09 Nov 2020	Comments implementation
Draft 0.5	25 Jan 2021	Comments implementation
Final 1.0	03Feb2021	Document Finalization
Draft 1.1	26Sep2024	Update SAP per protocol amendment 4
Draft 1.2	04Feb2025	Updated SAP due to study early close out per study team decision
Final 2.0	25Feb2025	Document Finalization

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CIs	Confidence Intervals
cm	centimeters
CRP	c-reactive protein
DILI	Drug Induced Liver Injury
DSA	Donor-specific antibodies
ECG	Electrocardiogram
eCRF	Electronic case report form
EO(s)	External Opening(s)
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IO(s)	Internal Opening(s)
IS	Immunosuppressive
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MRI	Magnetic resonance imaging
MedDRA	Medical Dictionary for Regulatory Activities

PADP	Perianal Disease Progression
PASS	Post Authorization Safety Study
PD	Protocol Deviation
PDAI	Perianal Disease Activity Index
PRO-2	Patient reported outcomes measure derived from CDAI
PT	Preferred Term
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SOC	System Organ Class
SSR	Special situation report
TEAEs	treatment-emergent adverse events
TESAEs	treatment-emergent serious adverse events
WHODrug	World Health Organization Drug Dictionary

1.0 INTRODUCTION

This postauthorization safety study (PASS) is being undertaken to investigate the long-term safety and efficacy of a repeat administration with Darvadstrocel in concordance with the condition approved in the market authorization: subjects with CD and complex perianal fistula.

The aim of this study is to generate descriptive data of 3 years follow-up to gain insight into the safety and efficacy of a repeat administration of Darvadstrocel. Such information will be helpful to health authorities, payors, and physicians for the future use of Darvadstrocel.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Amendment 4 (29 April 2024)
- electronic Case Report Form (eCRF), Version 7.0 (12 May 2022)

2.0 OBJECTIVES

2.1 Primary Objectives

To evaluate the long-term safety of repeat administration of Darvadstrocel in subjects with Crohn's disease (CD) and complex perianal fistula by evaluation of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and pregnancy.

2.2 Secondary Objectives

To evaluate the long-term efficacy of repeat administration of Darvadstrocel in subjects with CD and complex perianal fistula.

2.3 Exploratory Objectives

To characterize the immunogenicity of Darvadstrocel Donor Specific Antibody (DSA) and the impact of immunogenicity on safety and clinical response.

2.4 Study Design

This is a PASS, multinational, single-arm clinical study of adult (aged 18 years or older) subjects with CD and complex perianal fistulas who have previously been administered Darvadstrocel (Alofisel) and whose physician determines that repeat administration is indicated. The study will be performed in countries where Darvadstrocel is currently marketed. For a study scheme please refer to the protocol section.

The decision to perform repeat administration with Darvadstrocel is taken at the discretion of the treating physician. Subjects are recruited into the study only after the physician and subject have decided to proceed with Darvadstrocel repeat administration of the original fistula tract or initial treatment of a new fistula tract. Only 1 repeat administration of Darvadstrocel is permitted during study. If the subject previously participated in a Darvadstrocel study and was not clear if they received Darvadstrocel, the subject will not be eligible for inclusion in this study.

Baseline information will be collected on demographics, clinical characteristics and CD clinical history, treatment history (including details of first administration of Darvadstrocel), fistula

history (prior procedures for perianal disease), and comorbidities/concomitant medications. Pelvic magnetic resonance imaging (MRI) will not be performed post repeat administration at week 156, early termination visits and unscheduled visits to accesses the fistula characteristics and for the presence of collections/abscesses per sponsor's decision due to early study withdrawal.

Subjects will be clinically assessed before repeat administration at the preparation visit, treatment visit, and at Weeks 6 (±8 days), 24 (±15 days), 52 (±15 days), 104 (±30 days), and 156 (±30 days) following repeat administration. The Week 6 assessment will be used primarily to capture immunogenicity/ donor-specific antibodies (DSA)/soluble factors.

Sites will employ all efforts to see subjects in the clinic for assessments. In unavoidable circumstances, such as the COVID-19 pandemic, exceptions may be granted for alternative methods for conducting subject visits with approval by the medical monitor and/or sponsor. Such instances will be documented in the study records. In general, in the final data analysis, these data collected with alternative methods, will be analyzed together with assessments collected on-site.

Blood samples for central laboratory tests and plasma samples for DSA levels and exploratory immunogenicity testing will be collected at the time points specified in Appendix A. Blood samples for these tests will be analyzed in batches as the study progresses; however, if there is a confirmed serious allergic reaction following the administration of Darvadstrocel, then DSA testing will be done as soon as logistically possible and data on DSA will be assessed in conjunction with SAEs reported in these subjects. Blood samples may be tested at a local laboratory for safety evaluation if it is not possible to have them tested at the central laboratory. The results of the laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results and transmitting normal ranges for adequate interpretation.

A schedule of assessments is listed in APPENDIX A.

3.0 ANALYSIS ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of the study will include assessment of the following safety parameters:

- Treatment-emergent AEs.
- Treatment-emergent SAEs.
- Pregnancy.
- Specific treatment-emergent AESIs, including:
  - Immunogenicity/alloimmune reactions.
  - Hypersensitivity.
  - Transmission of infectious agents.
  - Tumorigenicity, applying to malignant tumors only.
  - Ectopic tissue formation
  - Medication errors (reported to the pharmacovigilance department as special situation reports [SSRs]).
  - Based on the mechanism of action of darvadstrocel, certain AESIs have been predefined. The categories of AESIs are described in Appendix 7.3 AESIs from MedDRA Criteria Search. AESIs based on the CRF will also be presented.

3.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) drug whether or not it is considered related to the IMP.

TEAEs are events that occur on or after IMP administration or a worsening in severity of a preexisting condition occurring on or after IMP administration (a pre-existing condition is a condition that is present before the AE recording period starts and is noted on the medical history/physical examination form). AEs occurring up to, and including, week 156+30 days will be considered TEAEs; AEs occurring after week 156 +30 days will not be considered TEAEs.

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in DEATH.
- Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
- Results in persistent or significant DISABILITY/INCAPACITY.
- Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
- Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Please refer to APPENDIX B of this SAP).
    - Transmission of infection.

TESAEs are SAEs that occurs on or after IMP administration.

All AEs will be coded using MedDRA, the last available version at the time of data final cleaning.

AE duration will be derived with the formula:

AE duration (days) = (AE end date - AE onset date +1); in case of AE ongoing, the date of last contact with the subject will be used as AE end date for deriving the AE duration.

Handling of partial AE onset and end date are described in this SAP at section 5.1.6.1.

3.1.2 Special situation report (SSR)

An SSR consists of the following events:

- Abuse: Persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or psychological effects.
- Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.
- Medication error: An unintentional error in the drug treatment process (prescribing, dispensing or administration, including incorrect dose or poor-quality administration) of a medicinal product while in the control of the investigator, site staff, or patient that leads to harm or has the potential to lead to harm.
- Overdose: The administration of a quantity of medicinal product given per administration or per day, which is above the maximal recommended dose according to the protocol.

3.1.3 Adverse Events of Special Interest (AESIs)

An AESI (serious or nonserious) is one of the scientific and medical concerns specific to the compound or program. Refer to section 3.1 for a list of known AESIs.

AESI information includes:

- AESI associated AE term
- AESI description

3.2 Secondary Endpoints

Efficacy will be assessed by evaluating the following endpoints:

- Proportion of subjects who achieve clinical remission at Weeks 6, 24, 52, 104, 156 and early termination visits (Use the available data) after IMP repeat administration.
  - Clinical remission is defined as closure of all treated external fistula openings that were draining at baseline despite gentle finger compression.

- Proportion of subjects who achieve clinical response at Weeks 6, 24, 52, 104, 156 and early termination visits (Use the available data) after IMP repeat administration.
  - Clinical response is defined as closure of at least 50% of all treated external fistula openings that were draining at baseline despite gentle finger compression.
- Time to reopening of any of the treated external openings with active drainage as clinically assessed, measured in days relative to Week 24.
- Change from baseline to Weeks 6, 24, 52, 104, and 156 after IMP (If data are available) repeat administration in scores of discharge and pain items of Perianal Disease Activity Index (PDAI) score.

3.2.1 Fistula clinical assessment

Clinical fistula assessment is performed at Baseline, Week 6, Week 24, Week 52, Week 104, Week 156, Early Termination Visit and Unscheduled Visit.

Clinical fistula assessment on target (treated) fistulas includes:

- Physical examination of the fistula(s) performed [Yes, No]
- Date of examination
- Location of external opening A* [Anterior-right, Anterior-left, Anterior-middle, Middle-right, Middle-left, Posterior-right, Posterior-left, Posterior-middle]
- External opening A draining [Yes, No]
- Location of external opening B* [Anterior-right, Anterior-left, Anterior-middle, Middle-right, Middle-left, Posterior-right, Posterior-left, Posterior-middle]
- External opening B draining [Yes, No]
- Location of external opening C* [Anterior-right, Anterior-left, Anterior-middle, Middle-right, Middle-left, Posterior-right, Posterior-left, Posterior-middle]
- External opening C draining [Yes, No]
- Clinical suspicion of perianal abscess [Yes, No]

* Enumeration of external openings clockwise, assuming the patient is being examined in a supine position (even if it is not the case), in an alphabetical manner.

At post-baseline timepoints, in addition to above assessments on target (treated) fistulas, the appearance of any new external openings since the last visit [Yes, No] will also be captured, together with log of the new external opening(s):

- New external opening name [D, E, F, G, H, I, J, K, L]
- Location of new external opening [Anterior-right, Anterior-left, Anterior-middle, Middle-right, Middle-left, Posterior-right, Posterior-left, Posterior-middle]
- New external opening draining [Yes, No]
- Presence of a new fistula been confirmed by MRI? [Yes, No]
- Visit of first observation [Preparatory Visit, Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Early Termination]
- Date of first observation

A treated external fistula opening will be considered as closed once it is not draining anymore after gentle finger compression.

A treated external fistula opening which was draining at baseline will be considered as a 'responder fistula' if it is closed at any post baseline timepoint.

3.2.2 Fistula Pelvic MRI assessment

A pelvic MRI with and without intravenous contrast material will be performed at the baseline visit, Week 24, Week 156, early termination visit, and any unscheduled visits.

However, due to the Sponsor decision to early study closure, following the Alofisel withdrawn from the EU market in December 2024, the study team agreed that no additional MRIs will be performed at week 156, early termination and any unscheduled visits. In line with this decision, MRIs central reading will no longer be completed and therefore no endpoints involving combined remission will be a part of the analysis.

Pelvic MRI assessments will be detailed separately in the MRI charter; typically, these may include:

- Location of fistula
- Fistula extension
- Qualitative Hyperintensity on T2w images (fat-saturated T2 signal)
- Is the fluid collection >2 cm in at least two dimensions? [Yes, No]

3.2.3 Perianal Disease Progression (PADP)

PADP may be recorded during the study, following info will be collected:

- Event description [New External Opening; Abscess]
- Start and End date
- How was the confirmation obtained? [MRI; Ultrasound; Clinical Examination; Other]
- Event occurring on a treated fistula tract [Yes; No]
- Concomitant medication taken [Yes; No]
- Concomitant procedure performed [Yes; No]

The number of following info for perianal disease progression will be summarized by visits

- Abscess

3.2.4 Clinical remission at Weeks 6, 24, 52, 104, and 156 after IMP administration

Assessment of clinical remission is derived based on clinical fistula assessment.

Clinical remission is defined as closure of all treated external fistula openings that were draining at baseline despite gentle finger compression. For the definition of the baseline value, please refer to SAP section 5.1.3.

At a post-baseline visit, subjects will be considered in clinical remission if all the external fistula openings are responder fistulas (definition of responder fistula is provided in this SAP at section 3.2.1). It is understood that subjects who received concomitant medications or procedures due to PADP on a treated fistula tract (refer to SAP section 3.2.1.3), prior to a visit clinical fistula assessment, will not be considered as in clinical remission.

To be noted: fistulas that are responder at a timepoint may reopen thereafter; therefore, number of subjects in clinical remission at a timepoint may decrease at the following timepoint.

3.2.5 Clinical response at Weeks 6, 24, 52, 104, and 156 after IMP administration

Assessment of clinical response is derived based on clinical fistula assessment.

Clinical response is defined as closure of at least 50% of all the treated external fistula openings that were draining at baseline despite gentle finger compression. For the definition of the baseline value please refer to SAP section 5.1.3.

At a post-baseline visit, subjects will be considered in clinical response if at least 50% of the external fistula openings are responder fistulas (definition of responder fistula is provided in this SAP at section 3.2.1). It is understood that subjects who received concomitant medication or procedure due to PADP on a treated fistula tract (refer to SAP section 3.2.1.3), prior to a visit clinical fistula assessment, will not be considered as in clinical response.

Of note: all subjects in clinical remission also meet criteria for clinical response.

To be noted: fistulas that have responded at a timepoint may reopen thereafter; therefore, number of subjects in clinical response at a timepoint may decrease at the following timepoint.

3.2.6 Time to reopening

Time to reopening of any of the treated external openings with active drainage as clinically assessed after gentle finger compression, measured in days relative to Week 24.

Time to reopening is defined as the time from clinical remission at Week 24 until first reopening of a treated fistula with clinical remission, and subjects who received concomitant medications or procedures due to PADP on a treated fistula tract prior to a visit clinical fistula assessment, will not be considered as in clinical remission on and after that visit; time to reopening does not include deaths nor study termination. Subjects who will die for any cause or who will terminate the study without having experienced reopening, will be censored at the time of last clinical fistula assessment.

Time to reopening (days) = (Date of reopening [i.e. first date reopening of a treated fistula] – Date of clinical remission at Week 24 + 1).

Time to reopening will be presented at one decimal place precision.

3.2.7 New perianal abscess in treated fistula

New perianal abscesses in treated fistulas are abscesses appearing in treated fistulas by clinical assessment which were not present at baseline.

3.2.8 Perianal Crohn's Disease Activity Index (PDAI)

PDAI score assessment is performed at all study visits except for the preparatory visit to evaluate the severity of perianal CD.

PDAI includes five items: (a) discharge; (b) pain /restriction of activities; (c) restriction of sexual activity; (d) type of perianal disease; and (e) degree of induration.

Each element of the PDAI is graded on a five-point Likert scale; possible points at each element are: 0 (no symptoms), 1, 2, 3, 4 (severe symptoms).

Change from baseline to post baseline will be derived as:

Change from baseline = (Post baseline visit score – Baseline visit score)

For baseline definition please refer to SAP section 5.1.3.

3.2.9 Patient reported outcomes measure derived from CDAI (PRO-2)

PRO-2 combines the average daily liquid or soft stools frequency and the average daily abdominal pain severity. The PRO-2 will be completed by subjects at home 7 days before each visit and the total score will be calculated by the investigator at each visit and reported in the CRF. PRO-2 score information includes:

- Number of liquid or very soft stools
- Abdominal Pain
- PRO-2 Total Score

Change from baseline to post baseline PRO-2 Total Score will be derived as:

Change from baseline = (Post baseline visit PRO-2 Total Score – Baseline visit PRO-2 Total Score).

3.3 Exploratory Endpoints

Exploratory endpoint consist of the following.

- Immunogenicity responses as measured by DSA levels.

3.3.1 Plasma sample for DSA and Immunogenicity

Subjects will be assessed at baseline visit, before repeat administration at visit 1, at Weeks 6 (±8 days) and 24 (±15 days) following repeat administration, and at early termination visit.

Plasma sample for DSA and immunogenicity information captured in CRF includes:

- Sample collected [Yes, No]
- Date of Collection
- Reason for sample not collected

DSA and immunogenicity samples will be analyzed in an external lab and then integrated in the clinical database.

Change from baseline at Week 6, Week 24, and Early Termination Visit will be derived as follow:

Change from baseline = (Post baseline result – Baseline result).

For baseline definition please refer to SAP section 5.1.3.

4.0 DETERMINATION OF SAMPLE SIZE

Complex perianal fistula is a rare disease, with orphan disease designation granted by the European Commission.

This study planned to enroll 50 subjects as part of a regulatory commitment, who have received previous Darvadstrocel treatment and need to be re-treated for the same fistula tract or a new fistula tract according to their physician.

This planned sample size is intended to provide initial data on the safety and efficacy of a repeat administration with Darvadstrocel treatment.

5.0 METHODS OF ANALYSIS AND PRESENTATION

5.1 General Principles

5.1.1 Data Quality Assurance

All tables, figures, and data listings to be included in the clinical study report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

5.1.2 Software

All report outputs will be produced using a server-based SAS® version 9.3 [1] or a later version in a secure and validated environment. The REPORT procedure (SAS PROC Report) will be used to produce all tables and listings; SAS/GRAPH will be used to produce all figures.

5.1.3 General Study Definitions

Baseline values are defined as the last observed value, including unscheduled, on or before the repeat administration (i.e. on or before IMP administration).

5.1.3.1 Definition of Draining at baseline

The closure of all treated external openings that were draining at baseline (i.e., baseline visit) if met below 3 scenarios:

1. If external opening was draining after gentle figure compression during screening visit.
2. Or if external opening was draining spontaneously during screening visit
3. Or if external opening was confirmed to belong to Active draining fistula during screening visit.

Then external opening will be considered as draining during screening visit and used for all treated external openings that were draining at baseline.

5.1.4 Definition of Study Day

Study Day 1 is defined as the date of repeat administration (i.e. actual day of the IMP administration).

Other study days are defined relative to the Study Day 1 as follow:

- assessments taken before the IMP administration:
  Relative Study Day = assessment date - IMP administration date
- assessments on or after the repeat administration:
  Relative Study Day = assessment date - IMP administration date + 1.

5.1.5 Definition of Study Visit Window

Summary tables will be presented by visit:

- Week 6
- Week 24
- Week 52
- Week 104
- Week 156
- Early Termination

Schedule of Study Visits is described in below Table 1. And study visits details including reason for not done or done remotely, method of contact and assessments done per adjusted method of contact will be listed by subject as defined in SAP section 5.1.7.1

Table 1 Study Visit Window

Visit	*Scheduled time window*	*Visit Window*
Baseline / Enrollment Visit	Repeat administration (Visit 1) should take place within 8 weeks of the baseline visit. There will be a maximum of 5	-

Visit	*Scheduled time window*	*Visit Window*
	weeks from the baseline visit to the preparation visit.	
Preparatory Visit to Visit 1	From preparation visit to repeat administration (Visit 1) there will be a minimum of 2 weeks and maximum of 3 weeks (necessary to have Darvadstrocel treatment ready for administration). If there is any problem administering Darvadstrocel during Visit 1, the visit will need to be rescheduled within a minimum of 2 weeks and a maximum of 3 weeks of the original Visit 1.	-
Visit 1 (Repeat Administration)	Day 1	For definition of Study Day 1 please refer to section 5.1.4. For definition of Baseline please refer to SAP section 5.1.3

Visit	*Scheduled time window*	*Visit Window*
Visit 2 (6 Weeks ±8 days)	Visit is scheduled between relative study day 34 and 50 (inclusive)	Measurement collected between relative study days 2 to 101 (inclusive) will be considered as belonging to Week 6
Visit 3 (24 Weeks ±15 days)	Visit is scheduled between relative study day 153 and 183 (inclusive)	Measurement collected between relative study days 102 to 266 (inclusive) will be considered as belonging to Week 24
Visit 4 (52 Weeks ±15 days)	Visit is scheduled between relative study day 349 and 379 (inclusive)	Measurement collected between relative study days 267 to 538 (inclusive) will be considered as belonging to Week 52
Visit 5 (104 Weeks ±30 days)	Visit is scheduled between relative study day 698 and 758 (inclusive)	Measurement collected between relative study days 539 to 910 (inclusive) will be considered as belonging to Week 104
Visit 6 (156 Weeks ±30 days)	Visit is scheduled between relative study 1062 and 1122 (inclusive)	Measurement collected between relative study days 911 to maximum relative days (inclusive) will be

Visit	*Scheduled time window*	*Visit Window*
		considered as belonging to Week 156
Early Termination Visit	Related procedures will be performed excluding MRI and documented ±30 days of the early termination visit	-
Unscheduled Visit	-	Subjects who experience significant new perianal symptoms will attend an unscheduled visit.

Actual visit will be used to assign week based on "Relative Study Days", except for the Early Termination Visit. 'Relative study days' will be used to assign the measurement to the correct week:

- Week 6: 2 ≤ relative study day ≤ 101;
- Week 24: 102 ≤ relative study day ≤ 266;
- Week 52: 267 ≤ relative study day ≤ 538;
- Week 104: 539 ≤ relative study day ≤ 910;
- Week 156: 911 ≤ relative study day ≤ maximum relative days.

In case of assessments available at the scheduled visit, such assessments will be used in the analysis while unscheduled assessments will only be listed.

In case of assessments missing at a scheduled visit but available from an unscheduled visit, the following rules apply:

- If multiple unscheduled data points are available within the time window (Table 1, column 'scheduled time window'), the data point corresponding to the closest relative day will be kept in the analysis.
- If no data point is available within the scheduled time window (Table 1, column 'scheduled time window), then the data points within the visit window (Table 1, column 'Visit Window') will be considered; in this case if multiple data points correspond to the same week, the data point corresponding to the closest relative day will be kept in the analysis.

5.1.6 Missing Data

In general, missing data will not be imputed.

Specific rules for handling partial AE dates are respectively detailed in sections 5.1.6.1.

As a sensitivity analysis, a non-responder imputation (NRI) rule for the efficacy analysis of binary endpoints will be defined for each visit as follows: if the value is missing at the visit or if the subject discontinued from the study prior to the visit, then subject be classified as non-responder for the endpoint(s) with missing value. The sensitivity analysis will be applied to secondary efficacy binary endpoints as specified in SAP section 5.10.2.

5.1.6.1 Conventions for Missing Adverse Event Dates

Any Adverse Events (AEs) with incomplete start and end dates will be treated as follows:

- Adverse events with completely unknown start date will be considered as treatment-emergent; for the scope of AE duration derivation, these AE will be considered as occurred on Study Day 1.
- Adverse events with unknown start day and month but with known start year will be considered:
  - as treatment-emergent if the start year coincides or is after IMP administration year; for the scope of AE duration derivation, these AEs will be considered as occurred on Study Day 1 if the start year coincides with IMP administration year,

as occurred on 1st January otherwise (i.e. in case the start year is after the IMP administration year);

- as non-treatment emergent if start year is before the IMP administration year; for the scope of AE duration derivation, these AEs will be considered as occurred on informed consent date.

- Adverse events with unknown start day but with known start month and year will be considered:
  - as treatment-emergent if the start month and year coincide or are after the IMP administration month and year; for the scope of AE duration derivation, these AE will be considered as occurred the day of IMP administration if the start month and year coincides with IMP administration month and year, as occurred on 1st day of the month otherwise (i.e. in case the month and year is after the month and year of IMP administration);
  - as non-treatment emergent if start month and year is before the month and year of IMP administration; for the scope of AE duration derivation, these AE will be considered as occurred on 1st day of the month or on informed consent, whichever comes later.
- Adverse events with completely unknown end dates will be considered as ended on the day of last contact with the subject.
- Adverse events with unknown end day and month but with known end year:
  - if the AE end year is before the year of last contact with the subject, AE will be considered as ended on 31st December.
  - if the AE end year coincides with the year of last contact with the subject, AE will be considered as ended on day of last contact with the subject.
  - if AE end year is after the year of last contact with the subject, for the scope of AE duration derivation, the date of last contact with the subject will be used as the AE end date.

- Adverse events with unknown end day but known end month and end year:
  - if the AE end month and year are before the month and year of last contact with the patient, AE will be considered as ended on last day of the month.
  - if the AE end month and year are coinciding with the month and year of last contact with the patient, AE will be considered as ended on the date of last contact with the patient.
  - if AE end month and year are after the month and year of last contact with the patient, for the scope of AE duration derivation, the date of last contact with the patient as AE end date.

Adverse events with completely or partial unknown start and end dates as above will be shown as not known (NK), for the respective unknown part, in the listings.

5.1.7 Data Presentation

5.1.7.1 Listings

All original and derived parameters will be listed.

Listings will include both scheduled and unscheduled measurements; such measurements will appear in chronological order together with the scheduled time points.

All listings will be sorted by study site, subject number and time (visit). Study site will always be shown in listing together with subject number.

Unless otherwise specified, a relative study day will be provided for each date.

Unless otherwise specified, listings will be presented based on all treated subjects.

5.1.7.2 Tables and descriptive statistics

Summaries will be provided by study visit.

Where appropriate, variables will be summarized descriptively by study visit.

In general, variables with multiple categories will be summarized according to natural ordering (e.g., age category, number of fistula openings); where a natural ordering does not exist

(example: gender, race, AE SOC, AE PT), categories will be displayed by descending frequencies.

For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. As specified in this SAP at section 5.10, 95% 2-sided confidence intervals (CIs) can be presented for selected proportion-based efficacy endpoints. Clopper Pearson technique will be used to produce 95% 2-sided CIs; in case the Clopper Pearson 95% CIs has to be estimated for a proportion equal to 0%, the lower bound of the CI will be set to 0% while the upper bound will be calculated as (1-0.051/n)*100; in case the Clopper Pearson 95% CIs has to be estimated for a proportion equal to 100%, the upper bound of the CI will be set to 100% while the lower bound will be calculated as (0.051/n)*100 [2].

For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

The following rules will apply to all descriptive statistic displays, where 'd' denotes the decimal places in the original reported value:

- n (number of non-missing observations): 0 decimal places (d.p.)
- Mean: d + 1 d.p.
- SD: d + 2 d.p.
- Median: d + 1 d.p.
- Minimum: d
- Maximum: d
- Statistics in percentage: 1 d.p.
- CIs: d + 1 d.p.
- A maximum of 3 decimal places will be displayed.

All confidence intervals will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated.

5.1.7.3 Figures

Figures will be produced in black and white.

5.2 Analysis Sets

The primary analysis set for this study will be the safety analysis set (SAF), which will consist of all subjects who enroll in the study and receive treatment with Darvadstrocel.
Subjects who did not receive Darvadstrocel will not be included in SAF, these will be considered as screening failures.
Unless otherwise specified, SAF will be the primary analysis set to be used for all statistical analysis of the demographic and baseline characteristics, as well as safety and efficacy analysis.
Unless otherwise specified, listings will be presented based on SAF; Screening Failures, and SAF subjects will be flagged differently.
Assignment to Analysis Sets will be listed by subject as defined in SAP section 5.1.7.1

5.3 Disposition of Subjects

5.3.1 Study Information

Summary of study information will include date first subject signed ICF, date of last subject's last visit/contact, MedDRA Version, WHODrug Version, SAS Version.

5.3.2 Subjects Enrollment

Subject Enrollment summaries will be presented based on all subjects who signed informed consent (all screened subjects), percentages will be calculated based on number of screened subjects.
Subject Enrollment summaries will be provided overall and by site and will include:

- Number of subjects screened;

- Number and percentage of Screen Failures along with reasons for Screen Failures (Screen Failures are subjects screened which for any reason did not receive the IMP);
- Number and percentage of subjects who received IMP but with no post dosing safety information;
- Number and percentage of subjects who received IMP and with post dosing safety information (i.e. SAF analysis set).

5.3.3 Subjects Disposition

Subject Disposition summaries will be presented based on SAF.

Subject Disposition summaries will be provided overall and by site and will include:

- Number and percentage of subjects who prematurely discontinued the study for any reason along with the reason
- Number and percentage of subjects who completed the study.

Subject disposition listing will be provided based on all screened subjects. Subject disposition listing will include the date of informed consent, the date of first IMP administration (Not Applicable for Screen Failures), the date of last contact, the subject status with respect to study completion (Screen Failure, Premature Discontinuation, Completer), the reason for premature discontinuation (or the reason for Screen Failure), and if applicable the date of death and primary cause for death.

Listing of failed Inclusion and Exclusion Criteria will be presented based on all screened subjects; this listing will include the subject status with respect to study completion (Screen Failure, Premature Discontinuation, Completer) and the reason for premature discontinuation (or the reason for Screen Failure).

Subjects who received IMP but with no post dosing safety information will be flagged in these listings.

Rescreened subjects and screen failures will be listed by subject on all screened subjects as defined in SAP sections 5.1.7.1.

5.3.4 Protocol Deviations

A protocol deviation (PD) is any change, divergence or departure from the study design or procedures of a study protocol. Major PDs are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.
Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.
During the study, investigator will keep trace of significant PDs by logging them in the CRF.
All PDs will be discussed during a Data Review Meeting (DRM) and addressed with the final classification, as well their overall effect will be evaluated on a subject by subject basis. During DRM all PDs and their possible impacts will be discussed between PAREXEL and the Sponsor and will be assessed as 'Minor' or 'Major'. At the time of DRM, the definition of a per protocol analysis set will be evaluated, based on the nature of the PDs observed. Should a per protocol analysis set be defined, selected analysis will be repeated based on this population to confirm results obtained and summarized in primary analysis set (SAF).
All protocol deviations will be listed by subject.
In accordance with FDA [3] and EMA [4] guidance for Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic, PDs caused by or related to COVID-19 pandemic will be identified and flagged in the protocol deviation listing. Significant PDs will be flagged as well in the PD listing.

5.4 Demographic and Other Baseline Characteristics

5.4.1 Demographics

Demographic variables include:

- Gender
- Country
- Year of birth
- Age at Informed Consent (years, as collected in CRF)

- Ethnicity
- Race
- Height

Demographic variables will be listed by subject and summarized descriptively as defined in SAP sections 5.1.7.1 and 5.1.7.2.

5.4.2 Subject Habits

Subject habits variables include following substance use detail:

- Status of alcohol consumption at informed consent, amount of alcohol consumption, date of alcohol consumption stops and alcohol consumption (years)
- Status of cigarettes smoking at informed consent, number of cigarettes smoked, date of stop smoking (for former smokers) and smoking duration (years)
- Status of cigars smoking at informed consent, number of cigars smoked, date of stop smoking (for former smokers) and smoking duration (years)
- Status of pipes smoking at informed consent, number of pipes smoked, date of stop smoking (for former smokers) and smoking duration (years)

Subject habits variables of substance use detail will be listed by subject as defined in SAP section 5.1.7.1.

Subject status concerning alcohol consumption, cigarettes, cigars and pipe smoking will be summarized descriptively as defined in SAP section 5.1.7.2.

5.4.3 Prior CD and Perianal Disease History

Prior CD and Perianal Disease History include:

- Availability of a CD diagnosis [Yes, No] and Date of CD diagnosis
- Family history of CD [Yes, No]
- Any surgical procedures related to CD or Perianal Fistula/area of disease [Yes, No] (together with category, type, date and location of surgery)

- Date of first Darvadstrocel administration
- Prior participation in a Darvadstrocel trial and prior subject ID
- Number of Internal Opening (IO) treated
- Number of External Opening (EO) treated
- Type of response after first administration
- Duration of response after first administration
- Duration between CD diagnosis and repeated administration
- Duration between first administration and the repeated administration
- Reason for Darvadstrocel repeated administration

Prior CD and perianal disease history, prior CD and perianal disease surgical procedures, Darvadstrocel subject participation history and prior and repeated Darvadstrocel administration will be listed by subject as defined in SAP sections 5.1.7.1.

Family history of CD, surgical procedures related to CD or Perianal Fistula/area of disease (together with category, type and location of Surgery), type of response after first administration and reason for Darvadstrocel repeated administration will be summarized descriptively as defined in SAP section 5.1.7.2.

5.4.4 Prior Systemic Gastrointestinal Therapies

Prior Systemic Gastrointestinal Therapies information include:

- Intake any of the following Immunosuppressive (IS) agents for Fistulizing CD within 2 years (including for each agent: intake status at IC signature, dose, frequency and Primary Reason for Discontinuation)
    - Azathioprine
    - Mercaptopurine
    - Methotrexate
- Intake of monoclonal antibody for Fistulizing CD within 2 years:

- Monoclonal Antibody
- Treatment Setting
- Intake status at Signing of Informed Consent
- Dose
- Frequency
- Primary Reason for Discontinuation

Prior Systemic Gastrointestinal Therapies will be listed by subject as defined in SAP sections 5.1.7.1

Intake of IS agents and IS agents assumed, as well as intake of monoclonal antibody assumed will be summarized descriptively as defined in SAP section 5.1.7.2.

5.4.5 Target fistula(s) information and treatment history

Target fistula(s) information include:

- Target fistula description [Previous treated fistula not in complete remission; Relapse of the previous treated fistula; New Fistula; Previously treated and a new fistula treatment]
- Previous treated fistula
  - Date of Onset
  - Type of fistula previously treated
  - Number of EO of the fistula previously treated
- New fistula
  - Type of new fistula
  - Number of EO of the new fistula
  - Date new fistula was discovered
- Treatment History of Target Fistula(s)
  - Type of surgery
  - Date of surgery
  - Fistula previously treated with Darvadstrocel [Yes, No]

Target fistula information will be listed by subject and summarized descriptively as defined in SAP sections 5.1.7.1 and 5.1.7.2.

5.4.6 Luminal Crohn's disease activity involving the rectum

Data related to luminal Crohn's disease activity involving the rectum include:

- Colonoscopy performed within 6 months prior to screening [Yes, No]
- Date of Colonoscopy
- Presence of proctitis as measured by flexible sigmoidoscopy or rectoscopy [Yes, No]
- Severe rectal ulcers >0.5 cm making a surgery procedure impossible [Yes, No]

Luminal Crohn's disease activity involving the rectum is an optional baseline assessment.

Luminal Crohn's disease activity data involving the rectum will be listed by subject as defined in SAP section 5.1.7.1.

5.4.7 Fistula preparation techniques

Fistula preparation techniques include:

- Subject undergoing fistula examination under anesthesia [Yes, No] IOs identified [Yes, No]
    - Number of IOs and location
    - Fistula curettage and adequate drainage confirmed [Yes, No]
    - Seton(s) placed [Yes, No] and number of setons placed
    - Antibiotics prescribed
- External Openings A, B and C location
- Location of additional External Openings, if any.

Fistula preparation techniques including surgery preparation and surgery procedures checklist, openings details and screening MRI will be listed by subject as defined in SAP sections 5.1.7.1 .

Fistula preparation of surgery preparation and antibiotics prescription, and fistula preparation with openings details will be summarized descriptively as defined in SAP sections 5.1.7.2.

The distribution of the topography of internal and external openings (tracts) at the preparation

visit will be summarized.

5.4.8 IMP Administration

Variables collected as part of the IMP administration include and summarize:

- Treatment Administration performed [Yes, No] and reason for non-performed as well as need to reschedule Visit 1
- Date and time of treatment administration
- Treatment kit number
- Treatment kit adequate temperature records [Yes, No]
- Investigational Medicinal Product (IMP) containers are sealed [Yes, No]
- Central MRI report / images available at the surgical intervention [Yes, No]
- Anesthetic strategy [General anesthesia, Spinal – intradural, Spinal – epidural, Local anesthesia]
- Setons removed prior to treatment administration [Yes, No]
- Fistula curettage and adequate drainage confirmed [Yes, No]
- IO1 and IO2 (separately)
    - Location
    - Administered volume in mL
    - Closure with absorbable suture prior to treatment administration
    - Number of stitches placed
- EOA, EOB and EOC (separately)
    - Location
    - Administered volume in mL

IMP administration details will be listed as defined in SAP sections 5.1.7.1 as well as IMP accountability by opening.

Number and location of fistula tracts treated will be listed by subject and summarized descriptively as defined in SAP sections 5.1.7.1 and 5.1.7.2.

5.5 Medical History and Concurrent Medical Conditions

Medical history includes all medical and surgical events within 2 years before the baseline visit, including all significant lifetime medical history as well as number of pregnancies, history of blood transfusions, transplantation, anal canal or colorectal malignancy, and clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at baseline/enrollment examination, according to the judgment of the investigator.

The medical history and concurrent medical condition will be presented by system organ class and preferred term.

Collection and analysis of prior CD and perianal disease history are described in section 5.4.3 of this SAP.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at the time of repeated Darvadstrocel administration. These concurrent medical conditions will be recorded in EDC medical history form with ongoing checked box.

Medical conditions start and stop dates will be compared to the date of repeated Darvadstrocel administration:

- Medical conditions that start and stop prior to the date of repeated Darvadstrocel administration will be classified as prior medical history.
- If a medical condition starts before the date of repeated Darvadstrocel administration and stops on or after that date, it will be concurrent medical condition.

If medical condition start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of repeated Darvadstrocel administration.

Medical history and concurrent diagnosis will be listed together and will include at least the following:

- Reported Term for Medical History
- System Organ Class (SOC)
- Preferred Term (PT)

- Start date and end date (or ongoing, if applicable) [partial start date and end date will be printed as received]
- End date relative to Signing Informed Consent [before/after].

All medical history and concurrent medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA), last available version at the time of data final cleaning. Listing will be provided for medical history and concurrent medical conditions.

5.6 Comorbidities of interest

Comorbidities of interest variables include the presence of specific CD related comorbidities:

- Arthritis/Arthralgia [Yes, No]
- Iritis/Uveitis [Yes, No]
- Erythema nodosum [Yes, No]
- Pyoderma gangremosum [Yes, No]
- Aphthous Stomatitis [Yes, No]
- Fever during the past week [Yes, No]
- Psoriasis [Yes, No]
- Primary Sclerosing Cholangitis [Yes, No]

Comorbidities of interest variables will be listed by subject and summarized descriptively as defined in SAP sections 5.1.7.1 and 5.1.7.2.

5.7 Prior and Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. At each study visit, all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, are recorded in the eCRF. Prior medications are all medications received within 2 years before the baseline visit, including but not limited to medications for the treatment of CD or perianal fistulas.

Medications administered prior to repeated Darvadstrocel administration which stopped prior to repeated Darvadstrocel administration will be considered as prior medications and flagged in the listing.

Medications which started before, on or after the repeated Darvadstrocel administration and which stopped after repeated Darvadstrocel administration (including medications which stopped the day of repeated Darvadstrocel administration) will be considered as concomitant medications.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of repeated Darvadstrocel administration. Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to repeated Darvadstrocel administration. If there is clear evidence to suggest that the medication stopped prior to repeated Darvadstrocel administration, the medication will be assumed to be Prior.

Prior and concomitant medications will be listed and will summarize at least the following:

- Reported name of drug, medication or therapy
- Dose per administration, dose unit and dosing frequency
- Route of administration
- Start date of medication (If unknown, indication if start date was BEFORE or AFTER signing Informed Consent is collected in CRF)
- End date of medication (If unknown, indication if end date was ONGOING or UNKNOWN at End of Study is collected in CRF)
- Indication
- If applicable, the related AEs.
- If applicable, treatment category
    - Systemic Antibiotics
    - Systemic Corticosteroids
    - Immunomodulators (6-MP, AZA, methotrexate)

- Biologics (anti-TNF-α agents, vedolizumab, ustekinumab)
- 5-ASAs
- Narcotic (opioid)
- Analgesics
- Antidiarrheals (loperamide, diphenoxylate)

Concomitant medication will be coded using the World Health Organisation-Drug Dictionary (WHO-DD) (last available version at the time of data final cleaning) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

5.8 Concomitant Procedures

Procedures will be defined as concomitant if performed after to the repeated Darvadstrocel administration, or on the day of repeated Darvadstrocel administration.

If medication start and/or end dates are missing or partial, the dates will be compared as far as possible with the date of repeated Darvadstrocel administration. Procedures will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the procedure stopped prior to repeated Darvadstrocel administration.

Concomitant procedures will be listed and will summarize at least the following:

- Procedure Name
- Start date (If unknown, indication if start date was BEFORE or AFTER signing Informed Consent is collected in CRF)
- End date (If unknown, indication if end date was ONGOING or UNKNOWN at End of Study is collected in CRF)
- Indication
- If applicable, the related Adverse Event(s) (AEs).

5.9 Outcome Study Drug Exposure and Compliance

The drug being administered in this study is Darvadstrocel (Cx601) 24 mL suspension. Subjects will receive a single open-label Darvadstrocel dose of 120 million cells (5 million cells/mL) for local injection in the fistula.

All cases of overdose (with or without associated AEs) will be documented as a medication error on the AESI page of the eCRF.

Date of IMP administration, and dose administered (in volume) will be listed by subject as defined in SAP sections 5.1.7.1 and 5.4.8.

5.10 Efficacy Analysis

5.10.1 Primary Efficacy Endpoint(s)

Not Applicable. Primary study Endpoint involve safety assessments. Efficacy Endpoints are secondary and exploratory.

5.10.2 Secondary Efficacy Endpoint(s)

Unless otherwise specified, efficacy parameters will be listed and summarized based on SAF.

5.10.2.1 Fistula clinical assessment

Clinical fistula assessment information will be listed by subject and summarized descriptively (with the exception of date of examination) as defined in SAP sections 5.1.7.1 and 5.1.7.2. At post baseline visits, percentage of closed external fistula openings which were draining at baseline will also be included in the listing.

Subjects in clinical remission and subjects in clinical response at a specific visit will be flagged in clinical fistula assessment listing.

Clinical remission and clinical response will also be listed by subject and visit, as defined in SAP section 5.1.7.1.

Additionally, a shift table will be presented for any draining opening (refer to SAP section 3.2.1) to show change in draining status from baseline to Week 6, Week 24, Week 52, Week 104,

Week 156 and Early Termination Visit. In shift tables, a missing category will be used for missing assessment of clinical fistula at specific timepoints.

5.10.2.2 Perianal Disease Progression (PADP)

The number of perianal disease progression will be summarized by visits as defined in SAP section 3.2.3.

PADP information will be listed by subject as defined in SAP section 5.1.7.1.

5.10.2.3 Clinical remission at Weeks 6, 24, 52, 104, and 156 after IMP administration

Number and percentage of subjects in clinical remission will be summarized descriptively as defined in SAP section 5.1.7.2; additionally, 95% 2-sided CIs will be provided for percentage of subjects in clinical remission. As a general approach, missing outcomes will not be imputed; furthermore, the analysis will be repeated using the NRI rule as a sensitivity analysis; please refer to Section 5.1.6.1.

Additionally, a shift table will be presented to show change in clinical remission status at Week 52, Week 104, and Week 156 assessments with respect to Week 24. In shift table, missing category will be used for missing assessment of clinical fistula at specific timepoints.

5.10.2.4 Clinical response at Weeks 6, 24, 52, 104, and 156 after IMP administration

Number and percentage of subjects in clinical response will be summarized descriptively as defined in SAP section 5.1.7.2; additionally, 95% 2-sided CIs will be provided for percentage of subjects in clinical response. As a general approach, missing outcomes will not be imputed; furthermore, the analysis will be repeated using the NRI rule as a sensitivity analysis; please refer to Section 5.1.6.1.

Additionally, a shift table will be presented to show the change in clinical response status at Week 52, Week 104, and Week 156 assessments with respect to Week 24. In shift tables, a missing category will be used for missing clinical fistula assessments at specific timepoints, including reference assessment at Week 24.

5.10.2.5 Time to reopening

The median time to reopening as well as 12-month and 24-month rates and the corresponding 95% CIs will be estimated using the Kaplan-Meier product-limit method. Number and percent of censored patients will be presented.

5.10.2.6 New perianal abscess in treated fistula

Number and percentage of subjects with new perianal abscess in treated fistulas (based on central MRI) will be summarized descriptively as defined in SAP section 5.1.7.2; additionally, 95% 2-sided CIs will be provided for percentage of subjects with new perianal abscess.

5.10.2.7 Perianal Crohn's Disease Activity Index (PDAI)

The total score and five items of the PDAI together with changes from baseline will be listed by subject and summarized descriptively as a continuous parameter as defined in SAP sections 5.1.7.1 and 5.1.7.2

5.10.2.8 Patient reported outcomes measure derived from CDAI (PRO-2)

PRO-2 score information (number of liquid or very soft stool and abdominal Pain) and total score change from baseline will be listed by subject and summarized descriptively as defined in SAP sections 5.1.7.1 and 5.1.7.2.

5.10.3 Exploratory Endpoint(s)

Plasma sample for DSA and immunogenicity will be listed by subject as defined in SAP section 5.1.7.1 and summarized descriptively as defined in SAP section 5.1.7.2.

The following analysis will be performed for the DSA and immunogenicity data.

- Frequency of the HLA+ as well as pre-sensitized (DSA+) and naïve subjects at baseline will be provided.
- Frequency and percentage of immunogenicity events (DSA+) will be summarized by visits. Subgroup analysis will include frequency of immunogenicity events for naïve and pre-sensitized groups.

- Analysis of endpoints clinical response and clinical remission at Weeks 6 and 24 will be summarized by subgroups of naïve vs pre-sensitized and for DSA+ and DSA- population within each subgroup.
- TEAE through Week 6 and through Week 24 will be summarized by subgroups of naïve vs pre-sensitized and for DSA+ and DSA- population within each subgroup.
- TESAE through Week 6 and through Week 24 will be summarized by subgroups of naïve vs pre-sensitized and for DSA+ and DSA- population within each subgroup.

5.11 Pharmacokinetic/Pharmacodynamic Analysis

Not Applicable

5.11.1 Pharmacokinetic Analysis

Not Applicable

5.11.2 Pharmacodynamic Analysis

Not Applicable

5.12 Other Outcomes

Not Applicable.

5.13 Safety Analysis

Study primary endpoint consists of the analysis of TEAEs, TESAEs, SSRs and AESIs.

5.13.1 Primary Safety Analysis

Unless otherwise specified, all listings will be produced based on all treated subjects while summary tables will be produced on the SAF.

5.13.1.1 Adverse Events

The following information will be included in the AE listing: identifier event number, reported term, System Organ Class (SOC), Preferred Term (PT), start date, end date, duration (days),

pattern, severity/intensity, relationship to study treatment, relationship to study procedure, outcome, seriousness flag, AESI flag.

A separate listing will be produced for SAEs as well as separate listing detail of SAE. The following information will be included in the SAE listing: identifier event number, reported term, System Organ Class (SOC), Preferred Term (PT), start date, end date, duration (days), narrative, relationship to study treatment, occurring of event with an overdose and seriousness criteria. If seriousness criteria consist in a persistent or significant disability/incapacity, the disability/incapacity will be reported; if the event resulted in death, then general cause and date of death will be reported as well as information whether autopsy was performed, and death certificate obtained; if the event required a prolonged hospitalization, date of hospitalization and discharge will be reported.

A separate listing will be produced for AESI.

The TEAEs will be presented using summary tables including:

- Overall Summary including TEAEs, treatment-related TEAEs, TESAEs, treatment-related TESAEs, TEAEs leading to study discontinuation, TESAEs leading to study discontinuation, fatal TESAEs
- TEAEs by SOC and PT
- TEAEs by decreasing frequency of PT
- Treatment-related TEAEs by decreasing frequency of PT
- TESAEs by SOC and PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related TESAEs by SOC and PT
- TEAEs by severity, SOC and PT
- TESAEs by severity, SOC and PT
- TEAEs leading to study withdrawal by SOC and PT
- TESAEs leading to study withdrawal by SOC and PT

- Treatment-emergent AESIs by SOC and PT for each AESI category from MedDRA terms
- Treatment-emergent AESIs by SOC and PT for each AESI category from CRF
- TEAEs related to the IMP administration procedure by SOC and PT
- TESAEs related to the IMP administration procedure by SOC and PT
- TEAEs by relationship, SOC and PT
- TESAEs by relationship, SOC and PT
- Fatal TESAEs by SOC and PT

In above summaries, both number of events and number of subjects by cumulative up to week 6, week 24, week 52, week 104, week 156 and overall with event will be reported. Incidences will be presented both as the proportion of subjects with the event and as rate of events per patient-year. Related events are defined as events with relationship to treatment/procedure of related or missing; unrelated events are defined as events with relationship to treatment/procedure of not related. Missing severity or outcome will be classed as unknown. After considering incomplete dates of any adverse Events (AEs) in section 5.1.6.1, the start and end dates of an Adverse Event (AE) will be used to determine which scheduled study visits it corresponds to. For instance, if an AE begins during one scheduled visit and continues into the next scheduled visit, it will be counted for both of these visits. This means that a single AE could potentially be associated with multiple scheduled visits, depending on its duration. However, if an adverse event is ongoing without end dates, then only start date will be used to determine which scheduled study visits it corresponds to.

5.13.1.2 Special situation reports (SSRs)

SSRs will be listed by subject as defined in section 3.1.1.2. However, only a medication error should be recorded as an AESI and reported as an SSR.

5.13.1.3 Adverse Events of Special Interest (AESIs)

AESIs will be listed by subject as defined in Appendices section 7.3.

The incidence of AESI will be presented in a summary table.

5.13.2 Clinical Laboratory Evaluations

Laboratory tests will be collected at Baseline / Enrollment Visit, Week 24, Week 156 and Early Termination Visit.

Laboratory tests collected are:

- Hematology: hemoglobin, hematocrit, erythrocytes, mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), leukocytes, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelet count.
- Biochemistry: c-reactive protein (CRP), urea, creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin (direct bilirubin if total bilirubin is above the upper limit of normal), potassium, sodium and chloride.

All clinical laboratory test results will be presented and summarized by visit using the International System of Units (SI units; Système International d'Unités). The original lab test units will be converted to SI according to Young, D.S and Huth, E.J; 1998; SI Units for Clinical Measurement; American College of Physicians; Philadelphia and Burtis, C.A, Ashwood, E.R and Bruns, D.E; 2008; Fundamentals of Clinical Chemistry; Saunders Elsevier; Missouri [Laboratory test converted to SI will be stored in SDTM LB domain as LBSTRESU and LBSTRESC].Laboratory tests will be listed by subject as defined in SAP section 7.1.7.1.

Shift from in range to out-of-range parameters will be presented in a shift table; missing category will be used for missing assessment.

Laboratory test results falling outside the reference range will be flagged accordingly. Values below the lower limit will be marked as 'L' (low), while those above the upper limit will be designated as 'H' (high). These flags, along with the corresponding CTCAE grade, will be incorporated into the listings for reference.

When calculating changes from Baseline, any laboratory parameters recorded in the database with inequality symbols (such as '<xx' or '>xx') will be treated as their absolute numerical value, disregarding the sign. For instance, a value of <2.2 will be considered as 2.2 in these calculations. This approach ensures consistent handling of out-of-range values and those reported with inequality symbols, maintaining accuracy in the analysis of changes from Baseline across all laboratory parameters.

5.13.3 Vital Signs and Weight

Vital Signs will be collected at all visits.

Vital Signs information include:

- Date and Time of measurement
- Reason if not measured
- Weight (kg)
- Body temperature (°C)
- Systolic blood pressure (mmHg), with subject position
- Diastolic blood pressure (mmHg), with subject position
- Pulse rate (bdm), with subject position

Change from baseline to post baseline in vital signs will be derived as:

Change from baseline = (Post baseline visit score – Baseline visit score)

For baseline definition please refer to SAP section 5.1.3.

Vital Signs and Weight information will be listed by subject as defined in SAP section 5.1.7.1.

Vital Signs and Weight and change from baseline will be summarized descriptively as defined in SAP section 5.1.7.2.

5.13.4 12-Lead ECGs

Not Applicable

5.13.5 Other Observations Related to Safety

5.13.5.1 Physical examination

Physical examination will be collected at all visits.

All abnormal findings from the physical examination will be listed as defined in SAP section 5.1.7.1.

5.13.5.2 Serum and Urine Pregnancy Test

Female Reproductive System Status (Childbearing Potential; Postmenopausal; Premenarche; Surgically Sterile; Other Female Reproductive System State) will be listed by subject as defined in SAP section 5.1.7.1.

Serum pregnancy test will be collected at Baseline Visit.

Urine pregnancy test will be collected at Preparation visit, Repeat Administration Visit, Week 6, Week 24, Week 52, Week 104, Week 156, Early Termination Visit and Unscheduled Visit.

Serum/Urine pregnancy test information includes:

- Lab Test Name (or reason for not collection)
- Sample Collection Date
- Pregnancy Test Result

Serum/Urine pregnancy test information will be listed as defined in SAP section 5.1.7.1 as well as pregnancy confirmation.

5.14 Interim Analysis

No interim analysis is planned for this study.

5.15 Changes in the Statistical Analysis Plan

1. Remove from SAP for the following exploratory endpoint of protocol section 5.2.3:

2. Provide clarification in SAP that central reading MRI will no longer be performed due to study early closure. Neither patient's MRIs from January 2025 and onwards.
3. Remove from SAP for relapse and combined remission since central MRI reading is no longer available.
4. Update SAP for Section 3.2.1.6 time to re-opening requires combined remission which will be replaced with clinical remission for analysis.

6.0 REFERENCES

[1] SAS® Version 9.3. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[2] John M. Lachin, Biostatistical Methods: The Assessment of Relative Risks, Copyright© 2000 John Wiley & Sons, Inc.

[3] FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic; Guidance for Industry, Investigators, and Institutional Review Boards; March 2020

[4] Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic Version 1 (20/03/2020)

7.0 APPENDICES

7.1 APPENDIX A – Schedule of Study Procedures

Appendix A Schedule of Study Procedures

Assessment	Baseline Visit [a]	Preparation Visit to Visit 1 [b]	Repeat Administration	6 Weeks ±8 days	24 Weeks ±15 days [c]	52 Weeks ±15 days [c]	104 Weeks ±30 days [c]	156 Weeks ±30 days [c]	Early Termination Visit	Unscheduled Visit [d]
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6		
Enrollment [e]	-	X								
ICF	X									
Inclusion and exclusion criteria check	X	X								
IWRS	X	X	X	X	X	X	X	X	X	X
Demographics, height and lifestyle [f]	X									
Weight	X	X	X	X	X	X	X	X	X	X
Medical history [g]	X									
Prior and repeated darvadstrocel administration	X									
Physical examination with vital signs [h]	X	X	X	X	X	X	X	X	X	X
CD history, fistula history, and treatment history [i]	X									
Target fistula(s) information (new fistula or previously treated fistula) [j]	X									
Serum pregnancy test	X									
Urine pregnancy test		X	X [l]	X	X	X	X	X	X	X
Comorbidities of interest	X									
Central laboratory tests [k]	X				X			X	X	
Plasma sample for DSA and immunogenicity	X		X [l]	X	X				X [m]	
[redacted]										
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Fistula preparation [n]		X								
Mandatory antibiotic prescription [o]		X								

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		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6		
Fistula treatment [p]			X							
IMP administration [q]			X							
Fistula clinical assessment [r]	X [s]	X	X	X	X	X	X	X	X	X
Pelvic MRI [t]	X				X			X	X	X
PDAI score	X		X	X	X	X	X	X	X	X
PRO-2 score [u]	X	X	X	X	X	X	X	X	X	X
If available, luminal disease activity involving the rectum [v]	X									
All AEs/SAEs, pregnancy, AESIs, and SSRs	X	X	X	X	X	X	X	X	X	X

5-ASA: 5-aminosalicylate; 6-MP: 6-mercaptopurine; AE: adverse event; AESI: adverse event of special interest; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AZA: azathioprine; CD: Crohn's disease; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; DSA: donor-specific antibodies; eCRF: electronic case report form; ICF: informed consent form; IMP: investigational medicinal product; IWRS: interactive web response system; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MRI: magnetic resonance imaging; PDAI: Perianal Disease Activity Index; PRO-2: patient-reported outcome-2; SAE: serious adverse event; SSR: special situation report; TNF-α: tumor necrosis factor-alpha; ULN: upper limit of normal.

[a] Repeat administration (Visit 1) should take place within 8 weeks of the baseline visit (may be longer if repeat administration needs to be rescheduled). There will be a maximum of 5 weeks from the baseline visit to the preparation visit.

[b] From preparation visit to repeat administration (Visit 1) there will be a minimum of 2 weeks and maximum of 3 weeks (necessary to have darvadstrocel treatment ready for administration). If there is any problem administering darvadstrocel during Visit 1, the visit will need to be rescheduled within a minimum of 2 weeks and a maximum of 3 weeks of the original Visit 1.

[c] Due to unavoidable circumstances (ie, COVID-19 pandemic), the Week 24 visit may be conducted within 60 days of the scheduled visit. Visits at Weeks 52, 104, and 156 may be conducted within 90 days of the scheduled visit.

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		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6		

[d] The unscheduled visit can take place in the form of a telephone-call in case the subject cannot attend the site for a visit or for any contact requested by the subject between scheduled visits. The following information will be recorded: date and reason for unscheduled telephone call; assessment of AEs/SAEs, pregnancy, AESIs, and SSRs; review and record concomitant medications taken since the last visit; remote evaluation of the fistula.

[e] Subjects will be enrolled once the physician has decided to readminister darvadstrocel and all study entrance criteria has been met at the preparation visit.

[f] Including age, sex, country, smoking history, and alcohol use.

[g] Including number of pregnancies, history of blood transfusions, transplantation, and anal canal or colorectal malignancy. Prior medication to include specific drug used, indication, dose received, route of administration, and start/end dates, within the last 2 years of use and may include the following: darvadstrocel, systemic antibiotics, systemic corticosteroids, immunomodulators including, but not limited to 6-MP, AZA, methotrexate, anti-TNF-α agents, vedolizumab, ustekinumab, 5-ASAs, narcotic (opioid) analgesics, antidiarrheals (loperamide, diphenoxylate).

[h] Physical examination and vital signs (temperature, heart rate, and blood pressure) will be recorded.

[i] Including family history, age at onset, medical and surgical history for any CD-related surgery, and surgeries to treat relapse of treated perianal fistula and new perianal fistula; preparation surgery will be completed before darvadstrocel administration.

[j] Target fistula information (clinical characteristics including date of onset, number of other fistulas, localization, and clock position [see Appendix B], including whether fistula to be treated was previously treated with darvadstrocel or if it is a new fistula).

[k] Hematology: hemoglobin, hematocrit, erythrocytes, MCV, MCH, MCHC, leukocytes, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelet count.

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

[l] Samples to be taken before repeat administration.

[m] Plasma samples do not need to be taken if the early termination visit takes place after the Week 24 visit.

[n] Fistula preparation will consist of examination under anesthesia, curettage, and seton placement. Seton placement/removal and curettage will be performed by the surgeon according to the surgery procedure manual (provided as a separate document).

[o] Mandatory antibiotics coverage will be administered during at least 7 days following the fistula curettage (ciprofloxacin and/or metronidazole are recommended).

[p] Identification of number and location of fistula tracts to be treated.

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[q] All procedures should be performed before darvadstrocel administration. If there is any problem administering darvadstrocel at the repeat administration visit, the visit should be rescheduled within a minimum of 2 weeks and a maximum of 3 weeks of the original Visit 1. It is not necessary to repeat the preparation visit, the setons will be maintained until the rescheduled treatment visit and will be withdrawn just before the administration of darvadstrocel. All repeat administration procedures are to be repeated, see Section 9.3.3. Details of darvadstrocel repeat administration will also be captured in the eCRF.

[r] Clinical response defined as closure of at least 50% of all treated external fistula openings that were draining at baseline, despite gentle finger compression. Clinical remission defined as closure of all treated external fistula openings that were draining at baseline despite gentle finger compression.

[s] Fistula must be actively draining for at least 6 weeks prior to the baseline visit.

[t] All MRI scans will be assessed centrally by 2 imaging readers (or 3 readers if adjudication is needed).

[u] PRO-2 score to be collected at baseline to confirm no or mildly active CD (score <14). The PRO-2 will be provided to the subject at each visit for their completion at home and is to be completed 7 days prior to the next visit.

[v] If available, check and record luminal disease activity involving the rectum (within 6 months prior to repeat administration).

7.2 APPENDIX B – Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome/malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

AE: adverse event.
Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

7.3 APPENDIX C – AESI from MedDRA Criteria Search

The following AEs are considered AESI.

- Tumorigenicity
  - SOC 'Neoplasms benign, malignant and unspecified (including cysts and polyps)'
  - SMQ 'Malignancies' (Broad and Narrow)
- Ectopic tissue formation
  - HLGT 'Benign neoplasms gastrointestinal'
- Hypersensitivity reactions
  - SMQ 'Hypersensitivity" (Broad and Narrow)
  - SMQ 'Anaphylactic reactions' (Broad and Narrow)
- Transmission of infectious agents
  - PT 'Transmission of an infectious agent via product'
- Medication errors
  - SMQ 'Medication errors' (Broad)
- Immunogenicity/Alloimmuno reactions
  - SMQ 'Immune-mediated/autoimmune disorders (Broad and Narrow)'
- Anal abscess, perirectal abscess and anal fistula
  - SMQ 'Gastrointestinal perforation, ulceration, haemorrhage or obstruction (Broad and Narrow)'

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