Clinical Study Protocol

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

Document Version and Date: Amendment 4, 29 Apr 2024

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.

TAKEDA PHARMACEUTICALS

PROTOCOL

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

Short Title

Postauthorization Safety Study of Darvadstrocel Repeat Administration

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA		
Study Number:	Alofisel-4001		
IND Number:	17707	**Abbreviated EU CT Number:**	2022-503014-23
		EUPAS number:	EUPAS31439
Compound:	Darvadstrocel Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue (expanded adipose stem cells)		
Date:	29 April 2024	**Amendment Number:**	4

Amendment History:

Date	Amendment Number	Amendment Type	Region
29 April 2024	Amendment 4	Nonsubstantial	Global
11 October 2023	Amendment 3	Nonsubstantial	Global
04 August 2021	Amendment 2	Substantial	Global
01 July 2020	Amendment 1	Nonsubstantial	Global
22 May 2019	Initial protocol	-	Global

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 2.1 and relevant guidelines provided to the site.

Contact Type/Role	European/Rest of World Contact
Serious adverse event, special situation reports, and pregnancy reporting	Fax: +1-224-554-1052 Email: PharmacovigilanceMailbox@Takeda.com
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted] (Refer to the contact information list)

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference for Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations (eg, European Union Clinical Trials Regulations), including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

ESignatures may be found on the last page of this document.

SIGNATURES

[redacted], PhD Date
[redacted], Statistics

[redacted], MD Date
[redacted]
Pharmacovigilance

[redacted], MD Date
[redacted], Clinical
Science

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations (eg, European Union Clinical Trials Regulations), including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix D).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix F of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 4 Summary of Changes

Protocol Amendment 4 Summary and Rationale:

This document describes the changes to the protocol incorporating Amendment 4.

The primary purpose of this amendment is to update the protocol to clarify informed consent for future use of exploratory biological samples.

In addition, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are applied throughout the document for clarification and administrative purposes.

The protocol amendment history for previous amendments is located in Appendix G.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 9.1.11.1 Collection, Storage, and Future Use of Biological Samples From Clinical Study Subjects	Added a statement that participation in future use of samples for exploratory biomarker research is voluntary, and subjects may decline to consent to future use of these samples while still participating in the main study.	To clarify that allowing biomarker samples to be retained for future use is not required for study participation.

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2.0 STUDY REFERENCE INFORMATION

2.1 Study-Related Responsibilities

The sponsor will perform all study-related activities except for those identified in the study-related responsibilities template. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

2.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the drug used in the study, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

2.3 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AOR	acknowledgment of receipt
AST	aspartate aminotransferase
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTA	Clinical Trials Regulations
DSA	donor-specific antibodies
eASC	expanded adipose stem cells
ECG	electrocardiogram
eCRF	electronic case report form
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRI	magnetic resonance imaging
PASS	postauthorization safety study
PCR	polymerase chain reaction
PDAI	Perianal Disease Activity Index
PRO-2	patient reported outcome score-2
SAE	serious adverse event
SAP	statistical analysis plan
SSR	special situation report
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
WOCBP	woman of childbearing potential

3.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** Darvadstrocel	
Title of Protocol: 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	**IND No.:** 17707	**Abbreviated EU CT Number:** 2022-503014-23 **EUPAS number:** EUPAS31439
Study Number: Alofisel-4001	**Phase:** 4	

Study Design:

This is a postauthorization safety study (PASS) to investigate the long-term safety and efficacy of a repeat administration with darvadstrocel in subjects with Crohn's disease (CD) and complex perianal fistula.

The study is a single-arm clinical study in subjects with CD and complex perianal fistulas, aged 18 years or older, who have previously been administered darvadstrocel (Alofisel) and repeat administration is planned by their physician. The study will be performed in countries where darvadstrocel is currently marketed.

The decision to retreat 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 complex perianal fistula tract. Only 1 repeat administration of darvadstrocel is permitted during study. If the subject has previously participated in a darvadstrocel study and it 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. In addition, a pelvic magnetic resonance imaging (MRI) will be performed and used to document fistula characteristics before repeat administration at the baseline visit. An MRI will also be performed post repeat administration at Week 24 to assess fistula characteristics and for the presence or absence of collection(s) >2 cm (in at least 2 dimensions) and at Week 156 to assess fistula characteristics and for the presence or absence of collection(s) >2 cm (in at least 2 dimensions). If subjects display significant new perianal symptoms, the subject will have an unscheduled visit and an MRI will be performed. Central reading of pelvic MRIs will be performed. All local MRIs will be assessed centrally by 2 imaging readers (or 3 readers if adjudication is needed).

Subjects will be 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 primarily to capture immunogenicity/donor-specific antibody (DSA)/soluble factors.

Blood samples for central laboratory tests and plasma samples for DSA levels and exploratory immunogenicity testing will be collected at specific time points in the study. 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 serious adverse events (SAEs) reported in these subjects.

Benefit-Risk Profile:

The decision to proceed with darvadstrocel repeat administration will be taken at the discretion of the treating physician before the subject enters the study; therefore, subject treatment will not be altered by their participation in this study.

The additional diagnostic and monitoring procedures conducted in this study pose minimal additional risk and

burden to the safety of the subjects compared with usual practice (blood extraction for immunologic analysis and contrast-enhanced MRI performance).

Darvadstrocel was safe and well tolerated. Overall, the data available to date present a positive benefit-risk profile for darvadstrocel.

Primary Objective:

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

Secondary Objective:

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

Exploratory Objectives:

- To characterize the immunogenicity of darvadstrocel (DSA) and the impact of immunogenicity on safety and clinical response.
- [redacted]

Subject Population:

Subjects with CD aged 18 years or older, with complex perianal fistulas who have previously received treatment with darvadstrocel and a repeat administration of darvadstrocel for the original fistula tract or for a new complex perianal fistula tract is planned by their physician.

Number of Subjects:	**Number of Sites:**
50 subjects	Approximately 20 to 30 sites
Dose Level:	**Route of Administration:**
Darvadstrocel (120 million cells)	Intralesional injection
Duration of Treatment:	**Period of Evaluation:**
Single dose	156 weeks after darvadstrocel repeat administration

Main Criteria for Inclusion:

Subject eligibility is determined according to the following criteria before entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form (ICF) and any required privacy authorization before the initiation of any study procedures.
3. The subject is male or female and aged 18 years or older.
4. The subject has complex perianal fistula(s) with a maximum of 2 internal openings and a maximum of 3 external openings based on clinical assessment and a reading of a locally performed contrast enhanced (gadolinium) pelvic MRI. Fistula(s) must have been draining for at least 6 weeks prior to baseline visit. A complex perianal fistula is defined as a fistula that meets 1 or more of the following criteria:
    a) High inter-sphincteric, high trans-sphincteric, extra-sphincteric or suprasphincteric.
    b) Presence of ≥2 external openings.
    c) Associated perianal abscess(es). Note: Abscesses that are larger than 2 cm in at least 2 dimensions on MRI must be confirmed to have been drained adequately by the surgeon during the preparation curettage in order to be eligible.
5. The subject has already received treatment with darvadstrocel for a complex perianal fistula at least 6 months prior to baseline visit for retreatment, and their physician has planned a repeat treatment

administration for the original tract (full remission not obtained or relapse of fistula draining) or for a new complex perianal fistula tract.

6. The subject has controlled or mildly active CD (defined as patient reported outcomes measure derived from Crohn's Disease Activity Index patient reported outcome score-2 score <14).
7. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use barrier method of contraception (eg, condom with or without spermicide) from signing of informed consent and until 1 year after repeat administration.
8. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use a highly effective/effective method of contraception from signing of informed consent and until 1 year after repeat administration.

Main Criteria for Exclusion:

A subject will not be included in the study if he/she meets ANY of the following criteria:

1. The subject has lack of clinical response to prior treatment with darvadstrocel, where 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 or in the case of a unique fistula, a partial closure of the fistula.
2. The subject has a history of hypersensitivity or allergies to darvadstrocel or related compounds.
3. The subject has a history of hypersensitivity or allergies to penicillin or to aminoglycosides; Dulbecco modified eagle medium; bovine serum; local anesthetics, or gadolinium.
4. The subject is currently participating in a double-blind clinical study with darvadstrocel. Subjects participating in the ongoing INSPIRE (Alofisel-5003) registry study would need to withdraw from that study in order to enroll in this study.
5. The subject is currently receiving or has received any other investigational medicinal product (IMP) within the last 3 months or at least 5 times the respective elimination half-life time, whichever is longer, before signing the ICF.
6. The subject has known or suspected coronavirus disease 2019 (COVID-19) by the investigator within the past 2 months (additional testing may be performed at the discretion of the investigator). Positive antibody testing for COVID without other evidence of current or recent active infection does not exclude participation.
    - Subjects who were in screening at the time that COVID 19–related factors resulted in discontinuation may also be rescreened with approval of the sponsor or designee.
7. The subject has major alterations in any of the following laboratory tests:
    a) Serum creatinine levels >1.5 times the upper limit of normal (ULN).
    b) Total bilirubin >1.5 × ULN.
    c) Aspartate aminotransferase or alanine aminotransferase >3.0 × ULN.
    d) Hemoglobin <10.0 g/dL.
    e) Platelets $<75.0 \times 10^9$/L.
    f) Albumin <3.0 g/dL.
8. The subject has an increased risk for a surgical procedure.
9. The subject has a known chronically active hepatopathy of any origin, including cirrhosis and subjects with persistent positive hepatitis B surface antigen and quantitative hepatitis B virus polymerase chain reaction (PCR) or positive serology for hepatitis C virus (HCV) and quantitative HCV PCR within 6 months prior to the baseline visit.
10. If female, the subject is pregnant or breastfeeding, or intending to become pregnant before participating in this study, during the study, or intending to donate ova during such time period.
11. If male, the subject intends to donate sperm during this study.
12. The subject has a contraindication to MRI scan (eg, due to the presence of pacemaker, hip replacement, severe claustrophobia, or renal insufficiency as defined by local clinical guidelines).
13. The subject has a contraindication to the anesthetic procedure.
14. The subject has severe rectal and/or anal stenosis that would make it impossible to follow the surgery procedure.
15. The subject has severe proctitis (rectal ulcers >0.5 cm) that would make it impossible to follow the surgery procedure.
16. The subject has any prior invasive malignancy diagnosed within the last 3 years before the baseline visit. Subjects with basal cell carcinoma of the skin completely resected outside the perineal region can be included.

17. The subject has a current or recent (within 6 months before the baseline visit) history of severe, progressive, and/or uncontrolled hepatic, hematologic, gastrointestinal (other than CD), renal, endocrine, pulmonary, cardiac, neurologic, or psychiatric disease that may result in subject's increased risk from study participation and/or lack of compliance with study procedures.
18. The subject has had major surgery of the gastrointestinal tract within 6 months before baseline, or any minor surgery of the gastrointestinal tract 3 months before the baseline visit.
19. The subject has had local major perianal surgery and/or treatment with darvadstrocel within 6 months before the baseline visit. The abscess drainage, cleaning surgery, or seton placement are not considered as "local major surgery" in this protocol.
20. The subject does not wish to or cannot comply with study procedures.

Main Criteria for Evaluation and Analyses:

Primary Endpoint:

The primary objective of safety will be assessed by evaluating the following safety parameters:

- Treatment-emergent AEs.
- Treatment-emergent SAEs.
- Pregnancy.
- Specific treatment-emergent AESIs:
  - Immunogenicity/alloimmune reactions.
  - Hypersensitivity.
  - Transmission of infectious agents.
  - Tumorgenicity, applying to malignant tumors only.
  - Ectopic tissue formation.
  - Medication errors (reported to the pharmacovigilance department as special situation reports).

Secondary Endpoints:

Efficacy will be assessed by evaluating the following endpoints:

- Proportion of subjects who achieve combined remission of perianal fistula(s) at Weeks 24 and 156 after darvadstrocel repeat administration, where combined remission is defined as:
  - The closure of all treated external openings that were draining at baseline, despite gentle finger compression,

    AND
  - Absence of collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by centrally read MRI assessment.
- Proportion of subjects who achieve clinical remission at Weeks 6, 24, 52, 104, and 156 after darvadstrocel 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, and 156 after darvadstrocel 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.
- Proportion of subjects with relapse from Week 24 combined remission, where relapse is defined as:
  - Reopening of any of the treated fistula(s) external openings with active draining as clinically assessed, that were in combined remission at Week 24,

OR

- The development of a collection >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by centrally read MRI assessment.

- Time to reopening of any of the treated external openings with active drainage as clinically assessed, measured in days relative to Week 24.
- Proportion of subjects with new perianal abscess in treated fistula.
- Change from baseline to Weeks 6, 24, 52, 104, and 156 after darvadstrocel repeat administration in scores of discharge and pain items of Perianal Disease Activity Index (PDAI) score.

Exploratory Endpoints:

- Immunogenicity responses as measured by DSA levels.
- [redacted]

Statistical Considerations:

Descriptive analysis of subject demographics and other baseline characteristics including CD characteristics and concurrent medications will be presented.

The safety analysis set will include all subjects retreated with darvadstrocel. Count and percentage of subjects with AEs, SAEs (defined as any SAE, regardless of relationship to study drug), and AESIs (immunogenicity/alloimmune reactions, hypersensitivity, tumorgenicity (applying to malignant tumors only), transmission of infectious agents, ectopic tissue formation, and medication errors) will be summarized descriptively by system organ class and preferred term. SAEs will also be summarized by severity and by relationship to study drug.

Categorical efficacy endpoints, including combined remission, clinical remission, clinical response, relapse, and new perianal abscess in the treated fistula will be summarized by visit.

Change from baseline in PDAI subscore (discharge and pain) will be summarized descriptively by visit.

The probability of reopening of any of the treated external openings with active drainage across time among subjects who achieve remission will be estimated using the Kaplan-Meier estimator.

Full details of the statistical analysis will be provided in the statistical analysis plan.

Sample Size Justification:

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

This study will plan to enroll approximately 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 complex perianal fistula tract according to their physician.

4.0 INTRODUCTION

4.1 Background

Adipose-derived mesenchymal stem cells are a promising new approach for the treatment of complex perianal fistulas because of their anti-inflammatory and immunomodulatory potential. Darvadstrocel, which is a suspension of expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue, is a promising new treatment. Darvadstrocel has immunomodulatory and anti-inflammatory properties resulting in the reduction of inflammation, which allows fistulas to heal through homeostatic mechanisms.

The efficacy of darvadstrocel was assessed in the Cx601-0302 ADMIRE-CD study. This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter clinical study to assess efficacy and safety of darvadstrocel for the treatment of complex perianal fistula(s) in subjects with Crohn's disease (CD). The study showed that a significantly greater proportion of subjects in the darvadstrocel group achieved the primary endpoint of combined remission at Week 24 compared with placebo. The safety data showed that darvadstrocel (Cx601) was well tolerated in the study population (Panes et al. 2016).

The repeat use of darvadstrocel was investigated in study Cx601-0101 where subjects received a single intralesional administration of darvadstrocel (20 million cells) and were followed-up for 24 weeks. Subjects who had incomplete fistula closure at Week 12 following first administration of darvadstrocel were administered a second dose (40 million cells). Twenty-four subjects initially received 20 million cells and 15 (65%) subjects received a second dose of darvadstrocel (repeat dose). Subjects who received a repeat dose showed comparable results in fistula healing compared with subjects who received a single dose. The adverse event (AE) profile following single dose and repeat dose was comparable. The generation of donor-specific antibodies (DSA) after a second administration of darvadstrocel was assessed. The evaluation of the impact of DSA generation on efficacy or safety of darvadstrocel was limited in this study due to the low number of subjects. However, no obvious detrimental effect of DSA on the efficacy and safety of darvadstrocel was observed (de la Portilla et al. 2013).

4.2 Rationale for the Proposed Study

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.

4.3 Benefit-Risk Profile

The decision to proceed with darvadstrocel repeat administration will be taken at the discretion of the treating physician before the subject enters the study, therefore subject treatment will not be altered by their participation in this study.

The additional diagnostic and monitoring procedures conducted in this study pose minimal additional risk and burden to the safety of the subjects compared with usual practice (blood extraction for immunologic analysis and contrast-enhanced magnetic resonance imaging (MRI) performance).

In clinical studies conducted to date, darvadstrocel appeared to be, overall, well tolerated up to 120 million cells per administration. No dose-dependent safety concern or toxicity has been identified to date. No ectopic tumor formation or hypersensitivity concerns have emerged to date. Overall, the data available to date presents a positive benefit-risk profile for darvadstrocel.

As with any other product containing human blood or plasma product, there is a theoretical possibility for transmission of viral agents, despite all controls performed by the manufacturer.

There are potential complications that may occur during surgery and/or on the days after the procedure and are related to the surgical procedure (eg, bleeding, wound infection, and procedural pain). Adverse reactions that were associated with the conditioning of the subject (curettage) or the surgical administration procedure included: proctalgia, procedural pain, postprocedural inflammation, and anal (perianal) abscess.

Known adverse drug reactions with darvadstrocel include proctalgia, anal abscess, and anal fistula.

There is currently limited experience in the efficacy and safety of repeat administration of darvadstrocel. Although subjects included in this study may not receive any benefit from their participation, the study will provide data on repeat administration that will be useful for maximizing the safe and effective use of darvadstrocel in the future.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 Secondary Objective

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

5.1.3 Exploratory Objectives

- To characterize the immunogenicity of darvadstrocel (DSA) and the impact of immunogenicity on safety and clinical response.

[redacted]

5.2 Endpoints

5.2.1 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.
  - Tumorgenicity, applying to malignant tumors only.
  - Ectopic tissue formation.
  - Medication errors (reported to the pharmacovigilance department as special situation reports [SSRs]).

5.2.2 Secondary Endpoints

Efficacy will be assessed by evaluating the following endpoints:

- Proportion of subjects who achieve combined remission of perianal fistula(s) at Weeks 24 and 156 after darvadstrocel repeat administration, where combined remission is defined as:
  - The closure of all treated external openings that were draining at baseline, despite gentle finger compression,

    AND

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

- Proportion of subjects who achieve clinical remission at Weeks 6, 24, 52, 104, and 156 after darvadstrocel 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, and 156 after darvadstrocel 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.
- Proportion of subjects with relapse from Week 24 combined remission, where relapse is defined as:
  - Reopening of any of the treated fistula(s) external openings with active drainage as clinically assessed that were in combined remission at Week 24,

    OR
  - The development of a collection >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by centrally read MRI assessment.
- Time to reopening of any of the treated external openings with active drainage as clinically assessed, measured in days relative to Week 24.
- Proportion of subjects with new perianal abscess in treated fistula.
- Change from baseline to Weeks 6, 24, 52, 104, and 156 after darvadstrocel repeat administration in scores of discharge and pain items of Perianal Disease Activity Index (PDAI) score.

5.2.3 Exploratory Endpoints

- Immunogenicity responses as measured by DSA levels.

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a PASS to investigate the long-term safety and efficacy of a repeat administration with darvadstrocel in subjects with CD and complex perianal fistula.

This study is a 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. A study schematic is presented in Figure 6.a.

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 complex perianal 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. In addition, a pelvic MRI will be performed and used to document fistula characteristics before repeat administration at the baseline visit. An MRI will also be performed post repeat administration at Week 24 to assess fistula characteristics and for the presence or absence of collection(s) >2 cm (in at least 2 dimensions) and performed at Week 156 to assess fistula characteristics and for the presence or absence of collection(s) >2 cm (in at least 2 dimensions). If subjects display significant new perianal symptoms, the subject will have an unscheduled visit and an MRI will be performed. Central reading of pelvic MRIs will be performed. All local MRIs will be assessed centrally by 2 imaging readers (or 3 readers if adjudication is necessary).

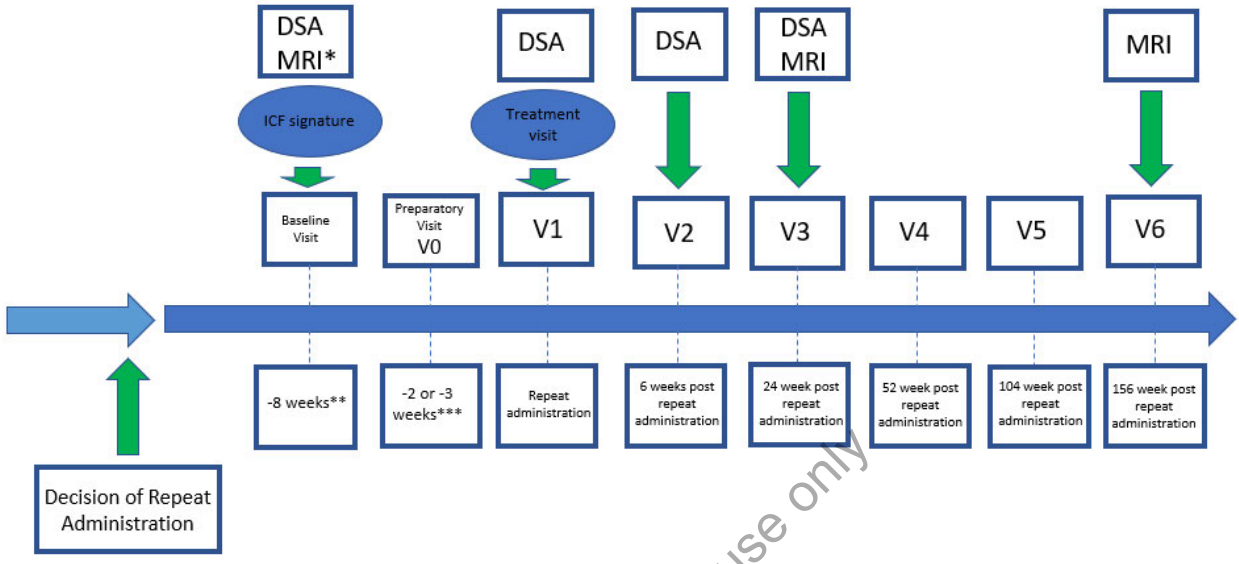
Subjects will be clinically assessed before repeat administration at the preparation visit, treatment visit and at Weeks 6 (±8 days), 24 (±15 days), 52 (±15 days), 104 (±30 days), and 156 (±30 days) following repeat administration. The Week 6 assessment will be used primarily to capture immunogenicity/DSA/soluble 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. These data collected with alternative methods may be handled differently in the final data analysis, with this documented in the statistical analysis plan.

Blood samples for central laboratory tests and plasma samples for immunogenicity and DSA testing and exploratory biomarker analyses 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. 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.

A schedule of assessments is listed in Appendix A.

Figure 6.a Study Schematic



DSA: donor-specific antibody; ICF: informed consent form; MRI: magnetic resonance imaging; V0: Visit 0; V1: Visit 1; V2: Visit 2; V3: Visit 3; V4: Visit 4; V5: Visit 5; V6: Visit 6.

Early termination visit can occur at any point of the study.

* Sample collection for DSA and MRI scan will take place after the subject has signed the ICF.

** Baseline visit will take place 8 weeks prior to repeat administration (may be longer if repeat administration needs to be rescheduled).

*** Preparation visit (Visit 0) will take place within a minimum of 2 weeks and a maximum of 3 weeks before the repeat administration visit. If there is any problem administering darvadstrocel at 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.

6.2 Justification for Study Design, Dose, and Endpoints

There is currently limited experience of the efficacy and safety of repeat administration of darvadstrocel. This study is being conducted as a PASS to evaluate the long-term safety and efficacy of a repeat administration with darvadstrocel in the treatment of complex perianal fistula in subjects with CD. To be eligible for this study, subjects must have previously been administered darvadstrocel, and their physician must be planning repeat administration.

Repeat administration is intended for patients who have 1 or more fistula tracks previously treated with darvadstrocel (who had a clinical response but did not achieve complete remission or who had a relapse of fistula draining after experiencing combined remission) or for patients who develop a new complex perianal fistula tract after prior administration of darvadstrocel. Repeat administration is not intended for patients who have received prior treatment with darvadstrocel resulting in lack of clinical response (treatment failure).

MRI will be used to delineate the classification of the location and fistula characteristics and to longitudinally assess the presence and size of collections and assess for absence of

collection(s) >2 cm (in at least 2 dimensions). This will enable comparison of the efficacy of repeat administration to initial darvadstrocel treatment.

The long-term follow-up of 3 years permits to have an evaluation of the maintenance of the efficacy and safety of this repeat administration.

Immunogenicity of repeat administration will be assessed on an ongoing basis, and data on DSAs will be assessed in conjunction with SAEs reported in these subjects to investigate any impact on the safety of darvadstrocel.

The endpoints used in this study are generally accepted as standard indicators of safety and disease activity in complex perianal fistulas in subjects with CD.

6.3 Study Start Definition

The study start date is the date when the first subject signs the informed consent form (ICF).

6.4 End of Study/Study Completion Definition

The study end date is the date when the last subject completes the last study visit.

6.5 Premature Termination or Suspension of Study or Study Site

6.5.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known benefit-risk profile for the product, such that the benefit-risk balance is no longer acceptable to include subjects in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.5.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.5.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

If the sponsor, independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, ICF and any required privacy authorization before the initiation of any study procedures.
3. The subject is male or female and aged 18 years or older.
4. The subject has complex perianal fistula(s) with a maximum of 2 internal openings and a maximum of 3 external openings based on clinical assessment and a reading of a locally performed contrast enhanced (gadolinium) pelvic MRI. Fistula(s) must have been draining for at least 6 weeks prior to baseline visit. A complex perianal fistula is defined as a fistula that meets 1 or more of the following criteria:
   a) High inter-sphincteric, high trans-sphincteric, extra-sphincteric or suprasphincteric.
   b) Presence of ≥2 external openings.
   c) Associated perianal abscess(es). Note: Abscesses that are larger than 2 cm in at least 2 dimensions on MRI must be confirmed to have been drained adequately by the surgeon during the preparation curettage in order to be eligible.
5. The subject has already received treatment with darvadstrocel for a complex perianal fistula at least 6 months prior to baseline visit for retreatment, and their physician has planned a repeat treatment administration for the original tract (full remission not obtained or relapse of fistula draining) or for a new complex perianal fistula tract.
6. The subject has controlled or mildly active CD (defined as patient reported outcomes measure derived from Crohn's Disease Activity Index [CDAI] patient reported outcome score-2 [PRO-2] score <14).
7. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential agrees to use barrier method of contraception (eg, condom with or without spermicide)* from signing of informed consent and until 1 year after repeat administration.
8. A female subject of childbearing potential* who is sexually active with a nonsterilized male* partner agrees to use a highly effective/effective method of contraception* from signing of informed consent and until 1 year after repeat administration.

   *Definitions and highly effective/effective methods of contraception are defined in Section 9.1.12 and reporting responsibilities are defined in Section 9.1.13.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has lack of clinical response to prior treatment with darvadstrocel, where 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 or in the case of a unique fistula, a partial closure of the fistula.
2. The subject has a history of hypersensitivity or allergies to darvadstrocel or related compounds.
3. The subject has a history of hypersensitivity or allergies to penicillin or to aminoglycosides; Dulbecco modified eagle medium; bovine serum; local anesthetics or gadolinium.
4. The subject is currently participating in a double-blind clinical study with darvadstrocel. Subjects participating in the ongoing INSPIRE[1] registry (Alofisel-5003) study would need to withdraw from that study in order to enroll in this study.
5. The subject is currently receiving or has received any other IMP within the last 3 months or at least 5 times the respective elimination half-life time, whichever is longer, before signing the ICF.
6. The subject has known or suspected COVID-19 by the investigator within the past 2 months (additional testing may be performed at the discretion of the investigator). Positive antibody testing for COVID without other evidence of current or recent active infection does not exclude participation.
    a) Subjects who were in screening at the time that COVID-19–related factors resulted in discontinuation may also be rescreened with approval of the sponsor or designee.
7. The subject has major alterations in any of the following laboratory tests:
    a) Serum creatinine levels >1.5 times the upper limit of normal (ULN).
    b) Total bilirubin >1.5 × ULN.
    c) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3.0 × ULN.
    d) Hemoglobin <10.0 g/dL.
    e) Platelets $<75.0 \times 10^9$/L.
    f) Albumin <3.0 g/dL.
8. The subject has an increased risk for a surgical procedure.
9. The subjects has a known chronically active hepatopathy of any origin, including cirrhosis and subjects with persistent positive hepatitis B surface antigen and quantitative hepatitis B

[1] The INSPIRE study is an observational postmarketing registry on effectiveness and safety of darvadstrocel in patients with Crohn's disease and complex perianal fistula.

virus polymerase chain reaction (PCR) or positive serology for hepatitis C virus (HCV) and quantitative HCV PCR within 6 months before the baseline visit.

10. If female, the subject is pregnant or breastfeeding, or intending to become pregnant before participating in this study, during the study, or intending to donate ova during such time period.
11. If male, the subject intends to donate sperm during this study.
12. The subject has a contraindication to MRI scan (eg, due to the presence of pacemaker, hip replacement, severe claustrophobia, or renal insufficiency as defined by local clinical guidelines).
13. The subject has a contraindication to the anesthetic procedure.
14. The subject has severe rectal and/or anal stenosis that would make it impossible to follow the surgery procedure.
15. The subject has severe proctitis (rectal ulcers >0.5 cm) that would make it impossible to follow the surgery procedure.
16. The subject has any prior invasive malignancy diagnosed within the last 3 years before baseline visit. Subjects with basal cell carcinoma of the skin completely resected outside the perineal region can be included.
17. The subject has a current or recent (within 6 months before the baseline visit) history of severe, progressive, and/or uncontrolled hepatic, hematologic, gastrointestinal (other than CD), renal, endocrine, pulmonary, cardiac, neurologic, or psychiatric disease that may result in subject's increased risk from study participation and/or lack of compliance with study procedures.
18. The subject has had major surgery of the gastrointestinal tract within 6 months before baseline or any minor surgery of the gastrointestinal tract 3 months before baseline.
19. The subject has had local major perianal surgery and/or treatment with darvadstrocel within 6 months before baseline. The abscess drainage, cleaning surgery, or seton placement are not considered as "local major surgery" in this protocol.
20. The subject does not wish to or cannot comply with study procedures.

7.3 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study include:

1. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
2. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the electronic case report form (eCRF).

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

3. Study termination. The sponsor, IEC, or regulatory agency terminates the study.
4. Physician's decision based on subject's well-being.
5. Other.

   Note: The specific reason(s) should be recorded in the "specify" field of the eCRF.

All efforts should be made to keep the subject in the study for safety assessments.

7.4 Procedures for Discontinuation or Withdrawal of a Subject

Subjects may withdraw consent and discontinue participation in the study at any time. Withdrawal will have no effect on their medical care or access to treatment.

The eCRF must indicate the study completion visit, the date of termination, and the unique reason for discontinuing the study, with all data corresponding to a formal visit filled in the early termination visit.

All information already collected as part of the study will be retained for analyses. A subject that discontinues from the study will not be replaced. No further efforts will be made to obtain or record additional information regarding the subject and outcomes.

If a subject withdraws before completing the study follow-up period, the primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in a subject's medical record and in the eCRF.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug or IMP refers to all or any of the drugs defined below.

Darvadstrocel (Cx601) is a 24 mL suspension of human expanded adipose stem cells (eASCs) of allogeneic origin in aseptic buffered human albumin solution presented in disposable vials with no preservative agents. The cells will be given at a dose of 120 million cells (5 million cells/mL) for local injection in the fistula.

Cells are obtained through lipoaspiration from healthy individuals and expanded ex vivo. Darvadstrocel for clinical use is supplied as a sterile, clear, white to yellowish suspension for local injection, provided in 4 × 6 mL vials (suspension of 5 million eASC per mL of Dulbecco modified eagle medium with human serum albumin).

Additional reference information and administration instructions can be found in the IMP handling instructions and surgery procedure manual.

8.1.1.1 Study Drug

The drug being administered in this study is darvadstrocel.

8.1.1.2 Sponsor-Supplied Drug

Darvadstrocel will be supplied by the sponsor. Details about the study medications are provided in Table 8.a.

Table 8.a Study Medications

Drug Name (Identification in the Protocol)	Alofisel
Product Class	Stem cell therapies
Designation	IMP
Marketing Authorization	Yes
Used Within Marketing Authorization	Yes
ATC Code	L04AX08
Route of Administration	Perilesional injection
Active Substance	Darvadstrocel
Dosage Level(s)	120 million cells (5 million cells/mL)
Dose Regimen	Single, open-label darvadstrocel dose
Duration	Single dose
Arm (Subjects Receiving the Medicinal Product)	Single-arm study
Dose Formulation	Darvadstrocel (24 mL cell suspension containing 120 million cells of eASCs): 5 million cells/mL
Dose Strength(s)	5 million cells/mL
Sourcing	Provided centrally/locally by the sponsor

ATC: Anatomical Therapeutic Chemical; eASC: expanded adipose stem cells.

8.1.1.3 Packaging and Labeling

Packaging and labelling of the study drugs will be performed by Takeda in Europe according to Good Manufacturing Practice principles and local regulation.

The product, darvadstrocel (cell suspension), is supplied in duly labeled glass vials, tightly closed with rubber stoppers, and sealed with an aluminum cap.

The packaging material comprises:

- Immediate package: type 1 glass sterile vials with sterile rubber stopper and aluminium seal.
- Labels of white polyethylene printed in black ink by thermal transfer printer.

- Secondary packaging: cardboard box with corporate design.

"IMP Handling Instructions," a printed document in which the product characteristics, indication, and method for use are described, is also enclosed with each product batch.

8.1.2 Storage and Handling of Study Medication

Darvadstrocel product will be shipped under temperature-controlled conditions, using appropriate transport for biological samples. Shipping material is also duly labeled and has an attached package content list and instructions for use 'see the label on the investigational product for expiration date and time'.

Specific instructions will be provided within a separate study manual.

Study medication will be shipped by specialized couriers to the hospital pharmacy or the corresponding operating room where the study treatment administration will be performed, according to local practice and regulations.

The investigator or designee will maintain adequate records of the receipt and disposition of study drug shipment to the site. All used and unused vials of study drug must be recorded and tracked until data are monitored. Vials then should be destroyed locally, and destruction will be documented as appropriate.

Study drug administration must be performed by authorized personnel with appropriate protocol training.

A specific surgery procedure manual will be provided to the site as a separate document, ensuring appropriate training.

8.1.3 Dose and Regimen

Subjects will receive a single open-label darvadstrocel dose of 120 million cells (5 million cells/mL) for local injection in the fistula as presented in Figure 6.a.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented as a medication error on the AESI page of the eCRF and reported to safety on a paper SSR form.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will receive open-label darvadstrocel dose of 120 million cells (5 million cells/mL) for local injection in the fistula as presented in Figure 6.a. The subject identification number will be

entered onto the eCRF. Sponsor-supplied drug will be shipped from the manufacturing site upon request from the investigator according to the separately specified procedures and delivered to the study site on the day of administration or the previous day.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. The investigator or designee will maintain adequate records of the receipt and disposition of study drug shipment to the site. All used and unused vials of study drug must be recorded and tracked until data are monitored by the contract research organization (CRO) monitor. Vials should then be destroyed locally, and destruction will be documented as appropriate. The only exception would be if a site's standard operating procedure does not allow for the used drug vials to be kept on site after surgery. The method for verifying the drug accountability and destruction will be clearly documented in the site initiation visit report and the monitor will review all detailed records at the next site visit.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot/medication identification (ID)/job number used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. Drug accountability will be performed at the site. All used vials will be stored at site until the local monitor has performed the corresponding documented reconciliation and drug accountability. Any dosage deviation should be clearly documented. The corresponding destruction will be documented as per local procedures and regulations (eg, destruction certificate issued and filed in the corresponding study files).

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are destroyed locally, unless a site's SOP prohibits the used drug vials from being stored locally until the monitors visit. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return and/or destruction, and a copy will be sent to the sponsor or designee.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible.

When the decision of a repeat administration with darvadstrocel has been made by the treating physician, eligible subjects will be informed about the study and given the opportunity to consent and enroll in this study.

The schedule of study procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained before the subject enters the study and before any protocol-directed procedures are performed. For any subject not meeting eligibility criteria at the baseline and/or preparation visits, and receives sponsor approval to rescreen, the subject will be asked to reconsent into the study.

A unique subject identification number (subject number) will be assigned to each subject at the time of enrollment; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information will be obtained at the baseline visit.

Medical history to be obtained will include history of CD, fistulizing CD and assessment of severity and history of cancer, including anal canal and colorectal malignancy, any transplantation or blood transfusion, any prior surgeries, and number of pregnancies. Medical history will also include determining whether the subject has any significant conditions or diseases relevant or severe at study entry. Other ongoing conditions will be considered concurrent medical conditions (see Section 9.1.10).

Medication history information to be documented in the eCRF includes all prior treatments received within 2 years before the baseline visit, including but not limited to medications for the treatment of CD or perianal fistulas, including details on first darvadstrocel administration and immunosuppressive agents including, but not limited to azathioprine, mercaptopurine, or methotrexate, tumor necrosis factor-alpha (TNF-α) antagonist, vedolizumab or ustekinumab,

including induction or maintenance, and if any, inadequate response, loss of response of perianal fistulas, or intolerance to each of these previous specific treatments.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment before first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) genitourinary system; and (12) other.

All subsequent physical examinations should assess clinically significant changes from the assessment before the first dose examination.

Any physical examination finding that is assessed by the investigator as a clinically significant worsening compared with a baseline value will be considered an AE and will be recorded and monitored as described in Section 10.2.

9.1.4 Height and Weight

Height and weight will be measured wearing indoor clothing and with shoes off. Height will be measured at the baseline visit only. Weight will be measured at all visits.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral, rectal, tympanic, or temporal measurement), sitting/supine blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (beats per minute).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

9.1.6 Primary Safety Measurement

The long-term safety of repeat administration of darvadstrocel will be assessed in CD subjects with complex perianal fistula by collection of AEs, SAEs, pregnancies, and AESIs. Specific AESIs assessed will include immunogenicity/alloimmune reactions (including assessment of DSA formation and the impact of immunogenicity on safety and clinical response), hypersensitivity, ectopic tissue formation, medication errors, tumorgenicity (applying to malignant tumors only), and transmission of infectious agents.

9.1.7 Efficacy Measurements

Note: in acknowledgement of hospital, local, state, or national government restrictions or other site-related factors caused by unavoidable circumstances such as the COVID-19 pandemic, it may be necessary to administer clinical interviews and assessments using alternative approaches (see Section 9.3). Such approaches could involve site staff visiting the subject's residence, and remote assessments, which may incorporate audio or video recording. In some cases, audio

and/or video recording of subject interviews may not be possible. This will be documented in the study records.

9.1.7.1 Fistula Clinical Assessment

Fistula clinical assessment will consist of a physical examination of the fistula by the investigator to evaluate the presence of drainage spontaneously or after gentle finger compression through the external openings treated or to be treated. The treated tracts and external openings must be clearly identified in the eCRF to ensure the same treated tracts are assessed during the study period.

9.1.7.2 Fistula 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 at any unscheduled visits.

The MRI central readers will report fistula characteristics and measurements of collection(s) greater than 1 cm in at least 2 dimensions. Analysis will also include assessment of collections >2 cm, (in at least 2 dimensions). Results will not be sent to study sites.

9.1.7.3 PDAI

The PDAI is a scoring system to evaluate the severity of perianal CD (Irvine 1995). From the 5-item instrument, discharge and pain will be assessed. Each category is graded on a 5-point Likert scale ranging from no symptoms (score of 0) to severe symptoms (score of 4); a higher score indicates more severe disease.

This assessment will take place at all visits except for the preparation visit.

9.1.7.4 PRO-2

PRO-2 includes 2 predictor variables of the CDAI (number of liquid stools and the abdominal pain) (Khanna et al. 2015). PRO-2 combines the average daily liquid or soft stools frequency and the average daily abdominal pain severity. PRO-2 score to be collected at baseline to confirm no or mildly active CD (score <14) and will be calculated by the investigator before the preparation visit using the subject's diary according to the scoring in Appendix C. The PRO-2 will be provided to the subject at each visit for their completion at home and is to be completed 7 days before the next visit and the total score will be calculated by the investigator at each visit.

9.1.8 Exploratory Biomarker Assessments

Blood will be taken for exploratory biomarker analysis with the goal of identifying markers of response or nonresponse to darvadstrocel. These exploratory biomarkers include [redacted] immunogenicity responses, [redacted].

Immunogenicity assessment will be conducted by analyzing plasma samples collected at the time points specified in Appendix A. Samples will be analyzed via a central laboratory. Results on the

presence and titer of DSA will be transferred for their integrated interpretation with potential interactions on safety or impact on efficacy.

[redacted]

9.1.9 Documentation of Prior and Concomitant Medications

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.

Concomitant medications are all medications taken on or after the date of baseline including those started before treatment administration (Visit 1) and that the subject is continuing to take on Visit 1. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of the ICF through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

The study follows an add-on design, thus, any ongoing treatments for CD (ie, immunosuppressants and/or biologics: anti-TNF, anti-integrin, or anti-interleukin 12/23) at the time of baseline shall continue throughout the study. Any change in medication dose (decrease, increase or suspension of medication) will be allowed and will be captured at the eCRF.

9.1.10 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at baseline examination, according the judgment of the investigator. The condition (ie, diagnosis) should be described and recorded as medical history.

9.1.11 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures and analyzed via a central laboratory. Details of these procedures and required safety monitoring will be provided in the laboratory manual. The laboratory manual describes procedures for specimen handling.

Blood samples for central laboratory tests will be collected at the time points specified in Appendix A.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**
Hemoglobin	C-reactive protein
Hematocrit	Urea
Erythrocytes	Creatinine
Mean corpuscular volume (MCV)	Glucose
Mean corpuscular hemoglobin (MCH)	AST
Mean corpuscular hemoglobin concentration (MCHC)	ALT
Leukocytes	Albumin
Lymphocytes	Total bilirubin (direct bilirubin if total bilirubin is above the ULN)
Monocytes	
Neutrophils	Potassium
Eosinophils	Sodium
Basophils	Chloride
Platelet count	
Serum	**Urine**
Beta hCG (for pregnancy)	hCG (for pregnancy)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; hCG: human chorionic gonadotropin; ULN: upper limit of normal.

The central laboratory will perform laboratory tests for hematology and serum chemistries (tests may be performed at local laboratories for safety evaluation if it is not possible to have them performed at the central laboratory). The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. In avoidable circumstances such as the COVID-19 pandemic, laboratory tests may be performed by local laboratories where possible, upon sponsor approval and in compliance with local regulations.

Plasma samples for DSA levels and exploratory immunogenicity testing will be collected at the time points specified in Appendix A. Plasma 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 DSAs will be assessed in conjunction with SAEs reported in these subjects.

9.1.11.1 Collection, Storage, and Future Use of Biological Samples From Clinical Study Subjects

The blood samples for standard clinical tests and biomarker analysis will be consumed or destroyed at or before the end of the study when all the test data have been analyzed. The blood samples collected for the biomarker exploratory research part of this study will be assessed or stored by the sponsor with its long-term storage partners for up to 15 years from the end of the study. After that time, the samples will be destroyed. Participation in future use of samples for exploratory biomarker research is voluntary, and subjects may decline to consent to future use of these samples while still participating in the main study.

Archived samples from those subjects who provided consent may be used for future research—including the study of diseases, conditions, or drugs that may not be included in the study—and

may inform the efficacy, design, and methods of future studies. These archived samples may also be shared with researchers collaborating with the sponsor.

Data generated with subject samples will be coded and, if shared with Takeda collaborators, will be anonymized. Personal information will never be shared with outside parties.

9.1.12 Contraception and Pregnancy Avoidance Procedure

9.1.12.1 Male Subjects and Their Female Partners

From signing of informed consent, and until 1 year after repeat administration, nonsterilized* male subjects who are sexually active with a female partner of childbearing potential** must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Women of childbearing potential (WOCBP) who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

9.1.12.2 Female Subjects and Their Male Partners

From signing of informed consent, and until 1 year after repeat administration, WOCBP** who are sexually active with a nonsterilized male partner* must use a highly effective/effective method of contraception (from the list below).

In addition, they must be advised not to donate ova during this period.

9.1.12.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* Sterilized males should be at least 1-year postbilateral vasectomy and have documentation of either the absence of sperm in the ejaculate or record of bilateral orchiectomy.

** A woman is considered to be a WOCBP (ie, fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods[2] of contraception are defined as those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

   - Nonhormonal methods:
     - Intrauterine device.
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success).
   - Hormonal methods: Hormonal contraception may be susceptible to interaction with concomitant medications, which may reduce the efficacy of the contraception method (evaluate on compound-by-compound and protocol-by-protocol basis and obtain clinical pharmacology justification).
     - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug, OR combined with a barrier method (male condom, female condom, or diaphragm) if for shorter duration, until she has been using the contraceptive for 3 months:
       - Oral.
       - Intravaginal (eg, ring).
       - Transdermal.
     - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug, OR combined with a barrier method (male condom, female condom, or diaphragm) if shorter duration, until she has been using the contraceptive for 3 months:
       - Oral.
       - Injectable.
       - Implantable.

[2] Reproductive and developmental toxicity studies have not been performed for darvadstrocel because nonclinical biodistribution studies indicated no migration and integration of darvadstrocel into reproductive organs following administration of darvadstrocel via different routes. Darvadstrocel is, therefore, unlikely to cause genotoxicity, teratogenicity, or embryotoxicity; however, the use of highly effective contraception has been included in this study as a conservative approach to contraception management.

2. If the investigational drug, comparator, background therapy or standard of care medications are unlikely to cause genotoxicity, teratogenicity, or embryotoxicity, effective methods of contraception (potential failure rate >1%) are:
    - Double-barrier method (contraceptive sponge, diaphragm, or cervical cap with spermicidal jellies or creams PLUS male condom).
    - Progestogen-only hormonal contraception in which inhibition of ovulation is not the primary mode of action, PLUS condom with or without spermicide.
3. Unacceptable methods of contraception are:
    - Periodic sexual abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
    - Spermicides only.
    - Withdrawal.
    - No method at all.
    - Use of female and male condoms together.
    - Cap/diaphragm/sponge without spermicide and without condom.
4. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the study.
5. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for WOCBP, and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures (see Section 9.1.12.4).
6. In addition to a negative serum hCG pregnancy test at baseline, WOCBP must have a negative urine hCG pregnancy test before receiving the medication.

9.1.12.4 General Guidance with Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Reasons for use of barrier methods (ie, condom) in males with female partners with childbearing potential.
- Assessment of subject compliance through questions such as:
    - Have you used the contraception consistently and correctly since the last visit?
    - Have you forgotten to use contraception since the last visit?

- Are your menses late (even in women with irregular or infrequent menstrual cycles, a pregnancy test must be performed if the answer is "yes").
- Is there a chance you could be pregnant?

9.1.13 Pregnancy

Pregnant or breastfeeding women are excluded from the study.

In addition, any pregnancies in the partner of a male subject during the study should also be recorded following authorization from the subject's partner. If the pregnancy occurs during the study, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0. Refer to Section 10.3.2 for details on reporting pregnancy.

9.1.14 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into this study.

9.2 Monitoring Subject Treatment Compliance

The volume of study drug administered will be recorded in the eCRF.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

In acknowledgement of hospital, local, state or national government restrictions or other site related factors caused by unavoidable circumstances (ie, COVID-19 pandemic), which may prevent investigators from conducting the study according to the schedule of procedures at the clinical study site, investigators may seek approval from the medical monitor to continue subjects in the study despite departure from the schedule of procedures. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for subject to continue. In evaluating such requests, the medical monitor will give the highest priority to the safety and welfare of the subjects. Subjects must be willing to remain compliant with the protocol. For subjects who are impacted, any procedures not conducted per the original study plan will be documented in the study records.

When a subject has to miss an in-person study visit, a health care provider will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact with the subject, the study qualified site staff should also at minimum conduct the following assessments: assessments of AEs, review and record concomitant medication, and a remote evaluation of the fistula. Other study assessments may be collected remotely by telephone. Additionally, sites may have study personnel see the subject outside of the on-site clinic to conduct study assessments contingent upon local regulations. Assessments that cannot be completed during the protocol specified window will be considered missing data and such

departures will be recorded in the study records, Alternatively, sites may seek approval to extend the visit window in order to conduct an on-site visit.

Visits at baseline, preparation, treatment administration, Weeks 24, and Week 156 should be performed in person. Alternative methods of data collection may be considered for the final visit (Week 156) when it is not possible for the subject to come to the study site. Under such circumstances, a preferred alternative to the final visit would be for a medical professional to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at subjects' residence should comply with applicable local regulations.

9.3.1 Baseline Visit

Subjects will be screened and enrolled in accordance with predefined eligibility criteria as described in Section 7.0. From the baseline visit to the preparation visit, there will be a maximum of 5 weeks.

- ICF signature.
- Enter subject into interactive web response system (IWRS) and obtain subject identification number.
- Inclusion/exclusion criteria check.
- Demographics, including weight, height, and lifestyle (smoking history and alcohol use).
- Medical history.
- Prior and repeated darvadstrocel administration.
- Physical examination with vital signs.
- History of CD and perianal fistula (date of diagnosis, perianal fistula [start and stop dates of previous perianal fistulas, start date of perianal fistula ongoing at baseline visit]) number and type of previous surgical procedures including previous administration of darvadstrocel.
- Target fistula(s) 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.
- Serum pregnancy test for WOCBP.
- Comorbidities of interest.
- Central laboratory tests:
  - Hematology: hemoglobin, hematocrit, erythrocytes, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, leukocytes, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelet count.
  - Serum biochemistry: C-reactive protein, urea, creatinine, glucose, AST, ALT, albumin, total bilirubin (direct bilirubin if total bilirubin is above the ULN), potassium, sodium, chloride.

- Plasma sample for DSA and immunogenicity.

[redacted]

- Previous medications.
  - Review and record previous medication within 2 years before the baseline visit, including but not limited to the treatment of CD, treatment of perianal fistulas and perianal abscesses. The information about inadequate response, loss of response or intolerance to immunosuppressants or biologics will be recorded for perianal fistula.
- Concomitant medications, including all medications taken by the subject at the time of baseline.
- Clinical evaluation of fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, and suspicion of perianal abscess. The tracts and external opening(s) must be clearly identified in the eCRF to ensure the same tracts are assessed during the study period. A detailed diagram is included in Appendix B to locate the external opening and draining status.
- Pelvic MRI (performed locally). A quality copy will be sent to the central imaging laboratory for central MRI reading. The MRI central readers will report fistula characteristics. Analysis will also include assessment of collections >2 cm, (in at least 2 dimensions).
- PRO-2 score.
- If available, check and record luminal disease activity involving the rectum (within 6 months prior to repeat administration).
- Assessment of AEs/SAEs, pregnancy, and SSRs.
- Schedule preparation visit (Visit 0).

For any subject not meeting eligibility criteria at the baseline and/or preparation visit, or if there are unavoidable circumstances (such as the COVID-19 pandemic, etc.) it may be possible to rescreen the subject later upon the sponsor's approval. Subject ID numbers assigned to subjects who fail screening should not be reused. Subjects who are screen failures and are approved to rescreen must repeat all assessments for screening, with the exception of an MRI, if it was previously completed within 3 months of the rescreen visit and the clinical condition remains unchanged.

For those subjects who require a rescreening due to an out-of-window preparation visit, and upon sponsors approval, the following procedures will need to be repeated and the preparation visit rescheduled based on protocol timelines:

- Reconsent for informed consent.
- Enter subject in IWRS and obtain a new subject identification number.
- Inclusion/exclusion criteria check.

- Physical examination including weight and vital signs.
- Central laboratory tests.
- Serum pregnancy test for WOCBP.
- Clinical assessment of perianal fistulas and CD (including the presence or absence of proctitis, localization, fistula draining status, and pattern of disease).
- Pelvic MRI: The repeated pelvic MRI scan could be waived if it was previously completed within 3 months of the rescreen visit and the clinical condition remains unchanged.

9.3.2 Preparation Visit (Visit 0)

A preparation visit will take place within a minimum of 2 weeks and a maximum of 3 weeks of the repeat administration visit. Darvadstrocel will need to be preordered and, thus, this supply request at the preparation visit will act as a trigger to start the manufacturing process of darvadstrocel for the subject.

Procedures to be completed at the preparation visit include:

- Study visit entered in IWRS.
- Inclusion/exclusion criteria check.
- Physical examination including weight and vital signs.
- Urine pregnancy test for WOCBP.
- Review and record concomitant medications taken since the last visit.
- Clinical evaluation of fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, and suspicion of perianal abscess before preparation procedures. The tracts and external opening(s) must be clearly identified in the eCRF to ensure the same tracts are assessed during the study period.
- Fistula preparation consisting of an examination under anesthesia (EUA), curettage and seton placement by the surgeon according to the surgery procedure manual.
- Mandatory antibiotics coverage will be administered during at least 7 days following the fistula curettage (ciprofloxacin and/or metronidazole are recommended).
- PRO-2 score.
- Assessment of AEs/SAEs, pregnancy, and SSRs.
- Schedule repeat administration visit (Visit 1). Date and time of visit to be recorded.

9.3.3 Repeat Administration (Visit 1)

Repeat administration visit will take place within a minimum of 2 weeks and a maximum of 3 weeks of the preparation visit. Procedures to be completed at repeat administration include:

- Study visit entered in IWRS.
- Physical examination including weight and vital signs.
- Urine pregnancy test for WOCBP.
- Plasma sample for DSA and immunogenicity.
- [redacted]
- Review and record concomitant medications taken since the last visit.
- Clinical evaluation of fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, and suspicion of perianal abscess before repeat administration. The tracts and external opening(s) must be clearly identified in the eCRF to ensure the same tracts are assessed during the study period.
- Identification of number and location of fistula tracts to be treated.
- IMP preparation and administration will be performed according to the surgery procedure manual. All setons must be withdrawn, fistula curettage should be performed, placing stitches to close each internal opening before treatment administration in accordance with the surgical procedure manual (provided as a separate document).
- PDAI score.
- PRO-2 score.
- Assessment of AEs/SAEs, AESIs, pregnancy, and SSRs, including AEs concerning surgical procedures and postsurgery complication status (including any CD-related surgery).
- Schedule Visit 2/Week 6 (±8 days).
- At the end of treatment, subjects will be observed after their surgical procedure until full recovery, with special attention to signs and symptoms of potential allergic reactions. Instructions for the immediate treatment of any acute anaphylaxis according to standard of care will be provided in the surgery procedure manual.
- If there is any problem administering darvadstrocel at the repeat administration visit (Visit 1), the visit will need to be rescheduled within a minimum of 2 weeks and to a maximum of 3 weeks from the date of the original Visit 1. It will not be necessary to repeat the preparation visit, the setons will be maintained until the rescheduled repeat administration visit and will be withdrawn just before the administration of darvadstrocel. All procedures required for repeat administration visit are to be repeated.

9.3.4 6 Weeks Following Repeat Administration (Visit 2/Week 6 ± 8 days)

The following procedures will be performed at Visit 2, Week 6:

- Study visit entered in IWRS.
- Physical examination including weight and vital signs.
- Urine pregnancy test for WOCBP.
- Plasma sample for DSA and immunogenicity.
- [redacted]
- Review and record concomitant medications taken since last visit.
- Clinical evaluation of the fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
- PDAI score.
- PRO-2 score.
- Assessment of AEs/SAEs, AESIs, pregnancy, and SSRs.
- Schedule Visit 3/Week 24 (± 15 days).

9.3.5 6 Months Following Repeat Administration (Visit 3/Week 24 ± 15 days)

The following procedures will be performed at Visit 3, Week 24:

- Study visit entered in IWRS.
- Physical examination including weight and vital signs.
- Urine pregnancy test for WOCBP.
- Central laboratory tests.
- Plasma sample for DSA and immunogenicity.
- [redacted]
- Review and record concomitant medications taken since last visit.
- Clinical evaluation of the fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
- Pelvic MRI (performed locally). A quality copy will be sent to the central imaging laboratory for central MRI reading. The MRI central readers will report fistula characteristics. Analysis will also include assessment of collections >2 cm, (in at least 2 dimensions).
- PDAI score.
- PRO-2 score.

- Assessment of AEs/SAEs, AESIs, pregnancy, and SSRs.
- Schedule Visit 4/Week 52 (± 15 days).

9.3.6 12 Months Following Repeat Administration (Visit 4/Week 52 ± 15 days)

The following procedures will be performed at Visit 4, Week 52:

- Study visit entered in IWRS.
- Physical examination including weight and vital signs.
- Urine pregnancy test for WOCBP.
- Review and record concomitant medications taken since last visit.
- Clinical evaluation of the fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
- PDAI score.
- PRO-2 score.
- Assessment of AEs/SAEs, AESIs, pregnancy, and SSRs.
- Schedule Visit 5/Week 104 (± 30 days).

9.3.7 24 Months Following Repeat Administration (Visit 5/Week 104 ± 30 days)

The following procedures will be performed at Visit 5, Week 104:

- Study visit entered in IWRS.
- Physical examination including weight and vital signs.
- Urine pregnancy test for WOCBP.
- Review and record concomitant medications taken since last visit.
- Clinical evaluation of the fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
- PDAI score.
- PRO-2 score.
- Assessment of AEs/SAEs, AESIs, pregnancy, and SSRs.
- Schedule Visit 6/Week 156 (± 30 days).

9.3.8 36 Months Following Repeat Administration (Visit 6/156 Weeks ± 30 days, Final Visit)

The following procedures will be performed at Visit 6, Week 156:

- Study visit entered in IWRS.
- Physical examination including weight with vital signs.
- Urine pregnancy test for WOCBP.
- Central laboratory tests.
- Review and record concomitant medications taken since last visit.
- Clinical evaluation of the fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
- Pelvic MRI (performed locally). A quality copy will be sent to the central imaging laboratory for central MRI reading. The MRI central readers will report fistula characteristics. Analysis will also include assessment of collections >2 cm, (in at least 2 dimensions).
- PDAI score.
- PRO-2 score.
- Assessment of AEs/SAEs, AESIs, pregnancy, and SSRs.

9.3.9 Early Termination Visit

All efforts should be made to keep the subjects in the study. If the subject decides to withdraw from the study, the following procedures will be performed and documented ±30 days of the early termination visit:

- Study visit entered in IWRS.
- Physical examination including weight and vital signs.
- Urine pregnancy test for WOCBP.
- Central laboratory tests.
- Plasma sample DSA and immunogenicity (sample does not need to be taken if the early termination visit takes place after the Week 24 visit).
- [redacted]
- Review and record concomitant medications taken since last visit.
- Clinical evaluation of the fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).

- Pelvic MRI (performed locally). A quality copy will be sent to the central imaging laboratory for central MRI reading. The MRI central reader will report fistula characteristics. Analysis will also include assessment of collections >2 cm, (in at least 2 dimensions).
- PDAI score.
- PRO-2 score.
- Assessment of AEs/SAEs, AESIs, pregnancy, and SSRs.

9.3.10 Unscheduled Visit

Subjects who experience significant new perianal symptoms will attend an unscheduled visit. The following assessments will take place at an unscheduled visit:

- Physical examination including weight and vital signs.
- Urine pregnancy test for WOCBP.
- Review and record concomitant medications taken since last visit.
- Clinical evaluation of the fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
- Pelvic MRI (performed locally), if the unscheduled visit is due to significant new perianal symptoms. A quality copy will be sent to the central imaging laboratory for central MRI reading, along with the scheduled MRI when all the visits have been completed. The MRI central readers will report fistula characteristics. Analysis will also include assessment of collections >2 cm, (in at least 2 dimensions).
- PDAI score.
- PRO-2 score.
- Assessment of AEs/SAEs, AESIs, pregnancy, and SSRs.

9.3.11 Unscheduled Telephone Call Visit

Unscheduled telephone calls are proposed for safety follow-up 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 phone-call.
- Remote evaluation of the fistula.
- Review and record concomitant medications taken since last visit.
- Assessment of AEs/SAEs, AESIs, pregnancy, and SSRs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

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 (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of an IMP drug whether or not it is considered related to the IMP.

- Medical disorders, including concomitant diseases present at the time of signing the informed consent, are only considered AEs if they worsen after this time. All baseline conditions should be recorded as part of medical history.
- Changes in laboratory parameters (biochemistry, hematology), as well as abnormal results of other tests (worsening results), detected after the administration of study medication and that the investigator considers to be clinically relevant should be recorded as AEs or SAEs, provided that the definitions given in this section and in Section 10.1.2 are met, respectively. In contrast, clinically significant changes in laboratory parameters or other tests that are associated to the disease under study will not be rated as AEs or SAEs, unless the investigator judges them to be more serious than expected based on the subject condition.
- Fluctuations or reoccurrences of the disease under study (CD) that are considered normal for the subject are recorded in the medical history and need not be reported as an AE. However, if the condition were to deteriorate (worsening) during the study, this would then be recorded as an AE.
- For the purpose of this study, drainage of the treated fistula(s) and abscess(es) will not be captured as an AE unless there is evidence suggesting a causal relationship between the IMP or the administration procedure. New fistula(s) identified during the course of the study, not previously treated by darvadstrocel, will be captured as an AE.

10.1.2 SAEs

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

1. Results in DEATH.
   Note that death is an outcome of an event. The event(s) causing death should be recorded.
2. 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.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. 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.
    - Transmission of infection.

10.1.3 AESIs

An AESI (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation to characterize and understand them, and as such would be described in protocols and instructions to investigators for how and when they should be reported to Takeda.

Refer to Section 10.2.1.3 for a list of known AESIs.

10.1.4 SSRs

SSRs are defined as medication errors, and uses outside what is foreseen in the protocol, including overdose, misuse, and abuse of the product. SSRs may or may not be associated with an AE/SAE.

Definitions:

- Abuse: Persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or phycological 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.

Note: Abuse, misuse, and overdose are not applicable as the subject will not be self-administrating this treatment.

10.1.5 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.

Not related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.6 Severity of AEs

Severity of the adverse events will be recorded at the time they occur and will be rated according to the following criteria:

- Mild (asymptomatic): An event easily tolerated by the subject, causing minimal discomfort that does not prevent the subject from fulfilling daily activities.
- Moderate: Symptomatic, but does not significantly interfere with function.
- Severe: Causes a significant interference with function.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as "related" if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as "not related."

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.9 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

10.1.10 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Drug

Not applicable.

10.1.12 Outcome

- Recovered/resolved: The subject returned to first assessment status with respect to the AE.
- Recovering/resolving: The intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved: There is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Resolved with sequelae: The subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal: The AE was considered to be the cause of death.
- Unknown: The course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time the subject signs the ICF. Routine collection of AEs will continue until final visit/early termination.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

PDAI questionnaire will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up, if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.1.3 AESIs

AESIs must be recorded as AEs in the eCRF.

If the AESI occurs during the treatment period or follow-up period and is considered to meet the seriousness criteria listed in Section 10.1.2, the SAE form should be completed. The completed SAE form should be reported to the pharmacovigilance department of the sponsor or sponsor designee as listed in Section 1.1 within 24 hours. The investigator should submit the original copy of the SAE form to the sponsor.

A medication error should be recorded as an AESI and reported as an SSR. See Section 10.3.1 for reporting SSRs.

AESIs include:

- Immunogenicity/alloimmune reactions.
- Hypersensitivity.
- Ectopic tissue formation.
- Medication errors.
- Tumorgenicity, applying to malignant tumors only.
- Transmission of infectious agents.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of awareness of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours of awareness of the event to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

The paper SAE forms should be submitted via fax (preferred method). In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt (AOR) can be returned via email within 1 business day.

Email submission of SAE forms with a PDF attachment should only be used in the case where fax is not possible within 24 hours of receiving the event. In case of email, site personnel need to confirm successful transmission by awaiting an AOR via email within 1 business day.

If SAE forms are submitted via fax or email, a confirmation of receipt will be sent to the sites indicating that the SAE has been received. It is the site's responsibility to ensure an AOR has been obtained when email or fax are used. If AOR is not received within 1 business day, site should escalate it immediately to their clinical research assistant.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately or within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 SSRs

All SSRs must be reported to the sponsor on a paper SSR form within 7 calendar days of awareness irrespective of whether the SSR is associated with an AE/SAE.

If the special situation is associated with an SAE, a separate SAE form must also be submitted to the sponsor within 24 hours of awareness in addition to the SSR form. All nonserious AEs associated with SSRs should be recorded in the eCRF as well as noted on the SSR form.

10.3.2 Pregnancy

Pregnancies must be reported to the sponsor on a paper pregnancy report form immediately or within 24 hours of awareness. If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the male subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

All pregnancies, including female partners of male subjects, will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor.

10.3.3 Summary of Safety Reporting

Safety Event	**How to Report Event to Sponsor Pharmacovigilance**	**Reporting Timelines to Sponsor** (from time of awareness)
SAEs	Complete and send paper SAE form to Sponsor Pharmacovigilance.	Within 24 hours
AESI	Complete AE eCRF (if electronic data capture is down, submit paper SAE from)	Within 24 hours
Pregnancy	Complete and submit paper pregnancy form	24 hours
SSRs	Complete and submit paper SSR form	7 calendar days

Contacts for SAE reporting can be found in Section 1.1.

10.3.4 Safety Reporting to Investigators, IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, all suspected unexpected serious adverse reactions will be submitted to the regulatory authorities as an expedited report within 7 days for

fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the study. The study site also will forward a copy of all expedited reports to his or her IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor or its designee will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. All eCRFs must be completed in English. Data are transcribed into eCRFs from source records.

After completion of entry on each form, system logic checks will fire queries as soon as you save the form in case of inconsistent entries, ie, dates, missing data, and questionable values. Manual queries may also be issued by sponsor personnel (or designees) to be answered by the site.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered into the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the study sponsor or designee. The sponsor or designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.0 and those documents that include (but are not limited to) the study-specific documents, the identification log of all

participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor, or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference for Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized as early as possible after finalization of the study protocol. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

The primary analysis set for this study will be the safety analysis set, which will consist of all subjects who enroll in the study and receive treatment with darvadstrocel. The safety analysis set 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.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects in the safety analysis set. For continuous variables, summary statistics (nonmissing values, mean, median, SD, minimum and maximum) will be generated. For categorical variables, the counts and percentages of each possible value will be generated.

Individual subject demographic and baseline characteristic data will be provided in the data listings.

13.1.3 Efficacy Analysis

The proportion of subjects with each of the following outcomes, along with 2-sided 95% confidence intervals will be provided by visit:

- Combined remission.
- Clinical remission.
- Clinical response.
- Relapse.
- New perianal abscess in treated fistula.

In addition to providing the proportion of subjects with each outcome at each of the scheduled assessments (Week 24, Week 52, Week 104, and Week 156), the proportion of subjects who changed in status with respect to each outcome since the previous assessment will be provided.

Change from baseline in PDAI discharge and pain subscores will be summarized descriptively by visit.

Among subjects who achieve combined remission, probability of reopening of any of the treated external openings with active drainage across time will be estimated using the Kaplan-Meier estimator.

Full details on the statistical analysis will be provided in the SAP.

13.1.4 Safety Analysis

Safety analysis will be performed on the safety analysis set.

Count and percentage of subjects with AEs, SAEs (defined as any SAE, regardless of relationship to study drug), and AESIs (immunogenicity/alloimmune reactions, hypersensitivity, transmission of infectious agents, tumorgenicity (applying to malignant tumors only), ectopic tissue formation, and medication errors) will be summarized descriptively by system organ class and preferred term using MedDRA terminology. Treatment-emergent adverse events and SAEs will also be summarized by severity, by relationship to study drug, and by outcome. In addition, treatment-emergent adverse events and SAEs leading to study withdrawal and fatal treatment-emergent SAEs will be summarized.

Clinical laboratory values will be summarized according to Common Terminology Criteria for Adverse Events criteria.

Change from baseline in vital signs will be summarized by study visit.

Full details of the statistical analysis will be provided in the SAP.

13.1.5 Other Analysis

The association of DSA levels, [redacted], and key safety and efficacy variables will be explored. The details of this exploratory analysis will be provided in the SAP.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned for this study.

13.3 Determination of Sample Size

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

This study will plan to enroll approximately 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 complex perianal fistula tract according to their physician.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative sites and ensure collection of high-quality data for this study. All sites will be trained on the protocol, study logistics, and the electronic data capture system. Retraining will be conducted as needed. Investigators will be reminded of the processes and importance of reporting adverse reactions, SAEs, and other information.

Initial monitoring will be performed to ensure that ICFs have been completed for all enrolled subjects. At monitoring visits, the progress of the study and any procedural or data issues will be discussed with the Investigator and/or designee. The investigator will make subject source documents available for review and will permit the sponsor, representatives of the sponsor, the IEC, or regulatory authorities to inspect facilities and original records relevant to this study. The investigator will allocate adequate time to discuss findings and relevant issues and, after the visit, to complete appropriate corrective actions as necessary.

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator guarantee access to source documents by the sponsor or its designee (CRO) and by the IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee, including but not limited to the investigator's binder, subject medical records, ICF documentation, documentation of subject authorization to use personal health information if separate from the ICFs, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will

require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IEC, as required) to determine the appropriate course of action. There will be no exemptions (ie, prospectively approved deviations) during study participation.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and institutional review board or IEC, as required). 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. A protocol deviation form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

The sponsor will assess any protocol deviation; if it is likely to affect, to a significant degree, the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

The sponsor will notify concerned EU Member States of any serious breach of EU CTR or the applicable protocol version through the EU portal no later than 7 days after becoming aware of the breach. In this instance a "serious breach" is one likely to affect, to a significant degree, the safety and rights of a subject or the reliability and robustness of study data.

All parties involved in the conduct of the clinical study must immediately report any events they encounter that might meet the definition of a serious breach to the contact point designated in the study manual.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, or the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IEC Approval

IECs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IEC. If any member of the IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IEC for the protocol's review and approval. This protocol, the product package insert, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IEC for approval. The IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor or designee will notify site once the sponsor or designee has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor (or designee) has received permission from competent authority to begin the study. Until the site receives notification no protocol activities, including screening at the baseline visit may occur.

Study sites must adhere to all requirements stipulated by their respective IEC. This may include notification to the IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IEC, and submission of the investigator's final status report to IEC. All IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IEC and sponsor or designee.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by the IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the ICF in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IECs to review the subject's original medical records (source data or documents),

including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

If a serious data breach affecting personal data is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study subjects, this would be done through the investigator.

Takeda applies certain measures to protect subjects' personal data and prevent data breaches, detailed in a separate document (Compliance with National Requirements on Data Protection).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the publication. All publications and presentations must be prepared in accordance with this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting study

information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of study enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Study Registration and Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

Public registration and disclosure of the study will be via electronic postauthorization study register maintained by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). At a minimum, a summary of the study design/methods and a summary of results will be provided along with the contact details of the study sponsor representative.

Once subjects receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of study enrollment, they should be referred to the sponsor.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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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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Assessment	Baseline Visit [a]	Preparation Visit to Visit 1 [b] Visit 0	Repeat Administration Visit 1	6 Weeks ±8 days Visit 2	24 Weeks ±15 days [c] Visit 3	52 Weeks ±15 days [c] Visit 4	104 Weeks ±30 days [c] Visit 5	156 Weeks ±30 days [c] Visit 6	Early Termination Visit	Unscheduled Visit [d]
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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Assessment	Baseline Visit [a]	Preparation Visit to Visit 1 [b] Visit 0	Repeat Administration Visit 1	6 Weeks ±8 days Visit 2	24 Weeks ±15 days [c] Visit 3	52 Weeks ±15 days [c] Visit 4	104 Weeks ±30 days [c] Visit 5	156 Weeks ±30 days [c] Visit 6	Early Termination Visit	Unscheduled Visit [d]

[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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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		

[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).

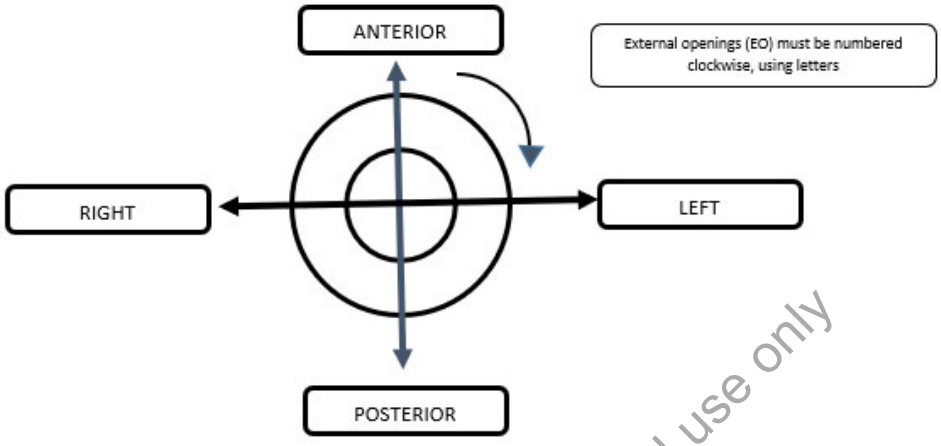
[u] PRO-2 score to be collected at baseline to confirm no or mildly active CD (score <14). The PRO-2 will be provided to the subject at each visit for their completion at home and is to be completed 7 days prior to the next visit.

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

Appendix B Anal Clock

Note that the anal clock is represented in a lithotomy position (gynecological).

VISIT nº. _____ **VISIT DATE: _____**
PATIENT NUMBER:



External Opening #A	DIRECTION		LATERAL		DRAINING	
	Anterior		Left		Yes	☐
	Posterior		Right		No	☐
	Middle		Middle			

External Opening #B	DIRECTION		LATERAL		DRAINING	
NA* ☐	Anterior		Left		Yes	☐
	Posterior		Right		No	☐
	Middle		Middle			

External Opening #C	DIRECTION		LATERAL		DRAINING	
NA* ☐	Anterior		Left		Yes	☐
	Posterior		Right		No	☐
	Middle		Middle			

New Opening #__**	DIRECTION		LATERAL		DRAINING	
NA* ☐	Anterior		Left		Yes	☐
	Posterior		Right		No	☐
	Middle		Middle			

*NA (not applicable) to be checked if there is no additional External Opening present

** The numbering for the new External Openings should start from letter D.

Investigator Name _____

Signature: _____

Appendix C PRO-2 Scoring

(b) Patient Reported Outcome 2 (PRO2)

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

Adapted from Khanna et al, 2015 (Khanna et al. 2015).

Appendix D Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix E Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the

subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) That personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IECs;
    b) It is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) That personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for subjects, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) That subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) That the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix F Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other personally identifiable information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix G Protocol History

Date	Amendment Number	Amendment Type	Region
29 April 2024	Amendment 4	Nonsubstantial	Global
11 October 2023	Amendment 3	Nonsubstantial	Global
04 August 2021	Amendment 2	Substantial	Global
01 July 2020	Amendment 1	Nonsubstantial	Global
22 May 2019	Initial protocol	-	Global

Rationale for Amendment 3

The primary purpose of this amendment was to update the protocol to align with the guidelines and requirements of the new European Union Clinical Trials Regulations (EU CTR).

In addition, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study were applied throughout the document for clarification and administrative purposes.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Title page, Section 3.0 Study Summary	Replaced EudraCT number by Abbreviated EU CT number.	To comply with new European Union Clinical Trials Regulations (EU CTR) guidelines and requirements.
2.	Section 3.0 Study Summary Section 5.1.1 Primary Objective Section 5.2.1 Primary Endpoint Section 9.3 Schedule of Observations and Procedures, Appendix A Schedule of Study Procedures	Replaced evaluation of special situation reports (SSRs) by that of pregnancy and added it to be recorded at all visits along with all adverse events (AEs) and SSRs etc. Also added pregnancy to be recorded for unscheduled visit in footnote d of the Schedule of Study Procedures.	To provide clarity and additional details regarding SSRs and pregnancy due to the new EU CTR guidelines and requirements.
3.	Section 3.0 Study Summary Section 5.1.3 Exploratory Objectives Section 5.2.3 Exploratory Endpoints	Rephrased the biomarker objective and endpoint for updating the word/phrase [redacted]	Clarification

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
4.	Section 3.0 Study Summary Section 5.2.1 Primary Endpoint	Removed the phrase "Incidence of" from all safety parameters. Updated adverse events of special interest (AESIs) to treatment-emergent AESIs. Updated medication errors to specify that these are medication errors reported to the pharmacovigilance department as SSRs.	Updated for consistency with other studies in the darvadstrocel program.
5.	Section 3.0 Study Summary Section 5.2.2 Secondary Endpoints	Updated the phrase "after darvadstrocel administration" to "after darvadstrocel repeat administration".	Minor correction because in this study, subjects receive a repeat dose of study drug.
6.	Section 3.0 Study Summary Section 6.1 Study Design Appendix A Schedule of Study Procedures	Updated the number of MRI readers in case of adjudication.	To clarify the number of readers in case of adjudication.
7.	Section 3.0 Study Summary	New section added: Benefit-Risk Profile	To comply with new EU CTR guidelines and requirements.
8.	Section 4.3 Benefit-Risk Profile	Updated the section with safety details.	Updated the language with details on the known adverse drug reactions since the previous version of the protocol.
9.	Section 6.3 Study Start Definition, Section 6.4 End of Study/Study Completion Definition	New sections added.	To comply with new EU CTR guidelines and requirements.
10.	Section 8.1.1.2 Sponsor-Supplied Drug	New table added with details of study medications.	To comply with new EU CTR guidelines and requirements.
11.	Section 8.1.4 Overdose	Added detail for overdose to be reported on paper SSR form.	To align with new EU CTR guidelines.
12.	Section 9.1.7.2 Fistula MRI Assessment	Updated the MRI reporting with respect to fistula dimensions.	To provide more details on the circumstances under which measurements of collections will be made by central MRI readers.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13.	Section 9.1.8 Exploratory Biomarker Assessments	Updated text for immunogenicity assessment [redacted] Removed the subheadings for this section and their text.	Clarification and simplification of details.
14.	Section 9.1.11.1 Collection, Storage, and Future Use of Biological Samples From Clinical Study Subjects	New section added.	To comply with new EU CTR guidelines and requirements.
15.	Section 9.1.13 Pregnancy	Removed pregnancy reporting details and added reference to newly added section.	To harmonize the details in 1 section.
16.	Section 10.1.4 SSRs	Updated section to remove pregnancy and created a dedicated pregnancy section. Added definitions of abuse, misuse, medication error, and overdose.	To comply with new EU CTR guidelines and requirements.
17.	Section 10.1.6 Severity of AEs	New section added with details on AE severity assessment.	To clarify with details for the severity classifications.
18.	Section 10.2.1.1 AE Collection Period	Corrected the start date of AE collection.	Correction to align with the Appendix A Schedule of Study Procedures.
19.	Section 10.2.1.3 AESIs	Deleted the details about an AESI form and added a statement for medication error to be captured both as an AESI and reported as an SSR.	To align with the EU CTR guidelines for reporting SSRs, and to clarify how to handle reports of medications errors defined as an AESI as well as an SSR.
20.	Section 10.2.2 Collection and Reporting of SAEs	Updated the serious adverse event (SAE) reporting to start from "awareness" instead of "first onset or notification".	To clarify the timing of SAE reporting language more accurately.
21.	Section 10.3.1 SSRs	New section added with details about SSR reporting.	To comply with new EU CTR guidelines and requirements.
22.	Section 10.3.2 Pregnancy	New section added with details about pregnancy reporting.	To comply with new EU CTR guidelines and requirements.
23.	Section 10.3.3 Summary of Safety Reporting	New section added with details about reporting timelines and methods.	To comply with new EU CTR guidelines and requirements.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
24.	Section 13.1.1 Analysis Sets	Updated definition of the safety analysis set.	Correction
25.	Section 13.1.4 Safety Analysis	Updated the text for analysis of treatment-emergent adverse events and SAEs.	Clarification on further safety analyses.
26.	Section 14.2 Protocol Deviations	Updated to include information on reporting requirements in the event of any serious breach of EU CTR regulations.	To comply with new EU CTR guidelines and requirements.
27.	Section 15.3 Subject Confidentiality	Updated to include information on reporting requirements in the event of a serious breach of personal data.	To comply with new EU CTR guidelines and requirements.

Rationale for Amendment 2

The primary reasons for this amendment were to:

- Legal entity change from Millennium Pharmaceuticals, Inc to Takeda Development Center Americas, Inc.
- Provide improved clarity to the eligibility criteria and study procedures.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Title Page Section 3.0 Study Summary	Update to the sponsor from Millennium Pharmaceuticals, Inc to Takeda Development Center Americas, Inc.	Sponsor was updated.
2.	Title Page Section 3.0 Study Summary	Added EUPAS number.	To provide EUPAS number.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
3.	Section 3.0 Study Summary Section 5.2.1 Primary Endpoint Section 9.1.6 Primary Safety Measurement Section 10.2.1.3 AESIs Section 13.1.4 Safety Analysis.	Update to adverse event of special interest (AESI) details.	This section has been updated to further clarify that the specific AESI of tumorgenicity applies to malignant tumors only.
4.	Section 3.0 Study Summary Section 5.2.2 Secondary Endpoints	Removal of wording "baseline visit" from the combined remission definition.	To provide flexibility, since it is possible the active draining fistula could be draining weekly, not daily and may not drain on the day of baseline visit.
5.	Section 3.0 Study Summary Section 5.2.2 Secondary Endpoints	Added the wording "of the treated perianal fistula(s)" to the relapse definition.	To provide clarity.
6.	Section 3.0 Study Summary Section 5.2.2 Secondary Endpoints	Update of wording "IMP" to "darvadstrocel".	To provide clarity.
7.	Section 3.0 Study Summary Section 6.1 Study Design Section 6.2 Justification for Study Design, Dose, and Endpoints Section 7.1 Inclusion Criteria (criterion 5) Section 13.3 Determination of Sample Size.	Update of wording "new fistula tract" to "new complex perianal fistula tract".	To provide clarity and additional details on new fistula.
8.	Section 3.0 Study Summary Section 7.1 Inclusion Criteria	Update to inclusion criterion 4.	A reading of a locally performed contrast enhanced (gadolinium) pelvic magnetic resonance imaging (MRI) has been added. In addition updates have been made to define complex perianal fistula.
9.	Section 3.0 Study Summary Section 7.1 Inclusion Criteria	Update to inclusion criterion 5.	To clarify that the subject has already received treatment with darvadstrocel for a complex perianal fistula at least 6 months prior to baseline visit for retreatment are eligible to enter the study.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
10.	Section 3.0 Study Summary Section 7.2 Exclusion Criteria	Update to exclusion criterion 4.	To add the study number, remove the wording "PASS", update the wording of the footnote to clarify the description of INSPIRE study, and minor editorial updates for clarification.
11.	Section 3.0 Study Summary Section 7.2 Exclusion Criteria	Update to exclusion criterion 19.	To clarify that abscess drainage, cleaning surgery, or seton placement are not considered as "local major surgery" in this protocol.
12.	Section 9.1.1 Informed Consent Procedure Section 9.3.1 Baseline Visit Section 9.3.2 Preparation Visit (Visit 0) Appendix A	Update to informed consent, preparation visit procedure.	To clarify that eligibility criteria will be confirmed at preparation visits.
13.	Section 9.3.2 Preparation Visit (Visit 0) Appendix A	Update to preparation visit procedure.	To clarify that inclusion/exclusion criteria check will be done at preparation visits
14.	Section 9.1.5 Vital Sign Procedure	Update to vital sign procedure.	To clarify types of measurements for body temperature.
15.	Section 9.3.1 Baseline Visit	Update to rescreening requirement for screen failures.	To clarify that screen failures must repeat all assessments with exception to pelvic MRI which could be waived if it was previously completed within 3 months of the rescreen visit and the clinical condition remains unchanged.
16.	Section 9.3.2 Preparation Visit (Visit 0) Section 9.3.3 Repeat Administration (Visit 1) Appendix A	Clinical fistula assessment was added at preparation visit and repeat administration.	In line with the actual conduct, at both visit investigator requires to perform clinical fistula assessment before they perform the procedure. To be consistent with other Alofisel protocols.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
17.	Section 9.3.10 Unscheduled Visit	Added text for MRI central reader at unscheduled visit.	To clarify that a quality copy will be sent to the central imaging laboratory for central MRI reading, along with the scheduled MRI when all the visits have been completed
18.	Section 10.1.2 SAEs	Editorial update to serious adverse event (SAE) definition.	To clarify that death should have been an outcome of an event and that the event(s) causing death should be recorded.
19.	Section 10.1.2 SAEs	Removal of the Takeda Medically Significant adverse event (AE) list.	In line with updated internal process, the EudraVigilance Expert Working Group Important Medical Event Terms list will now be implemented.
20.	Section 3.0 Study Summary Section 13.1.3 Efficacy Analysis	"Combined remission" was moved up in the order of the list.	To be consistent within the protocol (secondary endpoints).
21.	Section 3.0 Study Summary Section 13.1.3 Efficacy Analysis	Update of wording "relapse" to "reopening of any of the treated external openings with active drainage".	To be consistent within the protocol (secondary endpoints).
22.	Section 13.1.4 Safety Analysis	Added text "Clinical laboratory values will be summarized according to Common Terminology Criteria for Adverse Events criteria".	To be consistent with other Alofisel studies.
23.	Appendix A	Update to enrollment.	To clarify that enrollment will be done at preparation visit instead of baseline visit.

Rationale for Amendment 1

The primary reasons for this amendment were to:

- Provide improved clarity and completeness to the eligibility criteria and assessments that are to be conducted.

- Describe how to manage study procedures during unavoidable circumstances such as the coronavirus disease 2019 (COVID-19) pandemic.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study were included for clarification and administrative purposes only.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 5.1.3 Exploratory Objectives Section 3.0 Study Summary Section 9.3.1 Baseline Visit Section 9.3.2 Preparation Visit (Visit 0) Section 9.3.3 Repeat Administration (Visit 1) Section 9.3.4 6 Weeks Following Repeat Administration (Visit 2/Week 6 ± 8 days) Section 13.1.5 Other Analysis Appendix A Schedule of Study Procedures	Removal of stool and fistula swab microbiome analysis from exploratory objectives. In line with this update, Section 9.1.7.5 Exploratory Biomarker Samples, which described the microbiome assessments, has also been removed.	The exploratory objective to characterize microbiome diversity has been removed to avoid any additional burden on participants.
Section 5.2.2 Secondary Endpoints Section 3.0 Study Summary	The definition of the relapse endpoint has been corrected and an editorial update made.	The definition of relapse was corrected as follows “Reopening of any of the treated fistula(s) external openings with active drainage as clinically assessed that were in combined remission at Week 24, OR The development of a collection >2 cm (in at least 2 dimensions) confirmed by centrally read MRI assessment”.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 5.2.2 Secondary Endpoints Section 3.0 Study Summary	Week 6 assessment added to secondary endpoints to assess proportion of subjects who achieve clinical remission and clinical response.	A fistula clinical assessment was added to Week 6 in order to allow the capture of clinical response or clinical remission at that time point.
Section 5.2.2 Secondary Endpoints Section 3.0 Study Summary	Editorial update to the secondary endpoint: time to reopening of any treated external openings with active drainage.	To improve endpoint definition and clarify the time point for assessment.
Section 5.2.3 Exploratory Endpoints Section 3.0 Study Summary	Revised exploratory endpoints.	For improved clarity in the definition of the exploratory endpoints relating to plasma sample biomarker analysis (donor-specific antibody [DSA], immunogenicity, [redacted]).
Section 6.1 Study Design Section 3.0 Study Summary	Update to the description of the study to include where the study will be conducted.	To clarify that the study will be conducted in countries where darvadstrocel is currently marketed.
Section 6.1 Study Design Section 3.0 Study Summary Appendix A Schedule of Study Procedures	Revised wording for magnetic resonance imaging (MRI) assessment.	To clarify that MRI will be assessed by 2 imaging readers.
Section 6.1 Study Design Sections 9.3.3 Repeat Administration (Visit 1) Appendix A Schedule of Study Procedures	Details added on the requirements for rescheduling of the repeat administration visit.	To provide clarity on the procedure for rescheduling of the repeat administration visit.
Section 6.1 Study Design Section 9.1.7 Efficacy Measurements Section 9.1.11 Procedures for Clinical Laboratory Samples Section 9.3 Schedule of Observations and Procedures Appendix A Schedule of Study Procedures	Explicitly stated where study procedures are to be conducted and how to manage alternative strategies for collecting data and conducting study procedures during the coronavirus disease 2019 (COVID-19) pandemic.	The COVID-19 pandemic means that subjects may not be able to attend study visits as planned. Therefore it is necessary to clarify alternative arrangements for data collection and study procedures during unavoidable circumstances such as the COVID-19 pandemic.
Section 6.2 Justification for Study Design, Dose, and Endpoints	Details added to clarify the criteria for darvadstrocel repeat administration.	To provide further details and improved clarity on the criteria for receiving darvadstrocel repeat administration.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 7.1 Inclusion Criteria Section 3.0 Study Summary	Addition of inclusion Criterion 4.	To clearly specify the maximum number of internal and external openings in line with the darvadstrocel Summary of Product Characteristics.
Section 7.1 Inclusion Criteria Section 3.0 Study Summary	Addition of inclusion Criterion 5 to specify entry requirements for subjects who have previously received darvadstrocel.	To provide clarity on entry requirements.
Section 7.1 Inclusion Criteria Section 3.0 Study Summary	Update to inclusion Criterion 6.	To provide clarity on entry requirements.
Section 7.2 Exclusion Criteria Section 3.0 Study Summary	Update to exclusion Criterion 1 to specify a unique fistula.	To clarify subjects with a unique fistula must have a partial closure.
Section 7.2 Exclusion Criteria Section 3.0 Study Summary	Update to exclusion Criterion 4 and inclusion of footnote to describe the INSPIRE study.	To provide clarity on the eligibility criteria for subjects participating in the INSPIRE registry study.
Section 7.2 Exclusion Criteria Section 3.0 Study Summary	Update to exclusion Criterion 5.	To provide the maximum elimination half-life for other IMPs the subject may have received before study enrollment.
Section 7.2 Exclusion Criteria Section 3.0 Study Summary	Addition of exclusion Criterion 6	To exclude subjects with known or suspected COVID-19.
Section 7.2 Exclusion Criteria Section 3.0 Study Summary	Addition of laboratory parameters exclusion Criterion 7.	Laboratory tests will be conducted at the baseline visit. Subjects meeting the listed laboratory values will not be eligible for inclusion in the study.
Section 7.2 Exclusion Criteria Section 3.0 Study Summary	Addition of exclusion Criterion 8	To exclude subjects at increased risk of surgical procedures.
Section 7.2 Exclusion Criteria Section 3.0 Study Summary	Addition of exclusion Criterion 9 to define entry requirements for subjects with active hepatopathy.	To provide improved clarity on subject entry requirements.
Section 7.2 Exclusion Criteria Section 3.0 Study Summary	Update to exclusion Criterion 18 to define entry requirements for subjects who have had major/minor surgery of the gastrointestinal tract.	To provide improved clarity on subject entry requirements.
Section 7.2 Exclusion Criteria Section 3.0 Study Summary	Update to exclusion Criterion 19 to define entry requirements for subjects who have had perianal surgery.	To provide improved clarity on subject entry requirements.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 7.3 Criteria for Discontinuation or Withdrawal of a Subject	The primary reason for discontinuation or withdrawal was updated to include 'Physician's decision based on subject's well-being'.	Update made for completeness.
Section 7.4 Procedures for Discontinuation or Withdrawal of a Subject	Updated to clarify the details to be included in the electronic case report form for discontinuation or withdrawal of subject.	For improved clarity on reporting procedures.
Section 8.1.2 Storage and Handling of Study Medication	Text added to specify where expiration date and time for the investigational medicinal product can be found.	Editorial change made for completeness.
Section 8.3 Accountability and Destruction of Sponsor-Supplied Drugs	Editorial updates and additions on drug accountability.	To improve clarity on the procedure for drug accountability.
Section 9.1.1 Informed Consent Procedure	Inclusion of reconsent for subjects.	For any subject not meeting the eligibility criteria at the baseline visit and receives sponsor approval to rescreen, the subject will be asked to reconsent into the study.
Section 9.1.2 Demographics, Medical History, and Medication History Procedure Appendix A Schedule of Study Procedures	Update to medical history and medication history.	To provide improved clarity on the information to be collected for medical history.
Section 9.1.3 Physical Examination Procedure	Update to physical examination section.	To provide a complete list of all body systems that will be assessed during physical examination and clarification provided on adverse event (AE) reporting for worsening of physical examination findings.
Section 9.1.7.2 Fistula MRI Assessment	Revised wording for fistula MRI assessment.	To improve clarity on the procedural requirements for pelvic MRI assessment.
Section 9.1.7.3 PDAI Appendix A Schedule of Study Procedures	Removal of assessment from the preparation visit.	Update made for correctness.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.1.7.4 PRO-2 Appendix A Schedule of Study Procedures	Added Section 9.1.7.4 PRO-2	To include details on the patient-reported outcome-2 (PRO-2) assessment. Additional time points included for PRO-2 assessment.
Section 9.1.8.1 Immunologic Tests Section 9.3.1 Baseline Visit Section 9.3.4 6 Weeks Following Repeat Administration (Visit 2/Week 6 ± 8 days) Section 9.3.5 6 Months Following Repeat Administration (Visit 3/Week 24 ± 15 days) Section 9.3.8 36 Months Following Repeat Administration (Visit 6/156 Weeks ± 30 days, Final Visit) Section 9.3.9 Early Termination Visit Appendix A Schedule of Study Procedures	Removal of analysis of peripheral blood mononuclear cells.	To avoid any additional burden on participants
Section 9.1.9 Documentation of Prior and Concomitant Medications	Update to concomitant medications for completeness and clarity.	To provide clarity on the definitions for prior medication and concomitant medication, including reporting time frames. In addition, a paragraph was added to provide details on the add-on study design for completeness.
Section 9.1.12.3 Definitions and Procedures for Contraception and Pregnancy Avoidance	Inclusion of new footnote.	To clarify the reason for including the use of highly effective contraception by subjects participating in the study.
Section 9.3.1 Baseline Visit	Editorial change for clarity.	Removal of the word enrollment in combination with the word baseline throughout the protocol as they are synonymous.
Section 9.3.1 Baseline Visit Appendix A Schedule of Study Procedures	Removal of inclusion and exclusion criteria check at the preparation visit.	This check will only take place at the baseline visit.

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Sections Affected by Change	**Description of Each Change and Rationale**	
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Section 9.3.1 Baseline Visit – Section 9.3.10 Unscheduled Visit Appendix A Schedule of Study Procedures	Addition of interactive web response system (IWRS) at each visit.	For completeness to list of procedures required to be performed at each visit.
Section 9.3.1 Baseline Visit Appendix A Schedule of Study Procedures	Editorial changes to provide clarity on study assessments.	To provide clarity on study assessments for history of Crohn's disease (CD) and perianal fistula, previous medications, concomitant medications, clinical evaluation of fistula, PRO-2 score, and colonoscopy information.
Section 9.3.1 Baseline Visit Appendix A Schedule of Study Procedures	Inclusion of fistula clinical assessment procedure.	This assessment was included at the preparation visit in the initial protocol and has now been corrected to take place at the baseline visit.
[redacted]	[redacted]	To avoid any additional burden on participants.
Section 9.3.2 Preparation Visit (Visit 0) Appendix A Schedule of Study Procedures	Inclusion of assessment: review and record concomitant medications taken since the last visit.	Assessment added for completeness.
Section 9.3.2 Preparation Visit (Visit 0) Appendix A Schedule of Study Procedures	Inclusion of mandatory antibiotic administration after fistula preparation.	Mandatory antibiotics have been included as this is a procedure already in place in most hospitals after an exploration under anesthesia with curettage as prophylaxis of infections in the area.

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Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Sections 9.3.3 Repeat Administration (Visit 1) Section 9.3.4 6 Weeks Following Repeat Administration (Visit 2/Week 6 ± 8 days) Section 9.3.5 6 Months Following Repeat Administration (Visit 3/Week 24 ± 15 days) Section 9.3.6 12 Months Following Repeat Administration (Visit 4/Week 52 ± 15 days) Section 9.3.7 24 Months Following Repeat Administration (Visit 5/Week 104 ± 30 days) Section 9.3.8 36 Months Following Repeat Administration (Visit 6/156 Weeks ± 30 days, Final Visit) Section 9.3.9 Early Termination Visit Section 9.3.10 Unscheduled Visit	Assessments reorganized.	The order of assessments listed in the Schedule of Observations and Assessments has been updated to match with the order in the Schedule of Assessments table.
Section 9.3 Schedule of Observations and Procedures Appendix A Schedule of Study Procedures	Removal of Crohn's Disease Activity Index (CDAI) assessment throughout the study and replacing with PRO-2 score.	In light of COVID-19, if a subject is unable to attend a visit, it is deemed more appropriate to replace the CDAI assessment (which requires a blood sample for hematocrit value) with the PRO-2 score, which can still measure evolution the of CD in a simpler way without requiring clinical assessment.
Section 9.3.9 Early Termination Visit	Wording added to clarify that samples for DSA, immunogenicity [redacted] do not need to be taken at the early termination visit if the early termination visit takes place after the Week 24 visit.	To provide clarity on assessment procedures.

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Location	***Description***	***Rationale***
Section 9.3.10 Unscheduled Visit Appendix A Schedule of Study Procedures	Removal of plasma sample analysis from the unscheduled visit.	Update made for correctness.
Section 9.3.11 Unscheduled Telephone Call Visit Appendix A Schedule of Study Procedures	Added Section 9.3.11.	To allow subjects to have the option for a telephone call in case they are unable to attend the site visit.
Section 10.1.1 AEs	Update to AE definition. A sentence has been added to clarify that new fistula(s) identified during the course of the study will be captured as an AE.	To reinstate the International Conference for Harmonisation definition of an AE. The worsening of the treated fistula will be assessed as efficacy endpoint. Only the worsening of the nontreated newly developed fistula will be collected as an AE.
Section 10.1.2 SAEs	Addition of 'COVID-19 pneumonia' and 'COVID-19-related disease' to Takeda Medically Significant AE List.	Update made in line with recent industry and sponsor guidance.
Section 10.1.4 SSRs	Removal of breastfeeding as special situation report (SSR).	Only pregnancy is considered as an SSR and breastfeeding has therefore been removed.
Section 10.2.1.3 AESIs	Section updated to provide clarity on the process for reporting adverse event of special interests (AESIs) that meet the seriousness criteria.	For improved clarity on the AESI reporting procedure.
Section 10.2.2 Collection and Reporting of SAEs	Section updated to provide details on the procedure for reporting serious adverse events (SAEs).	For improved transparency on the SAE reporting procedure.
Section 13.1.3 Efficacy Analysis	Revised wording for efficacy analysis.	To provide specificity and clarification around the efficacy analysis.
Section 13.2 Interim Analysis and Criteria for Early Termination Section 6.1 Study Design Section 9.1.11 Procedures for Clinical Laboratory Samples	Sentence added to clarify that no interim analysis is planned for this study.	Update made for clarity to study procedures.
Section 13.3 Determination of Sample Size	Revised wording for determination of sample size.	To improve wording and clearly specify the reason for enrolling 50 subjects.

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Section 9.1.12.4 General Guidance with Respect to the Avoidance of Pregnancy Section 9.3.2 Preparation Visit (Visit 0) Appendix A Schedule of Study Procedures	Inclusion of urine pregnancy test.	Serum pregnancy test is only required at the baseline visit. Urine pregnancy tests will be performed at subsequent visits.
Section 9.3.8 36 Months Following Repeat Administration (Visit 6/156 Weeks ± 30 days, Final Visit) Appendix A Schedule of Study Procedures	Removal of plasma samples for DSA levels, immunogenicity, [redacted] at Week 156.	The Week 156 exploratory biomarker assessments have been removed to avoid any additional burden on participants.
Appendix B Anal Clock	Inclusion of appendix.	Added for completeness to protocol.
Appendix C PRO-2 Scoring	Inclusion of appendix.	Added for completeness to protocol.

Signature Page for Alofisel-4001 Protocol Amend 4 2024-04-29

Title: Amendment 4 to Postauthorization Safety Study of the Long-Term Safety and

Approval	[redacted] Statistics 30-Apr-2024 13:03:06 GMT+0000

Approval	[redacted] Pharmacovigilance 30-Apr-2024 13:11:38 GMT+0000

Approval	[redacted] Clinical 30-Apr-2024 13:22:13 GMT+0000

Document Number: TDN-000333585 v1.0