Clinical Study Protocol

EU PAS Number: EUPAS31439

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: Version 1.0, 22 May 2019

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 (ASPIRE)

Postauthorization Safety Study of Darvadstrocel Repeat Administration

Sponsor:	Millennium Pharmaceuticals, Inc (MPI) 40 Lansdowne Street Cambridge, MA 02139 USA		
Study Number:	Alofisel-4001		
IND Number:	Not Applicable	**EudraCT Number:**	2017-002491-10
Compound:	Darvadstrocel Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue (expanded adipose stem cells)		
Date:	22 May 2019	**Version:**	1.0

*Please note: Millennium Pharmaceuticals is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited and thereafter, any reference to the sponsor will use Takeda's name.

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 and pregnancy reporting	Fax: +1-224-554-1052 Email: eupv@tgrd.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 on Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and 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]

[redacted] Date

MPH, DPhil, [redacted] Epidemiology

[redacted] Date

MD, PhD, Pharmacovigilance [redacted]

[redacted] Date

MD, PhD, [redacted]

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, 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 B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D 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)

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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
AST	aspartate aminotransferase
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRP	c-reactive protein
DSA	donor-specific antibodies
eASC	expanded adipose stem cells
ECG	electrocardiogram
eCRF	electronic case report form
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
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 outcomes measure derived from CDAI
SAE	serious adverse event
SES-CD	simple endoscopic score for Crohn's Disease
SSR	special situation report
ULN	upper limit of normal
WOCBP	woman of childbearing potential

3.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc, a subsidiary of Takeda Pharmaceutical Company Limited	**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 (ASPIRE)	**IND No.:** Not Applicable	**EudraCT No.:** 2017-002491-10
Study Number: Alofisel-4001	**Phase:** 4	

Study Design:

This is a phase 4, multinational, single-arm clinical study in subjects with Crohn's disease (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 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 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, pelvic MRI will be performed and used to document fistula characteristics before repeat administration at baseline. 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, an MRI will be performed and the subject will attend an unscheduled visit. Central reading of pelvic MRIs will be performed. All local MRIs will be assessed centrally by the clinical research organization radiologist MRI central reader.

Subjects will be assessed before repeat administration at the baseline and preparatory 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 will be collected at baseline, Weeks 24 (±15 days), 156 (±30 days), and the early termination visit. Blood samples for DSA levels and exploratory immunogenicity testing will be collected at the baseline visit and at Weeks 6 (±8 days), 24 (±15 days), and 156 (±30 days). Blood samples for these tests will be analyzed in batches as the study progresses, and available results will be provided with the interim reports; 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.

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 special situation reports (SSRs).

Secondary Objective:

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

Exploratory Objectives:

[redacted]

- To assess the effect of darvadstrocel on microbiome diversity at Week 6.

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 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 current complex, draining, perianal fistulas with controlled or mildly active CD (defined as patient reported outcomes measure derived from CDAI [PRO-2] score <14) who have already received treatment with darvadstrocel, and their physician has planned a repeat administration for the original tract or for a new fistula tract.
5. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use barrier method of contraception (e.g. condom with or without spermicide) from signing of informed consent and until 1 year after repeat administration.
6. 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.
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 aminoglycosides; Dulbecco modified eagle medium; bovine serum; local anaesthetics or gadolinium or MRI contrast.
4. The subject is currently participating in other studies with darvadstrocel.
5. The subject is currently receiving or has received any other investigational medicinal product (IMP) within the last 3 months before signing the ICF.
6. 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.

7. If male, the subject intends to donate sperm during this study.
8. 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).
9. The subject has a contraindication to the anesthetic procedure.
10. The subject has severe rectal and/or anal stenosis that would make it impossible to follow the surgery procedure.
11. The subject has severe proctitis (rectal ulcers >0.5 cm) that would make it impossible to follow the surgery procedure.
12. The subject has any prior invasive malignancy diagnosed within the last 3 years before screening visit. Subjects with basal cell carcinoma of the skin completely resected outside the perineal region can be included.
13. The subject has a current or recent (within 6 months before the screening 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.
14. The subject has had major surgery of the gastrointestinal tract within 6 months before screening, including local perianal surgery, other than curettage/draining for the fistula, and/or treatment with darvadstrocel within 6 months before study entry.
15. 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 endpoints:

- Incidence of treatment-emergent adverse events
- Incidence of treatment-emergent serious adverse events
- Incidence of SSRs (pregnancy)
- Incidence of specific AESIs:
  - Immunogenicity/alloimmune reactions
  - Hypersensitivity
  - Transmission of infectious agents
  - Tumorgenicity
  - Ectopic tissue formation
  - Medication errors

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 IMP administration.
  - Combined remission of complex perianal fistula(s) is defined as the closure of all treated external openings that were draining at baseline (ie, screening visit), 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 24, 52, 104, and 156 after IMP 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 24, 52, 104, and 156 after IMP 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.
  - Relapse is defined as reopening of any of the treated fistula(s) external openings that were in clinical remission at Week 24, with active drainage as clinically assessed,

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

Exploratory Endpoint:

- [redacted]
- Change from baseline in microbiome diversity at Week 6.

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, 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.

All proportion-based efficacy endpoints will be summarized by visit.

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

Time to event endpoints will be analyzed using Kaplan-Meier survival methods.

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 attempt to enroll 50 subjects who have received previous darvadstrocel treatment and need to be retreated for the same fistula tract or a new fistula tract according to their physician. This planned sample size is intended to provide initial data on the safety and efficacy of a repeat administration with darvadstrocel treatment for the potential future use of repeat administration with darvadstrocel by physicians.

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 Cx601 was well tolerated in the study population [1].

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 [2].

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, anal (perianal) abscess.

Other than those previously mentioned, there are no other known specific adverse reactions that can be attributed to darvadstrocel.

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 Objectives

To assess 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 special situation reports (SSRs).

5.1.2 Secondary Objectives

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

5.1.3 Exploratory Objectives

- [redacted]
- To assess the effect of darvadstrocel on microbiome diversity at Week 6.

5.2 Endpoints

5.2.1 Primary Endpoint

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

- Incidence of treatment-emergent adverse events
- Incidence of treatment-emergent SAEs
- SSRs (pregnancy)
- Specific AESIs, including:
  - Immunogenicity/alloimmune reactions
  - Hypersensitivity
  - Transmission of infectious agents
  - Tumorgenicity
  - Ectopic tissue formation
  - Medication errors

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 investigational medicinal product (IMP) administration.
  - Combined remission of complex perianal fistula(s) is defined as the closure of all treated external openings that were draining at baseline (ie, screening visit), 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 24, 52, 104, and 156 after IMP 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 24, 52, 104, and 156 after IMP 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.
  - Relapse is defined as reopening of any of the treated fistula(s) external openings that were in clinical remission at Week 24, with active drainage as clinically assessed,

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

5.2.3 Exploratory Endpoints

[redacted]

- Change from baseline in the microbiome diversity at Week 6.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 4, multinational, single-arm clinical study of adult (aged 18 years or older) subjects with CD and complex perianal fistulas who have previously been administered darvadstrocel (Alofisel) and whose physician plans repeat administration. A study schematic is presented in Figure 6.a.

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 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.

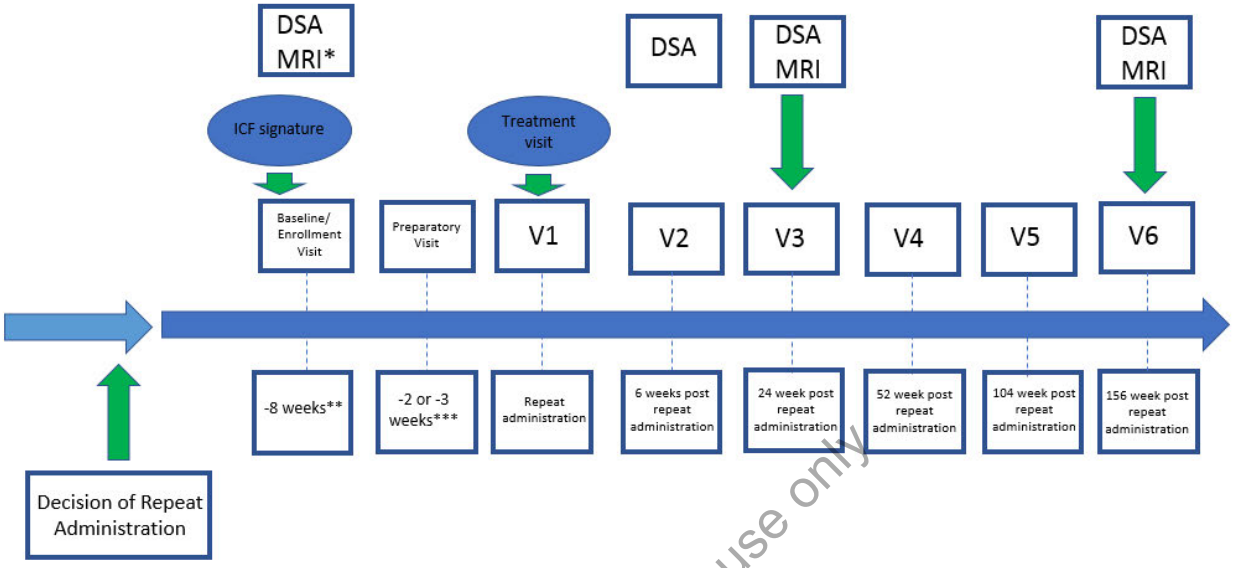
Baseline information will be collected on demographics, clinical characteristics and CD clinical history, treatment history (including details of first administration of darvadstrocel), fistula history (prior procedures for perianal disease), and comorbidities/concomitant medications. In addition, pelvic MRI will be performed and used to document fistula characteristics before repeat administration at baseline. 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, an MRI will be performed and the subject will attend an unscheduled visit. Central reading of pelvic MRIs will be performed. All local MRIs will be assessed centrally by the clinical research organization radiologist MRI central reader.

Subjects will be clinically assessed before repeat administration at a baseline and a preparatory 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.

Blood samples for central laboratory tests will be collected at baseline, Weeks 24 (±15 days), 156 (±30 days), and the early termination visit. Blood samples for DSA levels and exploratory immunogenicity testing will be collected at the baseline visit and at Weeks 6 (±8 days), 24 (±15 days), and 156 (±30 days). Blood samples for these tests will be analyzed in batches as the study progresses, and available results will be provided with the interim report; 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.

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; 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.

* DSA and MRI will take place after the subject has signed the ICF.

** Baseline/enrollment visit will take place 8 weeks prior to repeat administration.

*** Preparatory visit will take place within a minimum of 2 weeks and a maximum of 3 weeks before the repeat administration visit.

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 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.

MRI will be used to delineate the classification of the location and extent of fistula 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 Premature Termination or Suspension of Study or Study Site

6.3.1 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.

6.3.2 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.

6.3.3 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, 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 current complex, draining, perianal fistulas with controlled or mildly active CD (defined as patient reported outcomes measure derived from CDAI [PRO-2] score <14) who have already received treatment with darvadstrocel, and their physician has planned a repeat administration for the original tract or for a new fistula tract.
5. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential agrees to use barrier method of contraception (e.g. condom with or without spermicide)* from signing of informed consent and until 1 year after repeat administration.
6. 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 methods of contraception are defined in Section 9.1.11 and reporting responsibilities are defined in Section 9.1.12.

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.
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 aminoglycosides; Dulbecco modified eagle medium; bovine serum; local anesthetics or gadolinium or MRI contrast.
4. The subject is currently participating in other studies with darvadstrocel.
5. The subject is currently receiving or has received any other investigational medicinal product (IMP) within the last 3 months before signing the ICF.
6. 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.

7. If male, the subject intends to donate sperm during this study.
8. 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).
9. The subject has a contraindication to the anesthetic procedure.
10. The subject has severe rectal and/or anal stenosis that would make it impossible to follow the surgery procedure.
11. The subject has severe proctitis (rectal ulcers >0.5 cm) that would make it impossible to follow the surgery procedure.
12. The subject has any prior invasive malignancy diagnosed within the last 3 years before screening visit. Subjects with basal cell carcinoma of the skin completely resected outside the perineal region can be included.
13. The subject has a current or recent (within 6 months before the screening 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.
14. The subject has had major surgery of the gastrointestinal tract within 6 months before screening, including local perianal surgery, other than curettage/draining for the fistula, and/or treatment with darvadstrocel within 6 months before study entry.
15. 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. 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.

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.

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.

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 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.

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. Vials should then be destroyed locally, and destruction will be documented as appropriate.

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 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. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry and/or retest date, date and amount dispensed including initials, seal, or signature of the person dispensing the drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

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. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability and destruction, and originals will be provided 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.

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 and lifestyle information will be obtained at the baseline/enrollment visit.

Medical history to be obtained will include history of fistulizing CD and assessment of severity and history of cancer, including anal canal and colorectal malignancy. 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 9.1.9).

Medication history information to be obtained includes any medication relevant to efficacy/safety evaluation stopped at or within 2 years before signing of informed consent as well as details on first darvadstrocel administration.

9.1.3 Physical Examination Procedure

Physical examination results and vital signs will be recorded (systolic and diastolic blood pressure [mm Hg], heart rate [beats per min], and body temperature [°C]).

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/enrollment visit only. Weight will be measured at all visits.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral 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. Specific AESIs assessed will include immunogenicity/alloimmune reactions (including assessment of DSA formation and the impact of immunogenicity on safety and clinical response at baseline and at Weeks 6, 24, 156, early termination visit and unscheduled visit), hypersensitivity, ectopic tissue formation, medication errors, tumorigenicity, and transmission of infectious agents.

9.1.7 Efficacy Measurements

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 contrast-enhanced pelvic MRI will be performed at baseline, Week 24, Week 156, early termination visit and at any unscheduled visits.

All MRI scans, including MRI scans available from initial treatment, will be assessed by the MRI central reader. The MRI central reader will report number of fistulas, location, type, and measurements of any collection(s) in 3 dimensions. Analysis will include assessment of collections >2 cm, (in at least 2 dimensions).

9.1.7.3 Perianal Crohn's Disease Activity Index

The PDAI is a scoring system to evaluate the severity of perianal CD [5]. 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 preparatory visit and repeat administration visit.

9.1.7.4 Immunologic Tests

A blood sample will be taken for cell responses and immunologic tests at baseline, Weeks 6, 24, 156 and also at early termination and unscheduled visit. Samples will be analyzed via a central laboratory:

- Humoral responses:

- Presence and absence of antidarvadstrocel antibodies, including antibody titer, antidarvadstrocel capacity to bind darvadstrocel, and finally evaluation of antidarvadstrocel antibody capacity to induce complement dependent toxicity. Results on the presence and titer of antidarvadstrocel antibody will be transferred for their integrated interpretation with potential interactions on safety or impact on efficacy.

- Cell responses:
  - Phenotypical and functional characterization of peripheral blood mononuclear cells isolated from subjects, to define the potential immunologic impact of darvadstrocel treatment. Circulating cell distribution (repertoire of memory cells) and circulating cell function (including but not limited to secretion, proliferative, and cytotoxic capacity of subject's immune cells).

9.1.7.5 Exploratory Biomarker Samples

Microenvironment in and around the fistula may help to better characterize fistula as well as patient characterization. Therefore, an optional microbiome sample will be collected to comprehensively understand the microenvironment. A fistula swab sample will be taken from the fistula tract at the preparatory visit and repeat administration visit (Visit 1). Stool samples for microbiome will be collected before the preparatory visit and a second sample will be collected post-treatment (Week 6).

The detailed procedure for the sample collection and sample processing will be explained in the laboratory manual.

9.1.8 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. 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.

9.1.9 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/enrollment examination, according the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.10 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 baseline, Weeks 24 (±15 days), 156 (±30 days), and at the early termination visit.

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)	Aspartate aminotransferase (AST)
Mean corpuscular hemoglobin concentration (MCHC)	Alanine aminotransferase (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)

The central laboratory will perform laboratory tests for hematology and serum chemistries. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

Blood samples for DSA levels and exploratory immunogenicity testing will be collected at repeat administration baseline and at 6, 24, and 156 weeks and at the unscheduled and early termination visits.

Blood samples for these tests will be analyzed in batches as the study progresses, and available results will be provided with the interim reports; 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.

The central laboratory will perform laboratory tests for DSA and immunogenicity. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

9.1.11 Contraception and Pregnancy Avoidance Procedure

9.1.11.1 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.

9.1.11.2 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.

9.1.11.3 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 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 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/excluded, 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
- True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse from signing of informed consent and until 1 year after repeat administration.

- 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. 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. Sexual abstinence is NOT an acceptable method of contraception. Other unacceptable methods of contraception are:
   - Periodic 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 serum/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 9.1.11.4).
6. In addition to a negative serum/urine hCG pregnancy test at screening, WOCBP must have a negative serum/urine hCG pregnancy test before receiving the medication.

9.1.11.4 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 pregnant partners.
- 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?

9.1.12 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.

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 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. An evaluation after the birth of the child will also be conducted.

9.1.13 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.

9.3.1 Baseline/Enrollment

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

- ICF signature.
- Demographics, including weight, height, and lifestyle.
- Medical history.
- Physical examination with vital signs.
- CD, fistula history, and treatment history.
- Target fistula(s) information (clinical characteristics, including age of onset, number of other fistulas, localization, and clock position), including whether fistula to be treated was previously treated or if it is a new fistula.
- Serum pregnancy test for WOCBP.
- Comorbidities of interest.
- Blood sample for DSA/immunogenicity:
  - Blood sample for peripheral blood mononuclear cells (PBMC)
  - Plasma sample for immunogenicity

[redacted]

[redacted]

- Central laboratory tests:
  - Hematology: hemoglobin, hematocrit, erythrocytes, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelet count.
  - Serum biochemistry: c-reactive protein (CRP), urea, creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin (direct bilirubin if total bilirubin is above the upper limit of normal [ULN]), potassium, sodium, chloride.
- Previous and concomitant medications.
- Reason(s) for darvadstrocel repeat administration (must be specified).
- Stool sample for microbiome (optional). Sample will be collected by the subject at home between baseline and the preparatory visit.
- Clinical assessment of perianal fistulas and CD (including the presence or absence of proctitis, localization, fistula draining status, and pattern of disease).
- 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 number of fistulas, location, type, and other MRI fistula characteristics and measurements of any collection(s) in 3 dimensions. Analysis will include assessment of collections >2 cm, (in at least 2 dimensions).
- PDAI score.
- Crohn's Disease Activity Index (CDAI) score.
- If available, colonoscopy information about activity of CD (within 6 months prior to repeat administration):
  - PRO-2 score (to confirm no or mildly active CD [score <14]).
  - Luminal disease activity involving the rectum as determined by:
    - Presence or absence of proctitis as measured by flexible sigmoidoscopy or rectoscopy.
    - Rectum components of the Simple Endoscopic Score for Crohn's Disease (SES-CD).
- Assessment of AEs/SAEs, and SSRs.
- Schedule preparatory visit.
- Enter subject in eCRF and obtain subject identification number.

For any subject not meeting eligibility criteria at the baseline visit, it may be possible to rescreen the subject later upon the sponsor's approval.

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

- 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).

9.3.2 Preparatory Visit

A preparatory 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 preparatory visit will act as a trigger to start the manufacturing process of darvadstrocel for the subject.

Procedures to be completed at the preparatory visit include:

- Inclusion/exclusion criteria check.
- Physical examination including weight and vital signs.
- Serum pregnancy test for WOCBP.
- Fistula preparation consisting of an examination under anesthesia (EUA), curettage and seton placement by the surgeon according to the surgery procedure manual.
- Fistula swab sample for microbiome analysis (optional).
- Stool sample for microbiome (optional). Sample will be collected by the subject at home between baseline and the preparatory visit.
- PDAI score.
- CDAI score.
- Assessment of AEs/SAEs, and SSRs.

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 preparatory visit. Procedures to be completed at repeat administration include:

- Time since first administration of darvadstrocel.
- Physical examination including weight and vital signs.
- Urine pregnancy test for WOCBP.
- Blood sample for DSA/immunogenicity:
  - Plasma sample for immunogenicity
  - [redacted]
- Previous and concomitant medications.
- Fistula swab sample for microbiome (optional).
- Number and location of fistula tracts 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.
- PDAI score.
- CDAI score.
- Assessment of AEs/SAEs, AESIs, 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 the IMP at the repeat administration visit, the visit should be rescheduled in at least 2 weeks. It is not 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 the IMP. 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:

- Physical examination including weight and vital signs.
- Blood sample for DSA/immunogenicity:
  - Blood sample for PBMC
  - Plasma sample for immunogenicity

  [redacted]
- Previous and concomitant medications.
- Stool sample for microbiome (optional). The sample will be collected by the subject using an at home kit.
- Urine pregnancy test for WOCBP.
- 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.
- CDAI score.
- Assessment of AEs/SAEs, AESIs, 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:

- Physical examination including weight and vital signs.
- Blood sample for DSA/immunogenicity.
  - Blood sample for PBMC
  - Plasma sample for immunogenicity

  [redacted]
- Previous and concomitant medications.
- Urine pregnancy test for WOCBP.
- Central laboratory tests.

- 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 number of fistulas, location, type, and other MRI fistula characteristics and measurements of any collection(s) in 3 dimensions. Analysis will include assessment of collections >2 cm, (in at least 2 dimensions).
- PDAI score.
- CDAI score.
- Assessment of AEs/SAEs, AESIs, 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:

- Physical examination including weight and vital signs.
- Previous and concomitant medications.
- Urine pregnancy test for WOCBP.
- 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.
- CDAI score.
- Assessment of AEs/SAEs, AESIs, 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:

- Physical examination including weight and vital signs.
- Previous and concomitant medications.
- Urine pregnancy test for WOCBP.
- 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.
- CDAI score.

- Assessment of AEs/SAEs, AESIs, and SSRs.
- Schedule Visit 6/Week 156 (± 30 days).

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

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

- Physical examination including weight with vital signs.
- Previous and concomitant medications.
- Central laboratory tests.
- Blood sample for DSA/immunogenicity.
  - Whole blood sample for PBMC
  - Plasma sample for immunogenicity

  [redacted]
- Urine pregnancy test for WOCBP.
- 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 number of fistulas, location, type, and other MRI fistula characteristics and measurements of any collection(s) in 3 dimensions. Analysis will include assessment of collections >2 cm, (in at least 2 dimensions).
- PDAI score.
- CDAI score.
- Assessment of AEs/SAEs, AESIs, 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:

- Physical examination including weight and vital signs.
- Previous and concomitant medications.
- Urine pregnancy test for WOCBP.
- 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 number of fistulas, location, type, and other MRI fistula characteristics and measurements of any collection(s) in 3 dimensions. Analysis will include assessment of collections >2 cm, (in at least 2 dimensions).
- Central laboratory tests.
- Blood sample DSA and immunogenicity.
  - Whole blood sample for PBMC
  - Plasma sample for immunogenicity
    [redacted]
- PDAI score.
- CDAI score.
- Assessment of AEs/SAEs, AESIs, 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.
- Previous and concomitant medications.
- Urine pregnancy test for WOCBP.
- 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. The MRI central reader will report number of fistulas, location, type, and other MRI fistula characteristics and measurements of any collection(s) in 3 dimensions. Analysis will include assessment of collections >2 cm, (in at least 2 dimensions).

- [redacted] including immunogenicity sample.
- PDAI score.
- CDAI score.
- Assessment of AEs/SAEs, AESIs, 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 and abscesses, defining the primary endpoint, will not be captured as an AE unless there is evidence suggesting a causal relationship between the IMP or the administration procedure.

10.1.2 SAE

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

1. Results in DEATH.
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.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).
    - Transmission of infection.

Table 10.a Takeda Medically Significant AE List

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

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

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

An SSR includes any of the following events:

- Pregnancy: any case in which a pregnant subject is exposed to a Takeda product or in which a female subject or female partner of a male subject becomes pregnant following treatment with

a Takeda product. Exposure is considered either through maternal exposure or via semen following paternal exposure:

– Breastfeeding: infant exposure from breast milk.

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 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."

10.1.7 Start Date

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

10.1.8 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.

10.1.9 Frequency

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

10.1.10 Action Concerning Study Drug

Not applicable.

10.1.11 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 that the subject is first administered study drug (repeat administration). 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

If the adverse event of special interest (AESI)/abnormality, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be recorded in an AESI form or an SAE form if the AESI meets the seriousness criteria. The SAE form should be completed and 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 AESI form or the SAE form to the sponsor.

AESI/abnormality criteria include:

- Immunogenicity/alloimmune reactions.
- Hypersensitivity.
- Ectopic tissue formation.
- Medication errors.
- Tumorigenicity.
- Transmission of infectious agents.

AESIs must be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

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 first onset or notification 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 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.

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 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 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 fhirst 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 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 the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designees) and will 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 its designee. The sponsor or its 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 on 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, receive treatment with darvadstrocel, and provide any postbaseline safety information. 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

All efficacy endpoints will be summarized by visit, as applicable. The proportion of subjects with each of the following outcomes, along with 95% 2-sided confidence intervals will be provided by visit for the following proportion-based efficacy endpoints:

- Clinical remission
- Clinical response
- Combined remission
- Relapse
- New anal abscess in treated fistula

In addition, at the Week 52, Week 104, and Week 156 assessments the proportion of subjects who changed in status since the previous assessment will be determined.

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

Among subjects who achieve remission, time to relapse will be analyzed using Kaplan-Meier survival methods.

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, ectopic tissue formation, and medication errors) will be summarized descriptively by system organ class and preferred term using MedDRA terminology. TEAEs and SAEs will also be summarized by severity and by relationship to study drug.

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 changes in microbiome diversity 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

An interim analysis is planned for no later than Q4 2023.

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 attempt to enroll 50 subjects who have received previous darvadstrocel treatment and need to be retreated for the same fistula tract or a new fistula tract according to their physician. This planned sample size is intended to provide initial data on the safety and efficacy of a repeat administration with darvadstrocel treatment for the potential future use of repeat administration with darvadstrocel by physicians.

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 (contract research organization) 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.

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 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).

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

1. Panes J, Garcia-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. Lancet 2016;388(10051):1281-90.
2. de la Portilla F, Alba F, Garcia-Olmo D, Herrerias JM, Gonzalez FX, Galindo A. Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIa clinical trial. Int J Colorectal Dis 2013;28(3):313-23.

Appendix A Schedule of Study Procedures

	Post-treatment Period									
Assessment	**Baseline / Enrollment Visit** [a]	**Preparatory Visit to Visit 1** [b]	**Repeat Administration** Visit 1	**6 Weeks ±8 days** Visit 2	**24 Weeks ±15 days** Visit 3	**52 Weeks ±15 days** Visit 4	**104 Weeks ±30 days** Visit 5	**156 Weeks ±30 days** Visit 6	**Early Termination Visit**	**Unscheduled Visit**
Enrollment [c]	X									
ICF	X									
Inclusion and exclusion criteria check	X	X								
Demographics, height, and lifestyle [d]	X									
Weight	X	X	X	X	X	X	X	X	X	X
Medical history [e]	X									
Physical examination with vital signs [f]	X	X	X	X	X	X	X	X	X	X
CD, fistula history, and treatment history [g]	X									
Target fistula(s) information (new fistula or previously treated fistula) [h]	X									
Serum pregnancy	X	X								
Urine pregnancy			X	X	X	X	X	X	X	X
Comorbidities of interest	X									
Central laboratory tests [i]	X				X			X	X	
Blood sample for peripheral blood mononuclear cells	X			X	X			X	X	
Plasma sample for immunogenicity	X		X [j]	X	X			X	X	X
[redacted]										

	Post-treatment Period									
Assessment	**Baseline / Enrollment Visit [a]**	**Preparatory Visit to Visit 1 [b]**	**Repeat Administration Visit 1**	**6 Weeks ±8 days Visit 2**	**24 Weeks ±15 days Visit 3**	**52 Weeks ±15 days Visit 4**	**104 Weeks ±30 days Visit 5**	**156 Weeks ±30 days Visit 6**	**Early Termination Visit**	**Unscheduled Visit**
Previous and concomitant medications [k]	X		X	X	X	X	X	X	X	X
Reason(s) for darvadstrocel repeat administration	X									
Fistula preparation timing and techniques [l]		X								
Fistula swab sample for microbiome (optional)		X	X [m]							
Stool sample for microbiome (optional) [n]	X			X						
Number and location of fistula tracts treated			X							
IMP administration [o]			X							
Clinical fistula assessment [p]		X		X	X	X	X	X	X	X
Pelvic MRI [q]	X				X			X	X	X
PDAI score	X	X	X	X	X	X	X	X	X	X
CDAI score	X	X	X	X	X	X	X	X	X	X
PRO-2 score [r]	X									
Luminal disease activity involving the rectum (optional) [s]	X									
Full SES-CD and/or rectum components (optional) [s]	X									
All AEs/SAEs, AESIs, and SSRs	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE: adverse event; AESI: adverse event of special interest; CD: Crohn's disease; DSA: donor-specific antibodies; ICF: informed consent form; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PBMC: peripheral blood mononuclear cells; PDAI: Perianal Disease Activity Index; SAE: serious adverse event; SES-CD: Simple Endoscopic Score for Crohn's Disease; SSR: special situation report.

[a] Repeat administration (Visit 1) should take place within 8 weeks of the baseline visit. There will be a maximum of 5 weeks from the baseline visit to the preparatory visit.

[b] From preparatory 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).

[c] Subjects will be enrolled once the physician has decided to readminister darvadstrocel.

[d] Including age, sex, country, smoking history, alcohol use, and employment status.

[e] Including number of pregnancies, history of blood transfusions, transplantation, and anal canal or colorectal malignancy.

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

[g] 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; preparatory surgery will be completed before darvadstrocel administration.

[h] Clinical characteristics including age of onset, number of other fistulas, localization, and clock position.

[i] 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.

[redacted].

[k] Specific drug used, indication, dose received, route of administration, and start/end dates, ever/within last 2 years of use and may include the following: darvadstrocel, systemic antibiotics, systemic corticosteroids, immunomodulators (6-MP, AZA, methotrexate), biologics (anti-TNF-α agents, vedolizumab, ustekinumab), 5-ASAs, narcotic (opioid) analgesics, antidiarrheals (loperamide, diphenoxylate).

[l] Seton placement/removal curettage performed by surgeon according to the surgery procedure manual (provided as a separate document). Details of darvadstrocel repeat administration will also be captured.

[m] Fistula swab sample (optional) will be collected before IMP administration. Additional collection details will be provided in the laboratory manual.

[n] Microbiome collection (optional). The first microbiome sample will be collected between baseline and preparatory visit, and the second sample will be collected at 6 weeks ± 8 days post repeat administration. The sample will be collected by the subject using an at home kit. Additional details will be provided in the laboratory manual.

[o] All procedures should be performed before IMP administration. If there is any problem administering the IMP at the repeat administration visit, the visit should be rescheduled in at least 2 weeks. It is not necessary to repeat the preparatory visit, the setons will be maintained until the rescheduled treatment visit and will be withdrawn just before the administration of the IMP. All repeat administration procedures are to be repeated, see Section 9.3.3.

[p] 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.

[q] All MRI scans will be assessed centrally by the designated MRI reader.

[r] PRO-2 score to be collected at baseline to confirm no or mildly active CD (score <14).

[s] Luminal disease activity involving the rectum, as determined by the presence or absence of proctitis as measured by flexible sigmoidoscopy or rectoscopy and rectum components of the simple endoscopic score for Crohn's Disease (SES-CD) (only if a colonoscopy has been routinely performed within 6 months before repeat administration with darvadstrocel).

Appendix B 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 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 C 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 D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, 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.

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.

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.

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

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 (ASPIRE)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Safety Approval	30-May-2019 08:59 UTC
[redacted]	Clinical Science Approval	31-May-2019 08:33 UTC