Clinical Study Protocol

NCT Number: NCT04075825

Title: A Follow-up of a Phase 3 Study to Evaluate the Long-term Safety and Efficacy of Darvadstrocel in the Treatment of Complex Perianal Fistula in Subjects With Crohn's Disease Who Have Participated in ADMIRE II Study

Study Number: Darvadstrocel-3003

Document Version and Date: Amendment no. 2, 17 November 2022

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

TAKEDA PHARMACEUTICALS

PROTOCOL

A Follow-up of a Phase 3 Study to Evaluate the Long-term Safety and Efficacy of Darvadstrocel in the Treatment of Complex Perianal Fistula in Subjects With Crohn's Disease Who Have Participated in ADMIRE II Study

Short Title

Long-term Follow-up Study With Darvadstrocel in the Treatment of Complex Perianal Fistula

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA		
Study Number:	Darvadstrocel-3003		
IND Number:	017707	**EudraCT Number:**	2019 000333-39
clinicaltrials.gov:	NCT04075825		
Compound:	Darvadstrocel (Cx601) Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue (expanded adipose stem cells)		
Date:	17 November 2022	**Amendment Number:**	2

Amendment History:

Date	Amendment Number	Amendment Type	Region
17 November 2022	2	Substantial	Global
26 January 2022	1	Substantial	Global
22 March 2019	Initial protocol	-	Global

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	
Serious adverse event and pregnancy reporting	Contracted contract research organization's contact (Refer to the contact information list)
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Contracted contract research organization's contact (Refer to the contact information list)

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

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

[redacted] MSc Date
[redacted], Statistics

[redacted] Date
MBBS, FRSPH, MSc, DLSHTM, MRQA, EU
Qualified Person for Pharmacovigilance

[redacted] MD, MS Date
[redacted], Global Safety

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.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) 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)

1.3 Protocol Amendment 2 Summary of Changes

This document describes the changes to the protocol incorporating Amendment 2. The primary reasons for this amendment are to:

- Clarify the timing of the baseline assessments that will be used for the study's secondary and expoloratory analyses.
- Include an interim analysis (IA).
- Include the option of remote site visits in sites/countries where local legislation allows.
- Define the situations in which a subject will be considered a treatment failure.
- Define the end of the study.

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

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Title page	Addition of study's clinicaltrials.gov identifier.	Addition made in line with internal process.
Section 1.2 Approval	Revision to signatories.	Approvers were updated.
Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 8.0 Clinical Study Material Management	Editorial revision.	To clarify the timing of study unblinding.
Section 2.0 STUDY SUMMARY Section 6.1 Study Design	Language revision.	To clarify the timing of the study's primary efficacy analysis.
Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints Section 5.2.3 Exploratory Endpoints Section 13.1.3 Efficacy Analysis	Editorial revision.	To clarify the timing of the baseline assessments that will be used for the study's secondary and exploratory analyses.
Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints	Editorial revision.	To clarify the study's definition of "relapse".
Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 13.2 Interim Analysis	Addition of IA.	To support the long-term benefit-risk profile of darvadstrocel at the time of completion of Study Cx601-0303 ADMIRE-CD II.
Section 2.0 STUDY SUMMARY Section 13.1.3 Efficacy Analysis	Language addition.	To specify what is included in the study's statistical analysis plan (SAP).

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 6.1 Study Design	Language addition.	To define the situations in which a subject will be considered a treatment failure.
Section 6.3 End of Study/Study Completion Definition	Addition of section.	To define the end of the study.
Section 13.1 Statistical and Analytical Plans	Editorial revision.	To clarify when the SAP for the study will be finalized.
Section 13.1.2 Analysis of Demographics and Other Baseline Characteristics	Text deleted.	To remove duplicated text from Section 13.1.4.
Section 14.1 Study-Site Monitoring Visits	Inclusion of remote site visits.	Remote site visits improve efficiency and allow for a continuous verification of data. Additionally, some sites have restricted on-site monitoring activities due to the coronavirus disease 2019 (COVID-19) pandemic. These remote visits will occur only in those sites/countries where local legislation allows, and not prior to independent ethics committee (IEC)/institutional review board (IRB) notification.
Appendix E	COVID-19 and COVID-19 pneumonia Preferred Terms added to the list of Takeda medically significant adverse events (AEs).	Addition made to align with Takeda data standards.

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** Darvadstrocel (Cx601)	
Title of Protocol: A Follow-up of a Phase 3 Study to Evaluate the Long-term Safety and Efficacy of Darvadstrocel in the Treatment of Complex Perianal Fistula in Subjects With Crohn's Disease Who Have Participated in ADMIRE II Study	**IND No.:** 017707	**EudraCT No.:** 2019-000333-39
Study Number: Darvadstrocel-3003	**Phase:** 3	

Study Design:

This long-term extension (LTE) study is a follow-up of a phase 3 study to evaluate the long-term safety and efficacy of darvadstrocel (Cx601) in the treatment of complex perianal fistula in Crohn's disease (CD). To be eligible for the LTE study, subjects will have completed the final Week 52 assessment in the Cx601-0303 ADMIRE-CD II study (hereafter referred to as ADMIRE-CD II). Informed consent will be obtained at the Week 52 visit of the ADMIRE-CD II study or up to 4 weeks after the Week 52 visit.

For those subjects who have more than a 4-week gap between the Week 52 visit of the ADMIRE-CD II study and signing of the informed consent form (ICF) for the LTE study, a re-baseline visit will be scheduled; the re-baseline visit will include the same procedures included at the baseline visit with the addition of interval inflammatory bowel disease history and medical interventions since the Week 52 visit. Magnetic resonance imaging (MRI) assessment will not be included at the re-baseline visit. The re-baseline visit cannot be performed any later than 3 months after the Week 52 visit. MRI will be performed in all subjects at the Week 156 visit.

Study visits will take place annually for up to 2 years from enrollment into the LTE of ADMIRE-CD II or 3 years following treatment in ADMIRE-CD II. At these visits, clinical assessment of the fistula will be considered for clinical remission. Additional telephone call visits will be conducted every 3 months for safety assessments.

In addition, unscheduled visits may be performed for safety follow-up, and for subjects experiencing any clinically significant symptoms of perianal disease, an MRI will be performed.

The LTE study will be blinded until unblinding of the original study after final database lock, when all subjects have completed their participation at Week 52 of the ADMIRE-CD II study. After unblinding of the ADMIRE-CD II study, the LTE study will be conducted as an open-label study. Subjects will remain in the treatment group assigned in the ADMIRE-CD II study.

Enrollment into the LTE study will not prevent subjects with ongoing fistulizing disease or luminal CD from receiving any additional treatment (including any medical or surgical treatment) prescribed by his/her physician for the treatment of CD and/or perianal disease. Subjects who receive surgical and/or biologic treatment for the perianal fistulizing disease will be considered treatment failures, but should continue in the study. Those subjects who are prescribed darvadstrocel will be withdrawn from the LTE study and complete an early termination visit because the study will assess the long-term follow-up of investigational medicinal product (IMP) administration in the ADMIRE-CD II study.

ADMIRE-CD II is an ongoing phase 3, randomized, double-blind, parallel-group, placebo-controlled, international, multicenter study to assess the efficacy and safety of darvadstrocel, adult allogeneic expanded adipose-derived stem cells, for the treatment of complex perianal fistula(s) in subjects with CD over a period of 52 weeks. The primary efficacy analysis is to be conducted at Week 24. Thereafter, the double-blind design will be maintained up to Week 52 to allow for evaluation of longer term (Week 52) efficacy and safety. The study follows an add-on design, with subjects receiving any ongoing concomitant medical treatment for CD at stable doses at the time of screening and allowed to continue with it throughout the study. Study subjects are allocated to treatment, in a 1:1 ratio. A curettage and a seton placement will take place at randomization into ADMIRE-CD II. The study population consists of subjects whose perianal fistulas were previously treated and have shown an inadequate response, a loss of response, intolerance or contraindication to immunosuppressives or monoclonal antibodies, and subjects with complex

perianal fistula(s) draining at the screening visit despite previous standard medical treatment, with up to 2 internal openings and a maximum of 3 external openings. In the treatment administration visit, the seton is withdrawn, and a vigorous curettage of all fistula tracts and a suture of internal openings is performed in all subjects. After this, all subjects in the active treatment arm will receive a single dose of darvadstrocel while subjects in the control arm will receive saline solution (to mask the treatment).

The LTE study will evaluate the long-term safety of darvadstrocel, including adverse events (AEs), serious adverse events (SAEs) and specific adverse events of special interest (AESIs): immunogenicity/alloimmune reactions, tumorgenicity, and ectopic tissue formation. The study will also evaluate the long-term effect of darvadstrocel treatment on fistula remission [redacted].

Primary Objective:

To evaluate the long-term safety of a single dose of darvadstrocel in subjects with CD and complex perianal fistula by evaluation of AEs, SAEs, and AESIs.

Secondary Objective:

To evaluate the long-term efficacy of a single dose of darvadstrocel for the treatment of complex perianal fistula(s) in subjects with CD.

Exploratory Objective:

[redacted]

Subject Population: Male or female subjects who have participated in and completed the ADMIRE-CD II study for treatment of complex perianal fistula in CD.

Number of Subjects:	**Number of Sites:**
Estimated total: All subjects participating in the ADMIRE-CD II study will be offered enrolment into the LTE study. It is anticipated that approximately 150 subjects will enroll into the LTE study, however the study will not stop enrolling if this number is met.	Estimated total: All sites participating in the ADMIRE-CD II study will be offered participation in the LTE study.
Dose Level:	**Route of Administration:**
No drug administration in this study. Single dose of darvadstrocel/placebo previously administered in the ADMIRE-CD II study.	Not applicable.
Duration of Treatment:	**Period of Evaluation:**
No drug administration in this study.	104 additional weeks after completion of ADMIRE-CD II study (156 weeks from IMP administration in ADMIRE-CD II).

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 or, when applicable, the subject's legally acceptable representative signs and dates a written ICF and any required privacy authorization before the initiation of any study procedures.
3. The subject has participated in and completed the ADMIRE-CD II study (ie, did not discontinue).

Main Criteria for Exclusion:

Subjects will not be eligible for inclusion in the study if:

1. It has been more than 3 months since the subject completed the ADMIRE-CD II study.
2. Subjects are currently receiving, have received any investigational drug in the last 3 months before the inclusion in the study, or are planning to receive any investigational drug during the duration of this LTE study, except for prior participation in the ADMIRE-CD II study.

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

- AEs.
- SAEs.
- Specific AESIs:
  - Immunogenicity/alloimmune reactions.
  - Tumorgenicity.
  - Ectopic tissue formation.

Secondary Endpoints:

- Proportion of subjects who achieve clinical remission at Week 104 and Week 156 after IMP administration.
  - Clinical remission is defined as closure of all treated external fistula openings that were draining at baseline of ADMIRE-CD II despite gentle finger compression.
- Proportion of subjects who achieve clinical response at Week 104 and Week 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 of ADMIRE-CD II despite gentle finger compression.
- Proportion of subjects with a relapse where a relapse is defined as patients who were in combined remission at Week 52 of ADMIRE-CD II, and who have either:
  - Reopening of any of the treated fistula(s) external openings with active drainage as clinically assessed, or
  - The development of a perianal fluid collection >2 cm of the treated perianal fistulas confirmed by centrally read MRI assessment.
- Proportion of subjects who achieve combined remission at Week 156 after IMP administration.
  - Combined remission of complex perianal fistula(s), defined as the clinical assessment of closure of all treated external openings that were draining at baseline of ADMIRE-CD II, 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 blinded MRI assessment.
- Proportion of subjects with new anal abscess in treated fistula at Week 156.
- Change from baseline of ADMIRE-CD II to Week 104 and Week 156 in scores of discharge and pain items of Perianal Disease Activity Index (PDAI) score.

Exploratory Endpoints:

[redacted]

Statistical Considerations:

Demographic and baseline characteristics will be summarized by treatment group and overall based on all enrolled subjects. 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.

Safety analysis will be performed on the safety analysis set. All safety data will be summarized by treatment group. Count and percentage of subjects with AEs, SAEs (defined as any SAE, regardless of relationship to study drug), and AESIs (immunogenicity/alloimmune reactions, tumorgenicity, and ectopic tissue formation) will be summarized descriptively by System Organ Class and Preferred Term using Medical Dictionary for Regulatory Activities (MedDRA) terminology. SAEs will also be summarized by severity and by relationship to study drug. Change from baseline in vital signs will be summarized by treatment groups.

All efficacy endpoints will be summarized by visit and treatment group, as applicable. The proportions along with their 95% 2-sided CIs will be provided by visit and treatment group for the following proportion-based efficacy endpoints: clinical remission, clinical response, combined remission, relapse, new anal abscess in treated fistula.

The following continuous endpoints will be summarized descriptively by visit and treatment group: change from baseline of ADMIRE-CD II in PDAI subscore (discharge and pain), [redacted].

[redacted]. The association between donor specific antibody levels and key safety and efficacy variables will be explored.

Unless otherwise specified, the ADMIRE-CD II baseline visit will be considered as the baseline visit for efficacy analyses.

IA and reports will be done after ADMIRE-CD II is unblinded to support the long-term benefit-risk profile of darvadstrocel. The data cutoff date for the IA will be the date of the last ADMIRE-CD II subject's Week 52 visit. The IA will include safety analyses and selected efficacy analyses (such as clinical remission and clinical response, etc.) based on available data. The analysis details will be delineated in the statistical analysis plan (SAP).

Full details of the statistical analysis, including missing data imputation and the rescue medication and procedures that affect patient evaluability, will be provided in the SAP.

Sample Size Justification:

Eligible subjects from the ADMIRE-CD II study will be given the opportunity to participate in this long-term safety follow-up study.

Approximately 150 subjects are expected to enroll into this study from the ADMIRE-CD II study.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities except for those identified in the Clinical Study Sponsor Supplier list. The identified vendors in the list for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 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 study medication, 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.

3.3 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CD	Crohn's disease
eCRF	electronic case report form
CRO	contract research organization
Cx601	darvadstrocel
DSA	donor specific antibody
ECG	electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IBD	inflammatory bowel disease
IA	interim analysis
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
LFT	liver function test
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PDAI	Perianal Disease Activity Index
PTE	pretreatment event
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

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. The current hypothesis is that 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 (Panes et al. 2016).

4.2 Rationale for the Proposed Study

This study is an extension of the ongoing phase 3 randomized, double-blind, parallel-group, controlled, global, multicenter study to evaluate the efficacy and safety of darvadstrocel in subjects with CD and complex perianal fistula(s) over a period of 52 weeks (Cx601-0303 ADMIRE-CD II). This long-term extension (LTE) study is being undertaken as a postauthorization measure for the European Medicines Agency (EMA) to evaluate the long-term safety and efficacy of darvadstrocel.

There are limited long-term follow-up data currently available following darvadstrocel injection. The longest follow-up conducted to date was up to 104 weeks following darvadstrocel injection in the Cx601-0302 study. The results of this follow-up study showed consistency with the adverse events (AEs) previously reported up to the Week 52 visit and did not suggest any safety concerns; however, since these data were limited to a small sample of subjects, a larger sample size is required to evaluate long-term efficacy up to 156 weeks after treatment with darvadstrocel.

4.3 Benefit/Risk Profile

In studies conducted to date, darvadstrocel appeared to be, overall, well tolerated at a dose of up to 120 million cells per administration. No dose-dependent safety concern or toxicity has been identified to date. No safety concerns have been identified from the small amount of postmarketing exposure data. Overall, the data available to date presents a positive benefit-risk profile for darvadstrocel.

No additional risks associated with administration of darvadstrocel are anticipated in this LTE study as no investigational medicinal product (IMP) is to be administered during the study.

The safety profile of darvadstrocel has been evaluated in clinical studies until Week 104 and was not significantly different compared with Week 52; however, unknown or not previously reported effects could occur during the course of the study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 Secondary Objective

To evaluate the long-term efficacy of a single dose of darvadstrocel for the treatment of complex perianal fistula(s) in subjects with CD.

5.1.3 Exploratory Objective

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

- AEs.
- SAEs.
- Specific AESIs:
  - Immunogenicity/alloimmune reactions.
  - Tumorgenicity.
  - Ectopic tissue formation.

5.2.2 Secondary Endpoints

- Proportion of subjects who achieve clinical remission at Week 104 and Week 156 after IMP administration.
  - Clinical remission is defined as closure of all treated external fistula openings that were draining at baseline of ADMIRE-CD II despite gentle finger compression.

- Proportion of subjects who achieve clinical response at Week 104 and Week 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 of ADMIRE-CD II despite gentle finger compression.
- Proportion of subjects with a relapse where a relapse is defined as patients who were in combined remission at Week 52 of ADMIRE-CD II, and who have either:
  - Reopening of any of the treated fistula(s) external openings with active drainage as clinically assessed, or
  - The development of a perianal fluid collection >2 cm of the treated perianal fistulas confirmed by centrally read magnetic resonance imaging (MRI) assessment.
- Proportion of subjects who achieve combined remission at Week 156 after IMP administration.
  - Combined remission of complex perianal fistula(s), defined as the clinical assessment of closure of all treated external openings that were draining at baseline of ADMIRE-CD II, 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 blinded MRI assessment.
- Proportion of subjects with new anal abscess in treated fistula at Week 156.
- Change from baseline of ADMIRE-CD II to Week 104 and Week 156 in scores of discharge and pain items of Perianal Disease Activity Index (PDAI) score.

5.2.3 Exploratory Endpoints

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This LTE study is a follow-up of a phase 3 study to evaluate the long-term safety and efficacy of darvadstrocel (Cx601) in the treatment of complex perianal fistula in CD. To be eligible for the LTE study, subjects will have completed the final Week 52 assessment in the Cx601-0303 ADMIRE-CD II study (hereafter referred to as ADMIRE-CD II). Informed consent will be obtained at the Week 52 visit of the ADMIRE-CD II study or up to 4 weeks after the Week 52 visit.

For those subjects who have more than a 4-week gap between the Week 52 visit of the ADMIRE-CD II study and signing of the informed consent form (ICF) for the LTE study, a re-baseline visit will be scheduled; the re-baseline visit will include the same procedures included at the baseline visit with the addition of interval inflammatory bowel disease (IBD) history and medical interventions since the Week 52 visit. MRI assessment will not be included at the re-baseline visit. The re-baseline visit cannot be performed any later than 3 months after the Week 52 visit. An MRI will be performed in all subjects at the Week 156 visit.

Study visits will take place annually for up to 2 years from enrollment into the LTE of ADMIRE-CD II or 3 years following treatment in ADMIRE-CD II. At these visits, clinical assessment of the fistula will be considered for clinical remission. Additional telephone call visits will be conducted every 3 months for safety follow-up. In addition, unscheduled visits may be performed for safety follow-up, and for subjects experiencing any clinically significant symptoms of perianal disease, an MRI will be performed.

The LTE study will be blinded until unblinding of the ADMIRE-CD II study after final database lock, when all subjects have completed their participation at Week 52. After unblinding of the ADMIRE-CD II study, the LTE study will be conducted as an open-label study. Subjects will remain in the treatment group assigned in the ADMIRE-CD II study.

Enrollment into the LTE study will not prevent subjects with ongoing fistulizing disease or luminal CD from receiving any additional treatment (including any medical or surgical treatment) prescribed by his/her physician for the treatment of CD and/or perianal disease. Subjects who receive surgical and/or biologic treatment for the perianal fistulizing disease will be considered treatment failures, but should continue in the study. Treatment failure is documented for a subject if they require rescue medication(s) or procedure(s), defined as switch to or addition of any new monoclonal antibody not ongoing at baseline, increase in dose or frequency of any prior ongoing monoclonal antibody in the LTE study, subjects starting any investigational drug(s) for CD or any other local investigational treatment(s) in the perianal region while participating in the LTE study or any new surgical procedure required in the perianal region for the fistula(s) or draining of collections or established abscess(es) or any ostomy required due to fistula(s).

Those subjects who are prescribed darvadstrocel will be withdrawn from the LTE study and complete an early termination visit because the study will assess the long-term follow-up of IMP administration in the ADMIRE-CD II study.

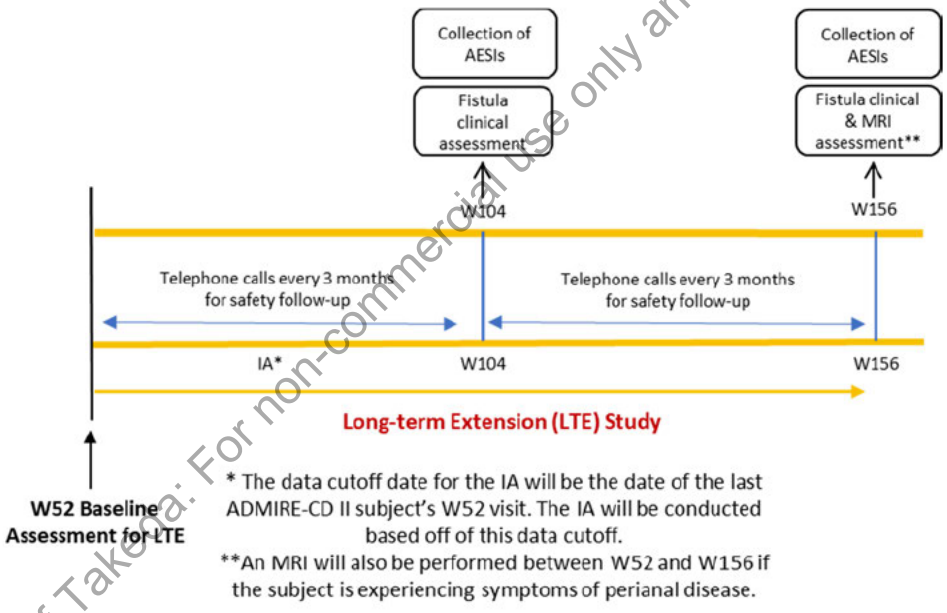
ADMIRE-CD II is an ongoing phase 3, randomized, double-blind, parallel-group, placebo controlled, international, multicenter study to assess the efficacy and safety of darvadstrocel, adult allogeneic expanded adipose-derived stem cells, for the treatment of complex perianal fistula(s) in subjects with CD over a period of 52 weeks. The primary efficacy analysis is to be conducted at Week 24. Thereafter, the double-blind design will be maintained up to Week 52 to allow for evaluation of longer term (Week 52) efficacy and safety. The study follows an add-on design, with subjects receiving any ongoing concomitant medical treatment for CD at stable doses at the time of screening and allowed to continue with it throughout the study. Study subjects are allocated to treatment, in a 1:1 ratio. A curettage and a seton placement will take

place at randomization into ADMIRE-CD II. The study population consists of subjects whose perianal fistulas were previously treated and have shown an inadequate response, a loss of response, intolerance or contraindication to immunosuppressives or monoclonal antibodies, and subjects with complex perianal fistula(s) draining at the screening visit despite previous standard medical treatment, with up to 2 internal openings and a maximum of 3 external openings. In the treatment administration visit, the seton is withdrawn, and a vigorous curettage of all fistula tracts and a suture of internal openings is performed in all subjects. After this, all subjects in the active treatment arm will receive a single dose of darvadstrocel while subjects in the control arm receive saline solution (to mask the treatment).

The LTE study will evaluate the long-term safety of darvadstrocel including AEs, SAEs, and AESIs: immunogenicity/alloimmune reactions, tumorgenicity, and ectopic tissue formation. The study will also evaluate the long-term effect of darvadstrocel treatment on fistula remission, [redacted].

A schedule of assessments is listed in Appendix A. A study schematic is presented in Figure 6.a.

Figure 6.a Study Schematic



AESI: adverse events of special interest; IA: interim analysis; LTE: long-term extension; MRI: magnetic resonance imaging; W: week.

6.2 Justification for Study Design and Endpoints

This LTE study is being conducted to evaluate the long-term safety and efficacy of darvadstrocel in the treatment of complex perianal fistula in CD.

There are limited long-term follow-up data currently available following darvadstrocel injection. The longest follow-up conducted to date was up to 104 weeks following darvadstrocel injection

in the Cx601-0302 study. The results of this follow-up study showed consistency with AEs previously reported up to the Week 52 visit and did not suggest any safety concerns; however, since these data were limited to a small sample of subjects, a larger sample size is required to evaluate long-term efficacy up to 156 weeks following treatment with darvadstrocel. The availability of a control arm for 2 years during this LTE study will help to identify which AEs and other occurrences are due to darvadstrocel, other treatment, or disease progression, which contributes to the scientific rigor of the study.

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

6.3 End of Study/Study Completion Definition

The end of the study is defined as the last scheduled procedure for the last participant in the study.

6.4 Premature Termination or Suspension of Study or Study Site

6.4.1 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 profile is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.4.2 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.

6.4.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

If the sponsor, an institutional review board (IRB)/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 or, when applicable, the subject's legally acceptable representative signs and dates a written ICF and any required privacy authorization before the initiation of any study procedures.
3. The subject has participated in and completed the ADMIRE-CD II study (ie, did not discontinue).

7.2 Exclusion Criteria

Subjects will not be eligible for inclusion in the study if:

1. It has been more than 3 months since the subject completed the ADMIRE-CD II study.
2. Subjects are currently receiving, have received any investigational drug in the last 3 months before the inclusion in the study, or are planning to receive any investigational drug during the duration of this LTE study, except for prior participation in the ADMIRE-CD II study.

7.3 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 who discontinues from the study will not be replaced. Follow-up of AEs will be conducted according to GCP/Clinical Trial Directives.

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

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

There will be no IMP administration in this LTE study. This study will be blinded until unblinding of the ADMIRE-CD II study after final database lock, when all subjects have completed their participation at Week 52.

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. 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 entering into the study, and before any protocol-directed procedures are performed.

The subject number will be maintained from the ADMIRE-CD II study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information and medical history will be obtained from the Week 52 visit of the ADMIRE-CD II study and this data will be used as the baseline of the LTE study.

Medical history will include history of fistulizing CD and assessment of severity and history of cancer including anal canal and colorectal malignancy. A targeted questionnaire will be used to collect detailed information on all malignancies. Medical history will also include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of the ICF. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.9).

Medication history information includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 52 weeks before signing of the ICF.

9.1.3 Physical Examination Procedure

A physical examination will be performed at the Week 52 visit of the ADMIRE-CD II study and this data will be used as the baseline of the LTE study.

9.1.4 Weight and Height

Weight will be obtained from the Week 52 visit of the ADMIRE-CD II study and this data will be used as the baseline of the LTE study. Height will be obtained from the screening visit of the ADMIRE-CD II study.

9.1.5 Vital Sign Procedure

Vital signs (including temperature, heart rate, and blood pressure) will be obtained from the Week 52 visit of the ADMIRE-CD II study and this data will be used as the baseline of the LTE study.

9.1.6 Primary Safety Measurement

The long-term safety of a single dose of darvadstrocel will be assessed in subjects with CD with complex perianal fistula, including assessment of SAEs, and AESIs (immunogenicity/alloimmune reactions, tumorgenicity, and ectopic tissue formation).

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. 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.

For the purpose of this study, drainage of the treated fistula and abscesses, will not be captured as AEs unless there is evidence suggesting a causal relationship between the IMP or meet the seriousness criteria. SAEs will be reported by the sponsor according to International Conference on Harmonisation (ICH) guidelines.

9.1.7.2 Fistula MRI Assessment

A central reading MRI will be performed at Week 156 following IMP administration. In addition, a pelvic MRI will be conducted at an unscheduled visit for those subjects who experience clinically significant symptoms of perianal disease, as assessed by the investigator.

All MRI scans will be assessed centrally by the designated MRI central laboratory in a blinded approach including treatment and period. Blinded central MRI results will include number of fistulas, location, type, collection in 3 dimensions, if any, with fistula location. Analysis will include assessment of collections >2 cm, in 3 axes and directly related to the fistula tracts treated, and any new tracts that might appear.

Before the MRI procedure, it would be necessary to confirm that there are no contraindications for performing it (eg, hypersensitivity to gadolinium, pacemarker, hip replacement, serum creatinine levels >1.5 times upper limit of normal or pregnancy).

9.1.7.3 PDAI

The PDAI is a scoring system to evaluate the severity of perianal CD (Best et al. 1976; Losco et al. 2009). From the 5-item instrument, discharge and pain will be used. 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.

9.1.7.4 Immunologic Tests

A blood sample will be taken for cell responses and immunologic tests:

- Presence/absence of antidonor antibodies if positive at completion of ADMIRE-CD II study.
- Cell responses: phenotypical and functional characterization of peripheral blood mononuclear cells.

9.1.7.5 [redacted]

[redacted]

9.1.8 Documentation of Concomitant Medications/Procedures

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, and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. In addition, any concomitant procedure conducted by the physician will be collected in the same way.

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 or physical examination abnormalities noted at screening/baseline 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. The maximum volume of blood at any single visit is approximately 40 mL, and the approximate total volume of blood for the study is 80 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Blood samples for donor specific antibody (DSA) levels and exploratory immunogenicity testing will be collected at Week 104 and Week 156 (baseline DSA status will be available from Week 52 visit of the ADMIRE-CD II study).

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

Baseline central laboratory data will be obtained from the Week 52 visit of the ADMIRE-CD II study.

9.1.11 Contraception and Pregnancy Avoidance Procedure

Not applicable.

9.1.12 Pregnancy

If a pregnancy occurs during the study, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1.

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.

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.

9.1.13 Documentation of Study Entrance

Only subjects who have attended the final Week 52 visit of the ADMIRE-CD II study and sign the ICF to participate in this LTE study will be eligible.

Subjects who have completed their participation in ADMIRE-CD II, can still be invited to enter the LTE study. In these subjects, a re-baseline visit will be conducted if there is a gap longer than 4 weeks from the ADMIRE-CD II Week 52 visit and the signing of the ICF for the LTE. The re-baseline visit cannot occur more than 3 months after the ADMIRE-CD II Week 52 visit. Collection of data at the re-baseline visit will be similar to data collected at the baseline visit with the exception of blood samples and MRI assessment.

If the subject is found to be not eligible for this LTE study, or the subject does not wish to participate, the investigator should record the primary reason on the applicable eCRF.

Subjects who are pregnant will be allowed to enter the study; however, an MRI must not be performed on those subjects.

9.2 Monitoring Subject Treatment Compliance

There will be no IMP administration during this study.

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 (Week 52 After Darvadstrocel Treatment)

Where possible, the final visit at Week 52 of the ADMIRE-CD II study will be the baseline visit for this LTE study. Informed consent will be obtained at the Week 52 study visit of the ADMIRE-CD II study or up to 4 weeks after the Week 52 visit. For subjects who do not wish to participate, the reason will be collected in a screening log at the site.

For those subjects who have more than a 4 week gap between the ADMIRE-CD II Week 52 visit and signing of the ICF for the LTE study, a re-baseline visit will be scheduled. The re-baseline

visit will include the same procedures included at the baseline visit with the addition of interval IBD history and medical interventions since the Week 52 visit. The immunologic tests and MRI will not be included at re-baseline visit. Re-baseline visit cannot occur more than 3 months after the ADMIRE-CD II Week 52 visit.

Baseline data from Week 52 include:

- Informed consent: a written informed consent will be obtained from the subject before any study procedure is performed.
- Demographics and medical history, including history of CD and smoking history.
- Physical examination covering all body systems, including weight and height.
- Vital signs, including systolic and diastolic blood pressure (mm Hg), heart rate (beats/min), and body temperature (°C)
- Concomitant medications and procedures.
- Clinical evaluation of fistula.
- MRI assessment of fistula (central reading).
- PDAI [redacted].
- Immunologic tests and T-cell responses.
- AE/SAE assessment.
- [redacted]
- Telephone calls will be made every 3 months for safety follow-up from baseline/re-baseline until the next visit.

The procedure for documenting screening failures is provided in Section 9.1.13.

9.3.2 Follow-up Period (Visit 1/Week 104 After Darvadstrocel Treatment)

The following procedures will be performed at Visit 1, LTE Week 52/Week 104 after darvadstrocel treatment:

- Physical examination covering all body systems, including weight.
- Vital signs, including systolic and diastolic blood pressure (mm Hg), heart rate (beats/min), and body temperature (°C).
- Concomitant medications and procedures since last visit.
- Clinical evaluation of fistula.
- PDAI score.
- Interval IBD history and medical interventions since last visit.

- Immunologic tests and T-cell responses.
- AE/SAE assessment.
- [redacted]
- Telephone calls will be made for safety follow-up every 3 months from Visit 1 to the next visit.

9.3.3 Final Visit (Visit 2/Week 156 After Darvadstrocel Treatment)

The final visit will be performed on Visit 2, LTE Week 104/Week 156 after darvadstrocel treatment or at the early termination visit. The following procedures will be performed and documented:

- Physical examination covering all body systems, including weight.
- Vital signs, including systolic and diastolic blood pressure (mm Hg), heart rate (beats/min), and body temperature (°C)
- Concomitant medications and procedures since last visit.
- Clinical evaluation of fistula.
- MRI assessment of fistula (central reading).
- PDAI score.
- Interval IBD history and medical interventions since last visit.
- Immunologic tests and T-cell responses.
- AE/SAE assessment.
- [redacted]

9.3.4 Unscheduled Visit/Early Termination Visit

The unscheduled visit will be conducted for safety follow-up if required, and for subjects experiencing clinically significant symptoms of perianal disease, as assessed by the investigator. The following procedures will be performed and documented for safety follow-up:

- Physical examination covering all body systems, including weight.
- Vital signs, including systolic and diastolic blood pressure (mm Hg), heart rate (beats/min), and body temperature (°C).
- Concomitant medications and procedures since last visit.
- Clinical evaluation of fistula.
- MRI assessment of fistula only if the subject is experiencing symptoms of perianal disease.
- PDAI score.

- Interval IBD history and medical interventions since last visit.
- Immunologic tests and T-cell responses.
- AE/SAE assessment.
- [redacted]

9.3.5 Telephone Visit

A telephone call for safety follow-up will be made to the subject every 3 months between Week 52 and Week 156.

10.0 TREATMENT-EMERGENT ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreament Events

Pretreament events (PTEs) will not be reported in this LTE study.

10.1.2 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 a drug whether or not it is considered related to the drug.

For the purpose of this study, drainage of the treated fistula and abscesses defining the efficacy endpoint, will not be captured as AEs unless there is evidence suggesting a causal relationship between the IMP or meet the seriousness criteria.

10.1.3 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered pretreatment events or AEs).
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Be considered unfavorable by the investigator for any reason.

AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or electrocardiogram [ECG] findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG retest and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

10.1.4 SAEs

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.
    - Transmission of infectious agents.

- Includes any event or synonym described in the Takeda Medically Significant AE List (Appendix E).

10.1.5 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 would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

Refer to Section 10.2.1.1 for a list of known AESIs.

10.1.6 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs and SAEs

The relationship of each AE/SAE to study procedures will be assessed using the following categories:

Related:	An AE 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 can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.8 Relationship to Study Procedures

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

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, including treatment administration. Otherwise, the relationship should be assessed as not related.

10.1.9 Start Date

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

10.1.10 Stop Date

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

10.1.11 Outcome

- Recovered/resolved: Subject returned to first assessment status with respect to the AE/SAE.
- 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/SAE 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/SAE state remaining "Not recovered/not resolved".
- Resolved with sequelae: The subject recovered from an acute AE/SAE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal: The AE/SAEs that are considered as the cause of death.
- Unknown: The course of the AE/SAE 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 AESIs

If the AESI/abnormality occurs during the study, it should be recorded in the appropriate AESI eCRF page. When an AESI meets the seriousness criteria, it should be reported to the clinical contract research organization (CRO)/ pharmacovigilance department within 24 hours as per the SAE reporting requirements.

AESI/abnormality criteria include:

- Immunogenicity/alloimmune reactions.
- Tumorgenicity reactions.
- Ectopic tissue formation.

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.
- 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.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevated >3 times the upper limit of normal (ULN) on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, a liver function test (LFT) increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms, and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.10 must also be performed. In addition, an LFT increases eCRF must be completed and transmitted with the Takeda SAE form (per Section 10.2.2).

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, 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, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the EMA, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the

countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs 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 IRB or 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/SAEs, 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 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 12.1 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 trail, 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, 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

The statistical analysis plan (SAP) will be prepared and finalized before interim database lock. 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

Safety analysis set: All subjects enrolled in the study, according to the actual treatment they received in the ADMIRE-CD II study.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

The safety analysis set will be the primary analysis set to be used for all statistical analysis of the demographic and baseline characteristics. Demographic and baseline characteristics will be summarized by the treatment group and overall based on all enrolled subjects. 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.

13.1.3 Efficacy Analysis

All efficacy endpoints will be summarized by visit and treatment group, as applicable.

The proportions along with their 95% 2-sided CIs will be provided by visit and treatment group for the following proportion-based efficacy endpoints:

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

The following continuous endpoints will be summarized descriptively by visit and treatment group:

- Change from baseline of ADMIRE-CD II in PDAI subscore (discharge and pain).

[redacted]

Unless otherwise specified, the ADMIRE-CD II baseline visit will be considered the baseline visit for efficacy analyses.

Full details of the statistical analysis, including missing data imputation and the rescue medication and procedures that affect patient evaluability, will be provided in the SAP.

13.1.4 Safety Analysis

Safety analysis will be performed on the safety analysis set.

All safety data will be summarized by treatment groups. Count and percentage of subjects with AEs, SAEs (defined as any SAE, regardless of relationship to study drug), and AESIs (immunogenicity/alloimmune reactions, tumorgenicity, and ectopic tissue formation) will be summarized descriptively by System Organ Class and Preferred Term using MedDRA terminology. SAEs will also be summarized by severity and by relationship to study drug.

Change from baseline in vital signs will be summarized by treatment groups.

Unless otherwise specified, the Week 52 visit from the ADMIRE-CD II study will be considered as the baseline visit for all analyses.

13.1.5 Other Analyses

The association between DSA levels 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

IA and reports will be done after ADMIRE-CD II is unblinded to support the long-term benefit-risk profile of darvadstrocel. The data cutoff date for the IA will be the date of the last ADMIRE-CD II subject's Week 52 visit. The IA will include safety analyses and selected efficacy analyses (such as clinical remission and clinical response, etc.) based on available data. The analysis details will be delineated in the SAP.

13.3 Determination of Sample Size

Eligible subjects from the ADMIRE-CD II study will be given the opportunity to participate in this long-term safety follow-up study.

Approximately 150 subjects are expected to enroll into this study from the ADMIRE-CD II study.

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 IRB/IEC, or regulatory authorities to inspect facilities and original records relevant to this study. The investigator will allocate adequate time to discuss findings and relevant issues and, after the visit, to complete appropriate corrective actions as necessary.

14.1 Study-Site Monitoring Visits

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

The sponsor will employ all efforts to conduct on-site monitoring visits. Per country/site regulations, remote monitoring practices may include remote source data verification and remote source data review. Any remote montoring practices will be documented in the monitoring plan.

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 IRB or 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 IRB 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, 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, 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 subjects (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised 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 B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and 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 IRB or IEC. If any member of the IRB or 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 IRB or 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 IRB or IEC for approval. The IRB's or 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 IRB or 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 will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor 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 IRB or IEC. This may include notification to the IRB or 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 IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and 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 IRB or IEC and sponsor.

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 IRB or 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 both the IRB or 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 IRB or 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 informed consent 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 IRBs and 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 document. 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 Americas investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial 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.

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

Best, W. R., Becktel, J. M., Singleton, J. W. and Kern, F., Jr. 1976. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology,* 70(3), 439-44.

Losco, A., Vigano, C., Conte, D., Cesana, B. M. and Basilisco, G. 2009. Assessing the activity of perianal Crohn's disease: comparison of clinical indices and computer-assisted anal ultrasound. *Inflamm Bowel Dis,* 15(5), 742-9.

Panes, J., Garcia-Olmo, D., Van Assche, G., Colombel, J. F., Reinisch, W., Baumgart, D. C., et al. 2016. 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,* 388(10051), 1281-90.

Appendix A Schedule of Study Procedures

Visit Number	Baseline	Re-Baseline [a]	Follow-up Period up to Week 156		Unscheduled Visit/Early Termination
			1 [b]	2 (Final Visit)	
LTE Week	**0**	**0**	**52**	**104**	
Week after Darvadstrocel Treatment	**52**	**>56 weeks [a]**	**104**	**156**	
Informed consent	X	X			
Inclusion/exclusion criteria	X	X			
Demographics and medical history	X	X			
Physical examination including weight	X	X	X	X	X
Vital signs	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X
Fistula clinical assessment	X	X	X	X	X
Fistula MRI assessment	X [c]			X	X [d]
PDAI score [e]	X	X	X	X	X
Interval IBD history and medical interventions		X	X	X	X
Immunologic tests and T-cell responses [f]	X		X	X	X
AE/SAE assessment [g]	X	X	X	X	X
[redacted]					
Telephone calls [h]	Every 3 months				

AE: adverse event; IBD: inflammatory bowel disease; ICF: informed consent form; LTE: long-term extension; MRI: magnetic resonance imaging; PDAI: Perianal Disease Activity Index; SAE: serious adverse event.

[a] Re-baseline visit will be conducted if there is a gap >4 weeks between ADMIRE-CD II Week 52 visit and signing of ICF for the LTE study. The re-baseline visit must take place within 3 months of the ADMIRE-CD II Week 52 visit.

[b] Visit 1 will be up to 52 weeks after completion of the ADMIRE-CD II study.

[c] Baseline MRI for the LTE study is the examination performed at Week 52 of ADMIRE-CD II study.

[d] Central reading MRI assessment of fistula (performed locally) only if the subject is experiencing symptoms of perianal disease.

[e] Only the PDAI items of discharge and pain will be used.

[f] An extra whole blood sample (40 mL) for T-cell responses, extracellular turnover markers, and immunologic tests (presence/absence of antidonor specific antibodies) will be obtained at each visit.

[g] Collection of AEs and SAEs will begin from the time the subject signs the ICF in this study and will continue through final visit/early termination; however, any new AEs/SAEs reported during Week 52 ADMIRE-II visit should be recorded as AEs in the ADMIRE-II database. Ongoing AEs/SAEs at the completion of the Week 52 ADMIRE-CD II study visit will be kept in the ADMIRE-CD II study database. New events or ongoing AEs/SAEs from ADMIRE-CD II that change severity after completion of the week 52 ADMIRE-CD II visit will need to be recorded as medical history for this LTE study if they occur before the ICF for LTE being signed.

[h] Telephone call visits will be conducted every 3 months throughout the study for safety follow-up.

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 responsibilities:

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 IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/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 IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined 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 IRB/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), IRB/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 IRB/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) IRBs/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 patients, 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. 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.
- IRBs and 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.

Appendix E Additional Information for the Investigator

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
COVID-19-related disease	Neuroleptic malignant syndrome/malignant hyperthermia
COVID-19 pneumonia	Spontaneous abortion/stillbirth and fetal death

AE: adverse event; COVID-19: coronavirus disease 2019; SAE: serious 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.

Appendix F Protocol History

Date	Amendment Number	Amendment Type	Region
17 November 2022	2	Substantial	Global
26 January 2022	1	Substantial	Global
22 March 2019	Initial protocol	-	Global

Rationale for Amendment 1

The primary reason for this amendment was for a legal entity change from Millennium Pharmaceuticals, Inc to Takeda Development Center Americas, Inc.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Title Page Section 2.0 STUDY SUMMARY	Revision of Millennium Pharmaceuticals, Inc to Takeda Development Center Americas, Inc.	Sponsor company name and address was updated.
Section 1.2 Approval	Revision to signatories	Approvers were updated

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Pharmacovigilance Approval	18-Nov-2022 22:15 UTC
[redacted]	Biostatistics Approval	19-Nov-2022 17:22 UTC
[redacted]	Clinical Science Approval	20-Nov-2022 03:11 UTC
[redacted]	Pharmacovigilance Approval	21-Nov-2022 11:33 UTC