**Clinical Study Protocol**

NCT Number: NCT04701411

Title: A Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Darvadstrocel in the Treatment of Complex Perianal Fistula in Pediatric Subjects With Crohn's Disease Over a Period of 24 Weeks and an Extended Follow-up Period for a Total of up to 52 Weeks

Study Number: Darvadstrocel-3004

Document Version and Date: Amendment 3, 22 MAY 2024

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

**TAKEDA PHARMACEUTICALS**

**PROTOCOL**

# A Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Darvadstrocel in the Treatment of Complex Perianal Fistula in Pediatric Subjects with Crohn's Disease over a Period of 24 Weeks and an Extended Follow-up Period for a Total of up to 52 Weeks

## Short Title

Darvadstrocel in the Treatment of Complex Perianal Fistula in Pediatric Crohn's Disease

| | | | |
|---|---|---|---|
| **Sponsor:** | Takeda Development Center Americas, Inc.<br>95 Hayden Avenue<br>Lexington, MA 02421 | | |
| **Study Number:** | Darvadstrocel-3004 | | |
| **IND Number:** | Not applicable | **Abbreviated EU CT Number:** | 2023-503973-39 |
| **Compound:** | Darvadstrocel (Cx601)<br>Human expanded allogeneic mesenchymal adult stem cells extracted from adipose tissue (expanded adipose stem cells) | | |
| **Date:** | 22 May 2024 | **Amendment Number:** | 3 |

**Amendment History:**

| Date | Amendment Number | Amendment Type | Region |
|---|---|---|---|
| 22 May 2024 | Amendment 3 | Substantial | Global |
| 12 February 2024 | Amendment 2 | Nonsubstantial | Global |
| 01 February 2021 | Amendment 1 | Substantial | Global |
| 24 June 2020 | Initial protocol | - | Global |

# 1.0 ADMINISTRATIVE INFORMATION

## 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 | European/Rest of World Contact |
|---|---|
| Serious adverse event,<br>special situation, and pregnancy reporting | SAEs: Report via EDC and paper SAE form (back-up method)<br>Special situation (including pregnancy)<br>Fax: +1-224-554-1052<br>Email: PharmacovigilanceMailbox@Takeda.com<br>(Rest of world)<br>Email: Takeda@e-medinfo.com (Japan-specific) |
| Medical Monitor<br>(medical advice on protocol and study drug) | Medical Director, Clinical Science |
| Responsible Medical Officer<br>(carries overall responsibility for the conduct of the study) | Medical Director, Clinical Science |

## 1.2 Approval

**REPRESENTATIVES OF TAKEDA**

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

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

**SIGNATURES**

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic signatures are provided on the last page of this document.

| | |
|---|---|
| [redacted], MD<br>[redacted] Clinical Science | Date |
| [redacted] MS<br>[redacted], Statistical & Quantitative Sciences | Date |

## 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 also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

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

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix J 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 3 Summary of Changes

### Protocol Amendment 3 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 3. The primary reason for this amendment is to include an interim analysis.

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

| **Protocol Amendment 3** | | | |
|---|---|---|---|
| **Summary of Changes Since the Last Version of the Approved Protocol** | | | |
| **Change Number** | **Sections Affected by Change** | **Description of Each Change and Rationale** | |
| | ***Location*** | ***Description*** | ***Rationale*** |
| 1. | Section 2.0 STUDY SUMMARY<br>Section 13.2 Interim Analysis and Criteria for Early Termination | Added interim analysis for evaluation of safety and efficacy. | Takeda's internal decision to review the safety and efficacy of davardstrocel in enrolled pediatric patients to support future submission to regulatory agencies. |

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## 2.0 STUDY SUMMARY

| **Name of Sponsor:** Takeda Development Center Americas, Inc. | **Compound:** Darvadstrocel | |
|---|---|---|
| **Title of Protocol:** A Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Darvadstrocel in the Treatment of Complex Perianal Fistula in Pediatric Subjects with Crohn's Disease over a Period of 24 Weeks and an Extended Follow-up Period for a Total of up to 52 Weeks. | **IND No.:** Not applicable | **Abbreviated EU CT No.:** 2023-503973-39 |
| **Study Number:** Darvadstrocel-3004 | **Phase:** 3 | |

**Study Design:**

This is a phase 3, open-label, multicenter study to evaluate the efficacy and safety of darvadstrocel (also known as Cx601) in the treatment of complex perianal fistula refractory to therapy in pediatric subjects with Crohn's disease (CD) aged 4 to <18 years.

At least 20 subjects are planned to be enrolled to receive a single dose of darvadstrocel (24 mL cell suspension containing 120 million cells of allogeneic expanded adipose-derived mesenchymal stem cells [eASCs]). The study will permit continuation of previous treatment of luminal CD in an add-on study design (ie, anti-tumor necrosis factor [TNF] therapy, immunosuppressants etc). Subjects receiving any ongoing concomitant medical treatment for CD at stable doses (stable dose is considered either the same dose or same weight-based dose adjusted for weight) at the time of the screening visit, will be allowed to continue treatment throughout the study.

The study consists of a screening period (within a minimum of 4 and a maximum of 5 weeks before the preparation visit), preparation visit (within a minimum of 2 and a maximum of 3 weeks before treatment), treatment visit (day of study drug administration [Visit 0]), and a follow-up period (for approximately 52 weeks after study drug administration).

After a successful screening period to determine eligibility, subjects will attend a preparation visit before receiving a single dose of darvadstrocel at Visit 0. At each visit, a clinical assessment of the fistula(s) will be performed.

A pelvic magnetic resonance imaging (MRI) scan will be performed locally at the screening visit and at Week 24 to assess fistula characteristics, fistula location, and for the presence or absence of abscesses >2 cm (in at least 2 dimensions). All MRIs will be assessed centrally by the MRI central reader.

A follow-up period of an additional 28 weeks after Week 24 (up to a total of 52 weeks) is incorporated into the study for continued evaluation of safety and efficacy.

Sites will employ all efforts to see subjects as described in the clinical assessments. In unavoidable circumstances, such as the coronavirus disease 2019 pandemic, exceptions may be granted for alternative methods for conducting subject visits with approval by the medical monitor and/or sponsor. Such instances will be documented in the study records. These data collected with alternative methods may be handled differently in the final data analysis, and will be documented in the statistical analysis plan.

**Benefit-Risk Profile:**

Because darvadstrocel has not yet been formally evaluated in pediatric subjects, the final benefit-risk assessment for the treatment of complex perianal fistula in pediatric patients with CD has not been determined.

In clinical studies conducted to date, darvadstrocel has been well tolerated in adult patients with complex perianal fistula(s) and CD up to 120 million cells per administration. In nonclinical studies conducted to date, no dose-dependent safety concern or toxicity, including in juvenile animals, has been identified and no ectopic tumor formation or hypersensitivity concerns have emerged. Overall, the data available present a positive benefit-risk profile for darvadstrocel.

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

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

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

Although a rare condition, as with adults there is a significant unmet medical need for treatment of complex perianal fistulas in the pediatric population with CD. Taking into consideration that there is no pathophysiological difference between perianal fistula in CD in the adult and pediatric populations and that the mechanism of action of darvadstrocel does not have any known age-dependent characteristics, based on the clinical data in adults, combined with nonclinical data, the benefit-risk balance in pediatric subjects is expected to be positive.

**Primary Objective:**

To evaluate the efficacy of darvadstrocel in combined remission at Week 24 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

**Secondary Objectives:**

To evaluate the efficacy of darvadstrocel in clinical remission at Week 24 and Week 52 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

To evaluate the efficacy of darvadstrocel in clinical response at Week 24 and Week 52 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

To evaluate the efficacy of darvadstrocel in time to clinical remission up to Week 52 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

To evaluate the efficacy of darvadstrocel in time to clinical response up to Week 52 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

To evaluate the efficacy of darvadstrocel on relapse by Week 52 in pediatric subjects with combined remission at Week 24.

To evaluate the safety of darvadstrocel for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years over 52 weeks.

**Subject Population:** Pediatric subjects with CD aged 4 to <18 years, with complex perianal fistula(s), whose perianal fistulas were previously treated and have shown an inadequate response (ie, a loss of response, intolerance or contraindication) to at least one of the following treatments: immunosuppressants, or biologics (anti-TNFs, anti-integrin or anti-interleukin [IL] 12/23).

| | |
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| **Number of Subjects:**<br>At least 20 subjects. | **Number of Sites:**<br>Estimated total: Approximately 30 sites in European Union, Israel, and Japan. |
| **Dose Level:**<br>Single administration of 120 million cells of darvadstrocel<br>(24 mL, 5 million cells/mL) | **Route of Administration:**<br>Perilesional injection |
| **Duration of Treatment:**<br>Single dose at Day 0/Visit 0 | **Period of Evaluation:**<br>Screening period (minimum of 4 and maximum of 5 weeks before preparation visit), preparation visit (minimum of 2 and a maximum of 3 weeks before treatment administration), treatment administration visit (1 day), follow-up period (for approximately 52 |

| | |
|---|---|
| | weeks after treatment administration). |

**Main Criteria for Inclusion:**

The list below includes the main criteria for inclusion. Refer to the main body of the protocol for the complete list of inclusion criteria:

- The subject is a male or female aged 4 to <18 years at the time of study treatment administration.
- The subject has a CD diagnosis based on accepted clinical, endoscopic, histological and/or radiologic criteria at least 6 months before the screening visit.
- The subject has complex perianal fistula refractory to at least one of the following treatments: immunosuppressants, or biologics (anti-TNFs, anti-integrin, or anti-IL 12/23). Fistula(s) refractory to therapy are defined in this study as follows:
  - Immunosuppressants: Inadequate response after 3 months, based on clinical assessment, or more treatment with azathioprine, 6 mercaptopurine or methotrexate.
  - Biologics: Inadequate response after 14 weeks (16 weeks for anti-IL 12/23), based on clinical assessment, or more standard treatment for induction and maintenance.
- A complex perianal fistula(s) that meets one or more of the following criteria, modified from the American Gastroenterological Association (AGA) technical review:
  - High intersphincteric, transsphincteric, extrasphincteric, or suprasphincteric as assessed by MRI.
  - Presence of 2 or 3 external openings (tracts) as assessed by clinical examination.
  - Associated fluid (abscess) collections as determined by MRI.

  This study requires that the subject has complex perianal fistulas with a maximum of 2 internal openings and a maximum of 3 external openings, based on clinical assessment. Darvadstrocel treatment is targeted for fistulas that connect between internal and external openings. A central reading of a locally performed pelvic MRI will be performed to confirm the location of the fistula and potential associated perianal abscess(es). Fistulas must have been draining for at least 6 weeks before the screening visit. Subjects with actively draining simple subcutaneous fistulas, at the time of the screening visit are not allowed in this study.
- The subject has inactive or mildly active luminal CD defined by meeting all of the following criteria:
  a) Colonoscopy, flexible sigmoidoscopy or rectoscopy performed either at screening or within the 6 months before screening, demonstrating no rectal ulcers larger than 0.5 cm. A subject who has documented rectal ulcers larger than 0.5 cm within the 6 months before screening but has undergone subsequent treatment may be eligible if there are no rectal ulcers larger than 0.5 cm on a sigmoidoscopy or rectoscopy performed after treatment or at the time of screening.
  b) The improvement of or no worsening in stool frequency, sustained for 1 week or more, in the interval between the colonoscopy, flexible sigmoidoscopy or rectoscopy in inclusion criteria 5(a) and the screening visit.
  c) No initiation or intensification of treatment with corticosteroids, immunosuppressants, or monoclonal antibody dose regimen between the colonoscopy, flexible sigmoidoscopy or rectoscopy in inclusion criteria 5(a) and the screening visit.

**Main Criteria for Exclusion:**

The list below includes the main criteria for exclusion. Refer to the main body of the protocol for the complete list of exclusion criteria:

- The subject has received any investigational compound within 12 weeks/84 days before screening.
- The subject has received darvadstrocel/eASC in a previous clinical study or as a therapeutic agent.
- The subject has a history of hypersensitivity or allergies to darvadstrocel or any of its excipients.
- The subject weighs <10 kg at screening.
- The subject has concomitant perianal fistula(s) with only internal or external opening(s).
- The subject has concomitant internal fistula(s) such as ileo-vesical, rectovaginal or ileo-colonic fistula(s).

- The subject has an abscess >2 cm, unless resolved in the preparation procedure.
- The subject has rectal and/or anal stenosis, and/or active proctitis, which would restrict the surgical procedure.
- The subject underwent surgery for the fistula other than drainage or seton placement.
- The subject has diverting stomas.
- The subject has ongoing systemic corticosteroid treatment or has been treated with systemic corticosteroids within 4 weeks before screening.
- The subject requires new treatment with immunosuppressants/anti-TNF agents during the screening period.
- The subject requires surgery in the perianal region for reasons other than fistulas at the time of screening or foreseen either during the study and/or during the 24 weeks after treatment administration.
- The subject has known allergies or hypersensitivity to antibiotics (including benzylpenicillin/streptomycin, gentamicin [used in the darvadstrocel manufacturing process]) human serum albumin, Dulbecco Modified Eagle's Medium, material of bovine origin, or local anesthetics.

**Main Criteria for Evaluation and Analyses:**

The primary endpoint for this study is the proportion of subjects who achieve combined remission at Week 24, where combined remission is defined as:

a) The closure of all treated external openings that were draining at baseline despite gentle finger compression

AND

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

Secondary endpoints for this study are: proportion of subjects who achieve clinical remission at Weeks 24 and 52, time to clinical remission up to Week 52, proportion of subjects with clinical response at Week 24 and 52, time to clinical response up to Week 52, and proportion of subjects with relapse by Week 52 in subjects with combined remission at Week 24.

The following safety endpoints will be assessed: adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), vital signs, and laboratory parameters (biochemistry, hematology, and urinalysis).

The **exploratory endpoints** are: change from baseline to Week 24 and Week 52 in subscores for discharge and pain domains from the Perianal Disease Activity Index (PDAI) scores, change from baseline to Week 24 and Week 52 in Pediatric Crohn's Disease Activity Index (PCDAI) scores, and change from baseline in perianal pain visual analog scale (VAS).

**Statistical Considerations:**

Analysis Sets:

- Intent-to-treat (ITT) analysis set: Includes all subjects who undergo the fistula preparation procedure regardless of being treated or not.
- [redacted]
- Safety analysis set: Includes all subjects who received the study treatment.

Interim Analysis:

An interim analysis (IA) will be conducted to evaluate the safety and efficacy of davardstrocel in enrolled subjects. The details of the IA will be described in the statistical analysis plan (SAP).

Efficacy Analyses:

Analysis of the primary endpoint will be performed on the ITT [redacted], with the ITT as the primary analysis set. Analysis of the secondary endpoints and the exploratory endpoints will be performed on the ITT

analysis set.

Primary Efficacy Analysis:

For the primary efficacy analysis, the estimates of the combined remission rate at Week 24 will be provided along with the 95% Clopper-Pearson confidence intervals (CI). Counts will be presented along with the proportions for the primary endpoint.

[redacted]

Secondary Endpoint Analysis:

The binary secondary endpoints are: proportion of subjects who achieve clinical remission at Weeks 24 and 52, proportion of subjects with clinical response at Week 24 and 52, and proportion of subjects with relapse by Week 52 in subjects with combined remission at Week 24. [redacted]

The time-to-event secondary endpoints (ie, time to clinical remission up to Week 52, and time to clinical response up to Week 52). will be analyzed [redacted] Subjects without documented event of interest by the end of study (Week 52), will be censored at the date of last assessment. [redacted]

Exploratory Endpoint Analysis:

The continuous endpoints of change from baseline at each time point (Week 24, Week 52) in PDAI, PCDAI and in VAS will be summarized using descriptive statistics at each time point.

[redacted]

Safety Analysis:

Counts and percentages for subjects with treatment emergent AEs, SAEs (defined as any SAE, regardless of relationship to study drug), and AESIs (immunogenicity/alloimmune reactions, hypersensitivity, ectopic tissue formation, medication errors, tumorigenicity, and transmission of infectious agents) will be summarized descriptively by System Organ Class and Preferred Term using Medical Dictionary for Regulatory Activities terminology. [redacted] Change from baseline in vital signs will also be summarized.

The final analysis will be performed after the data base lock when all subjects have completed the Week 52 visit.

Further details on all of the above analyses will be provided in the statistical analysis plan.

[redacted]

# 3.0 STUDY REFERENCE INFORMATION

## 3.1 Study-Related Responsibilities

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

## 3.2 Principal Investigator/Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, 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 |
| BMI | body mass index |
| CTR | Clinical Trials Regulations |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| CD | Crohn's disease |
| COVID-19 | coronavirus disease 2019 |
| DSMB | data and safety monitoring board |
| eASC | expanded adipose-derived mesenchymal stem cells |
| EMA | European Medicines Agency |
| ESR | erythrocyte sedimentation rate |
| EU | European Union |
| FCA | fistula clinical assessment |
| GCP | Good Clinical Practice |
| hCG | human chorionic gonadotropin |
| IA | interim analysis |
| ICH | International Conference for Harmonisation |
| IEC | independent ethics committee |
| IL | interleukin |
| IRB | institutional review board |
| ITT | intent-to-treat |
| [redacted] | [redacted] |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| PCDAI | Pediatric Crohn's Disease Activity Index |
| PDAI | Perianal Disease Activity Index |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SSR | special situation report |
| TNF | tumor necrosis factor |
| ULN | upper limit of normal |
| VAS | visual analog scale |
| WOCBP | women of childbearing potential |

# 4.0 INTRODUCTION

## 4.1 Disease Background

A perianal fistula is an abnormal connection or passageway that develops between the rectum, ie, the end of the large intestine that stores feces, and the skin. The presence of a fistula results in abnormal discharge of feces through a skin opening other than the anus. Perianal fistula, sometimes called a fistula-in-ano, may be due to noninflammatory causes such as congenital abnormalities of the anal crypts and glands or be acquired following trauma, surgery, malignancy, or radiation therapy. Perianal fistula may also be the result of a chronic, inflamed condition such as a manifestation of perianal Crohn's disease (CD) or an infection in the anal glands (cryptoglandular fistulas).

The incidence of CD in children is increasing worldwide, with an estimate of 2.5 to 11.3 per 100,000 (Ruemmele et al. 2014); similarly, the incidence rate quantiles of pediatric CD in European countries were estimated to be 1.2 to 13.9 per 100,000 (Benchimol et al. 2011). Perianal fistulas are a common feature in patients with CD. The cumulative incidence of perianal fistula in patients with CD is estimated to range from 23% to 38% in population-based studies (Marzo et al. 2015). The risk of perianal fistula correlates with the duration after diagnosis of CD, with an estimated risk of 15% at 5 years, 22% at 10 years, and 26% at 20 years (Schwartz et al. 2002; Tozer et al. 2011; Zhao et al. 2019). With limited pediatric data, the incidence of perianal fistula in pediatric patients with CD has been estimated to be between 13.6% to 62% (Keljo et al. 2009). In contrast to adult patients, childhood CD is associated with more aggressive perianal fistula development with fistula occurrence in 20% to 31% of children within 5 to 7 years after diagnosis of CD (Adler et al. 2017; Kugathasan et al. 2003; Vernier-Massouille et al. 2008). In one large cohort of pediatric CD, the age of diagnosis for perianal fistulas occurred mainly after 12 years (Herman et al. 2017). Based on a national population-based study, there are estimated to be more than 10,000 children with perianal fistula due to CD in the United States (Kappelman et al. 2013), however, there is no population-based study estimating the burden of pediatric fistulizing CD in Europe.

Based on the Parks classification (Parks et al. 1976), perianal fistulas can also be classified into 2 main categories; simple and complex:

- Simple perianal fistulas are anatomically low (superficial, low intersphincteric or low transsphincteric), have a single external opening, and are not associated with perianal abscess, connection to the vagina or bladder, or anal stenosis.
- A complex perianal fistula is anatomically high (high intersphincteric or high transsphincteric or extrasphincteric or suprasphincteric origin of the fistula tract), may have multiple external openings, may be associated with the presence of pain or fluctuation to suggest a perianal abscess, may be associated with the presence of a rectovaginal fistula, may be associated with the presence of an anorectal stricture, and may be associated with the presence of active rectal disease at endoscopy.

This classification has greater clinical relevance: simple perianal fistulas respond better to treatment whereas complex ones have lower cure rates with medical treatment and an aggressive surgical procedure will often lead to incontinence.

Perianal fistulas in CD are highly complex to treat and usually take a multidisciplinary approach, combining pharmacological treatment of the disease with surgery of the fistula to achieve fistula healing. The aim of therapy is to alleviate symptoms and treat complications of the disease in order to improve the patients' quality of life. Aggressive treatments such as immunomodulators and biologics have aimed to modify the natural course of CD (Lichtenstein et al. 2009). Current treatment options mostly focus on surgical closure of the fistula, while maintaining continence and resolving the acute ongoing inflammatory process. As pediatric perianal fistulas of any origin are rare, treatment for pediatric patients with CD and fistulizing CD usually follows the same course as in adult patients (Forsdick et al. 2019).

Current standard of care for patients with complex perianal fistula consists of pharmacologic management with antibiotics (metronidazole or ciprofloxacin) as a first step alongside biologic anti-tumor necrosis factor (TNF) agents such as infliximab, although the efficacy of antibiotics alone has been doubted due to lack of firm evidence (Crandall et al. 2009; de Zoeten et al. 2013). Glucocorticoids have potent anti-inflammatory activity and are often used in the management of CD, but have no demonstrated efficacy in treating fistulas (Nielsen et al. 2009). 5-aminosalicylate have no conclusive benefits to treatment of CD or fistulizing CD (Farrell and Peppercorn 2013; Nielsen et al. 2009).

Immunosuppressants such as azathioprine, are commonly used as second line therapy, but again there are no randomized clinical studies assessing the efficacy of this treatment on perianal fistula in subjects with CD. Data on efficacy has been derived from post-hoc analyses of randomized clinical studies in which immunosuppressants were used for treatment of active luminal disease. A meta-analysis of results with immunosuppressants showed efficacy in terms of achieving response (closure or reduction in drainage), but no data assessing the recommended end point of remission of fistulizing disease could be analyzed (Pearson et al. 1995).

Several anti-TNF monoclonal antibody treatments have been approved to treat patients with CD. To date, only the monoclonal antibody infliximab has demonstrated efficacy for the treatment of perianal fistula in patients with CD in an randomized clinical study (Sands et al. 2004). The study showed that 69% of patients responded at week 14 and of these 36% were in remission at week 54 (25% of the overall randomized population), making this therapy the most effective medical treatment in complex perianal fistulas. However, despite these results, a large number of patients continue to suffer from disease activity and high relapsing rates (Roumeguere et al. 2011), whereas only a small percentage of them have complete fistula healing (Alessandroni et al. 2011; Bourikas and Koutroubakis 2010). A major disadvantage of anti-TNF therapies is the risk for a variety of major adverse events (AEs) such as serious infections, serious infusion reactions, hepatitis B virus reactivation, and congestive heart failure. In addition, neutralizing antibodies to the monoclonal antibodies can develop and limit or eliminate effectiveness for long-term use. To minimize the development of antibody formation, other immunomodulators like azathioprine, mercaptopurine, cyclosporine or methotrexate, and corticosteroids are

frequently used concomitantly with anti-TNF therapy and adds to the patient's risk of experiencing a serious adverse event (SAE).

Surgical treatment of complex perianal disease aims to control sepsis through abscess drainage and intervention in the fistulous tracts, including placement of noncutting setons (van der Hagen et al. 2005). Fistulectomy or fistulotomy are now rarely indicated in complex perianal fistulas in view of the high rate of incontinence associated with the procedure. In severe cases with high fistulas, endorectal flaps are useful. In patients with severe refractory disease, diverting colostomy or ileostomy or even proctectomy might be necessary. Other procedures such as those involving fibrin glues have been shown to be useful, but only in small uncontrolled series

In conclusion, although a rare condition, there is a serious unmet medical need for the treatment of complex perianal fistulas that can reduce the requirement for debilitating surgery that can require a stoma or result in full or partial incontinence in both the adult and pediatric population.

## 4.2 Rationale for the Proposed Study

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

Treatment of pediatric fistulizing CD usually follows the same course as in adult patients. There are no known or reported differences in the pathophysiology of perianal fistulas in patients with CD between the pediatric and adult populations that may affect the efficacy or safety of darvadstrocel or the development of the product in the pediatric population (Abcarian 2011; Hadzhiev and Murdjeva 2010; Sandborn et al. 2003). The major difference between the 2 populations is both the lower incidence of the underlying disease in pediatric patients and the lower probability of developing a complex perianal fistula.

The ultimate therapeutic goal in perianal CD is a complete and sustained closure of the fistulas without development of abscesses and thereby avoiding the need for surgical interventions and improving the patients' quality of life. In a high number of patients, complete closure cannot be achieved despite medical treatment (including infliximab) and surgery in accordance with clinical practice.

The darvadstrocel clinical development program includes 2 completed studies (a phase 1/2 study [Cx601-0101] and a phase 3 study [Cx601-0302]). The available evidence based on the efficacy and safety data from these clinical studies suggest that darvadstrocel was well-tolerated and effective in closing the fistula, an effect that was sustained up to Week 52 in subjects with complex perianal fistula refractory to at least one of existing treatments (ie, antibiotics, immunosuppressants, or TNF antagonists).

The safety of darvadstrocel was initially investigated in a phase 1/2 study (Cx601-0101) where subjects received a single perilesional administration of darvadstrocel (20 million cells) and were

followed-up for 24 weeks. Subjects who had incomplete fistula closure at Week 12 following first administration of darvadstrocel were administered a second dose (40 million cells). Twenty-four subjects initially received 20 million cells and 15 (65%) subjects received a second dose of darvadstrocel (repeat dose). Subjects who received a repeat dose showed comparable results in fistula healing compared with subjects who received a single dose. The AE profile following single dose and repeat dose was comparable. The generation of donor-specific antibodies after a second administration of darvadstrocel was assessed. No obvious detrimental effect of donor-specific antibodies on the efficacy and safety of darvadstrocel was observed (de la Portilla et al. 2013).

The efficacy and safety of darvadstrocel was assessed in the pivotal phase 3, randomized, double-blind, placebo-controlled Cx601-0302 study for the treatment of complex perianal fistula(s) in subjects with CD. Darvadstrocel was administered as a single perilesional dose of 120 million cells and it demonstrated efficacy across a range of endpoints. 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 120 million cells of darvadstrocel was well-tolerated in the study population (Panes et al. 2016).

These data were submitted to the European Medicines Agency (EMA) in March 2016 to support Marketing Approval Authorisation to demonstrate that darvadstrocel treatment effectively induces fistula closure, an effect that is maintained for up to 52 weeks, in adult subjects with complex perianal fistulas that have shown an inadequate response to at least one conventional or biologic therapy. Marketing approval was granted by the EMA on 23 March 2018. Marketing Authorisation Applications have also been granted for Switzerland (30 December 2018) and Israel (22 January 2019).

Darvadstrocel is being investigated and developed in the adult population for the treatment of complex perianal fistula in patients with CD in 2 completed studies (a global phase 3 study [Cx601-0303] and a Japan phase 3 study [Darvadstrocel-3002]) intended to support future marketing applications in other regions. A total of 552 subjects had received double-blind treatment in the Cx601-0303 study. Results from the final analysis of Study Cx601-0303 showed that, although darvadstrocel demonstrated a safety profile consistent with that observed in other darvadstrocel studies, Study Cx601-0303 did not achieve statistical significance for its primary and key secondary efficacy endpoints. There were no new safety signals identified in the study. In the completed Study Darvadstrocel-3002, in which 22 Japanese subjects received open-label darvadstrocel treatment, darvadstrocel showed benefits in terms of combined remission at Week 24, and the benefits of darvadstrocel appear to be maintained from Week 24 to Week 156. Safety data up to Week 156 showed that darvadstrocel was well tolerated and no major safety concerns were identified in the 156-week study. The current study (Darvadstrocel-3004) will be the first to investigate the efficacy and safety of darvadstrocel in pediatric subjects with complex perianal fistulas due to CD.

In conclusion, darvadstrocel has been demonstrated to be well-tolerated and efficacious in the treatment of complex perianal fistula in adults and can avoid some of the disadvantages associated with surgery and systemic treatments and may have the potential to address the unmet

medical need of pediatric patients with complex perianal fistulas due to CD. In addition, taking into consideration that there is no pathophysiological difference between perianal fistula in CD in the adult and pediatric population, and that the mechanism of action of darvadstrocel does not have any known age-dependent characteristics, the aim is to extrapolate efficacy data, while collecting safety data in the pediatric population.

### 4.3 Benefit-Risk Profile

Because darvadstrocel has not yet been formally evaluated in pediatric subjects, the final benefit-risk assessment for the treatment of complex perianal fistula in pediatric patients with CD has not been determined.

In clinical studies conducted to date, darvadstrocel has been well tolerated in adult patients with complex perianal fistula(s) and CD up to 120 million cells per administration. In nonclinical studies conducted to date, no dose-dependent safety concern or toxicity, including in juvenile animals, has been identified and no ectopic tumor formation or hypersensitivity concerns have emerged. Overall, the data available present a positive benefit-risk profile for darvadstrocel.

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

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

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

Although a rare condition, as with adults there is a significant unmet medical need for treatment of complex perianal fistulas in the pediatric population with CD. Taking into consideration that there is no pathophysiological difference between perianal fistula in CD in the adult and pediatric populations and that the mechanism of action of darvadstrocel does not have any known age-dependent characteristics, based on the clinical data in adults, combined with nonclinical data, the benefit-risk balance in pediatric subjects is expected to be positive.

# 5.0 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 Objectives

### 5.1.1 Primary Objective

To evaluate the efficacy of darvadstrocel in combined remission at Week 24 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

### 5.1.2 Secondary Objectives

To evaluate the efficacy of darvadstrocel in clinical remission at Week 24 and Week 52 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

To evaluate the efficacy of darvadstrocel in clinical response at Week 24 and Week 52 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

To evaluate the efficacy of darvadstrocel in time to clinical remission up to Week 52 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

To evaluate the efficacy of darvadstrocel in time to clinical response up to Week 52 for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years.

To evaluate the efficacy of darvadstrocel on relapse by Week 52 in pediatric subjects with combined remission at Week 24.

To evaluate the safety of darvadstrocel for the treatment of complex perianal fistula in pediatric subjects with CD aged 4 to <18 years over 52 weeks.

### 5.1.3 Exploratory Objective

To evaluate the impact of darvadstrocel on perianal disease activity.

## 5.2 Endpoints

### 5.2.1 Primary Endpoint

**Efficacy Endpoint**

Proportion of subjects who achieve combined remission at Week 24, where combined remission is defined as:

a) The closure of all treated external openings that were draining at baseline despite gentle finger compression

   AND

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

### 5.2.2 Secondary Endpoints

**Efficacy at Week 24**

1. Proportion of subjects who achieve clinical remission at Week 24, where clinical remission is defined as the closure of all treated external openings that were draining at baseline despite gentle finger compression.
2. Proportion of subjects with clinical response at Week 24, where clinical response is defined as closure of at least 50% of all treated external openings that were draining at baseline despite gentle finger compression.

**Efficacy at Week 52**

1. Proportion of subjects who achieve clinical remission at Week 52, where clinical remission is defined as the closure of all treated external openings that were draining at baseline despite gentle finger compression.
2. Time to clinical remission (weeks) assessed at each clinic visit up to Week 52. This is defined as the time from treatment start to first visit at which clinical remission is observed before Week 52; where clinical remission is said to occur if a clinical assessment shows closure of all treated external openings that were draining at baseline despite gentle finger compression.
3. Proportion of subjects with clinical response at Week 52, where clinical response is defined as closure of at least 50% of all treated external openings that were draining at baseline despite gentle finger compression.
4. Time to clinical response (weeks) assessed at each clinic visit up to Week 52. This is defined as the time from treatment start to first visit at which clinical response is observed before Week 52; where clinical response is said to occur if a clinical assessment shows closure of at least 50% of all treated external openings that were draining at baseline despite gentle finger compression.
5. Proportion of subjects with relapse by Week 52, in subjects with combined remission at Week 24, where relapse is defined as reopening of any of the treated fistula(s) external openings with active drainage as clinically assessed in subjects who were in combined remission at Week 24.

**Safety Endpoints**

1. AEs.
2. SAEs.
3. AEs of special interest (AESIs).
4. Vital signs.
5. Laboratory parameters (biochemistry, hematology, and urinalysis).

### 5.2.3 Exploratory Endpoints

1. Change from baseline in subscale scores for discharge and pain domains from the Perianal Disease Activity Index (PDAI) scores.
2. Change from baseline in PCDAI scores.
3. Change from baseline in perianal pain visual analog scale (VAS).

## 6.0 STUDY DESIGN AND DESCRIPTION

### 6.1 Study Design

This is a phase 3, open-label, multicenter study to evaluate the efficacy and safety of darvadstrocel (also known as Cx601) in the treatment of complex perianal fistula refractory to therapy in pediatric subjects with CD aged 4 to <18 years.

At least 20 subjects are planned to be enrolled to receive a single dose of darvadstrocel (24 mL cell suspension containing 120 million cells of allogeneic eASCs). The study will permit continuation of previous treatment of luminal CD in an add-on study design (ie, anti-TNF therapy, immunosuppressants, etc.): subjects receiving any ongoing concomitant medical treatment for CD at stable doses (stable dose is considered either the same dose or same weight-based dose adjusted for weight) at the time of the screening visit, will be allowed to continue treatment throughout the study.

The study consists of a screening period (within a minimum of 4 and a maximum of 5 weeks before the preparation visit), preparation visit (within a minimum of 2 and a maximum of 3 weeks before treatment), treatment visit (day of study drug administration), and a follow-up period (for approximately 52 weeks after study drug administration).

After a successful screening period to determine eligibility, subjects will attend a preparation visit before receiving a single dose of darvadstrocel at Visit 0. At least 2 to 3 weeks before the treatment administration day, the investigator will perform a preparatory surgery (under anesthesia) comprising exploration of fistula anatomy, topography, assessment for potential associated complications, and fistula curettage. The location of the internal openings should be identified using only an injection of a sodium chloride 9 ng/mL (0.9%) solution through the external openings until it exits through the internal openings. In case of an abscess, incision and drainage will be performed, and setons should be placed, if appropriate, in accordance with routine surgical procedures. Mandatory antibiotic coverage for all subjects will be administered for at least 7 days following the fistula curettage (ciprofloxacin and/or metronidazole are recommended unless there is documented previous intolerance or contraindication to both). Subjects who fulfill the eligibility criteria at the preparation visit will be enrolled into the study. Before scheduling darvadstrocel administration, the surgeon must ensure that no abscesses are present. Seton(s) placed will be removed on the day of darvadstrocel administration. Appropriate training for preparation and darvadstrocel administration will be implemented to standardize the procedures between study sites.

On the treatment administration day (Day 0, Visit 0), eligible subjects will visit the study site and receive fistula curettage and fistula clinical assessment (FCA) under anesthesia of all fistula tracts, with special emphasis in the internal opening areas, using a metallic curette followed by suturing closed the internal openings. After conditioning of the fistula tracts, perilesional injection(s) of darvadstrocel will be administered. A surgical procedure manual will be provided to detail the procedure to administer darvadstrocel. Thereafter, study visits will take place as shown in Figure 6.a and Appendix A. At each visit, a clinical assessment of the fistula(s) will be performed.

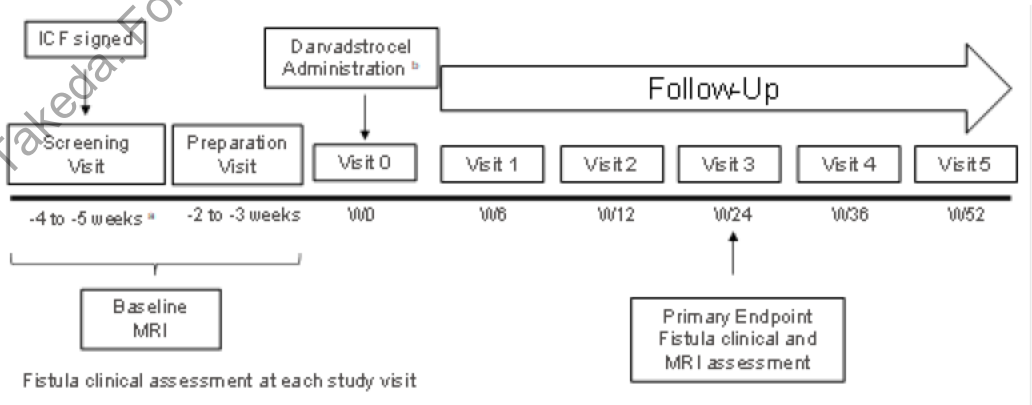
Sites will employ all efforts to see subjects in the clinic for assessments. In unavoidable circumstances such as the coronavirus disease 2019 (COVID-19) pandemic, exceptions may be granted for alternative methods for conducting subject visits with approval by the medical monitor and/or sponsor. Such instances will be documented in the study records. These data collected with alternative methods may be handled differently in the final data analysis and will be documented in the statistical analysis plan (SAP).

The primary endpoint of combined remission will be evaluated at Week 24 (where combined remission is defined as the closure of all treated external openings that were draining at baseline despite gentle finger compression, and the absence of abscess(es) >2 cm [in at least 2 dimensions] confirmed by central MRI assessment). An MRI will be performed locally at the screening visit and Week 24 to assess fistula characteristics, fistula location, and for the presence or absence of abscess(es) >2 cm (in at least 2 dimensions). All MRIs will be read centrally by a radiologist, who will be blinded to the subject's clinical characteristics and visit. See Section 9.1.6.2 for further details relating to the pelvic MRI assessment.

A follow-up period of an additional 28 weeks (up to a total of 52 weeks) is incorporated into the study for continued evaluation of safety and efficacy. The analysis will be performed after the database lock at Week 52.

Definition of end of study: Date of the last visit of the last subject at Week 52.

**Figure 6.a Study Schematic**




ICF: informed consent form; MRI: magnetic resonance imaging; W: week.
[a] Screening visit to take place within a minimum of 4 and a maximum of 5 weeks before the preparation visit.

[b] Study drug administration at Visit 0 must be performed within a minimum of 2 weeks and a maximum of 3 weeks of the preparation visit. Once the date for treatment administration surgery is set it cannot be moved due to the darvadstrocel preparation procedure and the limited window of manufacturing, shipment and study drug viability.

## 6.2 Justification for Study Design, Dose, and Endpoints

### Study Design

This study is planned to evaluate the efficacy and safety of darvadstrocel in the treatment of complex perianal fistulas in pediatric patients with CD.

The efficacy of darvadstrocel has been demonstrated in the pivotal phase 3, randomized, placebo-controlled study (Cx601-0302) in adult subjects with complex perianal fistula due to CD refractory to at least one standard of care therapy (ie, antibiotics, immunosuppressants, or biologics) (Panes et al. 2016).

Since the frequency of complex perianal fistulizing CD in pediatric patients is very low compared to adults and the pathophysiology of complex perianal fistula due to CD is similar among adults and pediatric patients, at least 20 subjects are planned to be enrolled into this study in an open-label, uncontrolled design.

### Dose Selection

The planned dose to be administered to pediatric patients is 120 million cells of darvadstrocel by local perilesional injection. This dose is approved in Europe for use in adults and is the same dose that was used in the completed pivotal global phase 3 study (Cx601-0303) in adult subjects with complex perianal fistula in CD and the completed Japan phase 3 study (Darvadstrocel-3002). Any adjustments to dose made by the surgeon (eg, due to unavoidable resistance at the injection site) will be recorded in the electronic case report form (eCRF).

The rationale for this dose is based on 1) nonclinical data and clinical data, including results from the completed phase 3 Cx601-0302 study which showed that this dose was efficacious and safe (Panes et al. 2016); 2) data showing that characteristics of complex perianal fistulas in pediatric patients are similar to those of adults; 3) published literature and feedback received from pediatric gastroenterologists and surgeons, and scientific advice from the EMA and the Pharmaceuticals and Medical Devices Agency, Japan.

*Clinical Data*

In the earlier phase 1/2 study for Cx601 (Study Cx601-0101) and in the clinical studies conducted during the development of an autologous product, Cx401, the pivotal phase 3 study (Cx401/FATT1) and the phase 1 study (Study Cx401[fCFIS]), the dose for a single fistula tract (out of up to 3 tracts) was 20 million cells followed by the administration of a further 40 million cells after 8 to 12 weeks in cases where the fistula was not completely closed.

To administer the 40 million cell dose, the fistula had to undergo another full curettage and debridement whereby any partially closed fistula was re-opened returning the fistula to baseline conditions. These studies supported that this dose was safe and efficacious for a single fistula tract but might not be adequate to treat a complex perianal fistula with multiple tracts, leading to

the proposal to use 120 million cells as a dose likely to be efficacious and safe for a complex fistula with multiple tracts.

In the pivotal phase 3 study (Cx601-0302), a dose of 120 million eASCs was shown to be efficacious and safe in the treatment of complex perianal fistula (Panes et al. 2016). In the completed phase 3 studies (Cx601-0303 and Darvadstrocel-3002) of complex perianal fistula in adults using the dose of 120 million cells, no new safety signals have emerged.

*Published Clinical Data*

A number of clinical studies in adults have demonstrated the efficacy and safety of stem cell therapy. The stem cell doses for fistulizing CD are variable and range from 3 million to 120 million cells per dose (Ciccocioppo and Corazza 2016).

*Similarity in the Characteristics of Complex Perianal Fistula in Adult and Pediatric Populations*

Pediatric patients with CD who develop perianal fistulas are typically adolescents, with the median age in reported studies ranging from 11.5 to 14.6 years (Adler et al. 2017; Herman et al. 2017; Keljo et al. 2009). Data show complex perianal fistula in pediatric patients and adults have similar characteristics on MRI, including similar fistula tract number, similar dominant fistula length, and similar anatomic location (Shenoy-Bhangle et al. 2014). The similarity of pediatric and adult complex perianal fistulas data support use of the same dose of 120 million cells.

*Nonclinical Studies*

Nonclinical safety studies conducted support the use of darvadstrocel in pediatric patients. Biodistribution, toxicity, and tumorigenicity studies in immunocompromised animals confirm darvadstrocel has a low order of toxicity. The safety of eASC was investigated in toxicology studies in animals with doses up to 2.5 million cells/animal (perianal maximum feasible dose) and 10 million cells/animal (subcutaneous) with follow-up out to 6 months post administration. Biodistribution studies in juvenile athymic rats (at least 5 weeks of age) confirmed a short persistence of eASC (maximal persistence of <14 days via intravaginal and <91 days via intravenous or perianal/intrarectal routes), and local distribution of eASCs and repeat-dose toxicity studies in rodents of eASCs up to 2.5 million cells (perianal maximum feasible dose) were well-tolerated. The nonclinical program did not reveal any sign of tumor promotion, tumor formation, or ectopic tissue formation. In vivo tumorigenicity assays in nude mice administered by subcutaneous injection (10 million cells/mouse) identified no evidence of tumor formation in studies with darvadstrocel. In vitro assays showed that tumorigenicity risk of the product is low.

*Summary*

The available evidence to date from clinical studies as well as limited postmarketing experience demonstrates that darvadstrocel is well tolerated up to 120 million cells per administration in adults. No dose-dependent safety concern or toxicity has been identified and no ectopic tumor formation concerns have emerged. Overall, the data available presents a positive benefit-risk profile for darvadstrocel.

### Endpoints

The purpose of this study is to demonstrate comparability in safety and efficacy of darvadstrocel between adult and pediatric subjects, therefore the same primary endpoint and similar secondary endpoints will be used in this study as those used in the phase 3 studies (Cx601-0302, Cx601-0303, and Darvadstrocel-3002).

Given the similar pathophysiology, clinical course, and treatment of complex perianal fistulas related to CD and that the mechanism of action of darvadstrocel does not have any known age-dependent characteristics, partial extrapolation of efficacy from the adult population is appropriate and will be further supported by using very similar inclusion and exclusion criteria and the same combined remission primary endpoint as used in the adult studies.

## 6.3 Definition of Study Start

The study start date is the date when the first subject signs the informed consent/pediatric assent form.

## 6.4 Definition of End of Study

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

## 6.5 Premature Termination or Suspension of Study or Study Site

### 6.5.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known benefit-risk profile for darvadstrocel, such that the benefit-risk 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.
- Subject enrollment is unsatisfactory.

### 6.5.2 Criteria for Premature Termination or Suspension of Study Sites

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

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

In the event that 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 a

study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

## 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before study drug administration.

### 7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to 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, informed consent/pediatric assent form and any required privacy authorization before the initiation of any study procedures.
3. The subject is male or female aged 4 to <18 years at the time of study treatment administration.
4. The subject has a CD diagnosis based on accepted clinical, endoscopic, histological and/or radiologic criteria at least 6 months before the screening visit.
5. The subject has complex perianal fistula refractory to at least one of the following treatments: immunosuppressants or biologics (anti-TNFs, anti-integrin, anti-interleukin [IL] 12/23). Fistula(s) refractory to therapy are defined in this study as follows:
   - Immunosuppressants: Inadequate response after 3 months, based on clinical assessment, or more treatment with azathioprine, 6-mercaptopurine or methotrexate.
   - Biologics: Inadequate response after 14 weeks (16 weeks for anti-IL 12/23), based on clinical assessment, or more standard treatment for induction and maintenance.
6. A complex perianal fistula(s) that meets one or more of the following criteria, modified from the American Gastroenterological Association (AGA) technical review (Sandborn et al. 2003):
   - High intersphincteric, transsphincteric, extrasphincteric, or suprasphincteric as assessed by MRI.
   - Presence of 2 or 3 external openings (tracts) as assessed by clinical examination.
   - Associated fluid (abscess) collections as determined by MRI.

   This study requires that the subject has complex perianal fistulas with a maximum of 2 internal openings and a maximum of 3 external openings, based on clinical assessment. Darvadstrocel treatment is targeted for fistulas that connect between internal and external openings. A central reading of a locally performed pelvic MRI will be performed to confirm the location of the fistula and potential associated perianal abscess(es). Fistulas

must have been draining for at least 6 weeks before the screening visit. Subjects with actively draining simple subcutaneous fistulas, at the time of the screening visit, are not allowed in this study.

7. The subject has inactive or mildly active luminal CD defined by meeting all of the following criteria:
   a) Colonoscopy, flexible sigmoidoscopy or rectoscopy performed either at screening or within the 6 months before screening, demonstrating no rectal ulcers larger than 0.5 cm. A subject who has documented rectal ulcers larger than 0.5 cm within the 6 months before screening but has undergone subsequent treatment may be eligible if there are no rectal ulcers larger than 0.5 cm on a sigmoidoscopy or rectoscopy performed after treatment or at the time of screening.
   b) The improvement of, or no worsening in stool frequency, sustained for 1 week or more, in the interval between the colonoscopy, flexible sigmoidoscopy or rectoscopy in inclusion criteria 7(a) and the screening visit.
   c) No initiation or intensification of treatment with corticosteroids, immunosuppressants, or monoclonal antibody dose regimen between the colonoscopy, flexible sigmoidoscopy or rectoscopy in inclusion criteria 7(a) and the screening visit.
8. A male subject who is *nonsterilized and sexually active with a female partner of childbearing potential agrees to use barrier method of contraception (eg, condom with or without spermicide)* from the time of signing of informed consent/pediatric assent throughout the duration of the study. The female partner of a male subject should also be advised to use a highly effective method of contraception.
9. A female subject of childbearing potential* who is sexually active with a nonsterilized male partner agrees to use a highly effective method of contraception* from the time of signing of informed consent/pediatric assent throughout the duration of the study.

   *Definitions and highly effective methods of contraception are defined in Section 9.1.10 and reporting responsibilities are defined in Section 9.1.11.

## 7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 12 weeks/84 days before screening.
2. The subject has received darvadstrocel/eASC in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling), or may consent under duress.
4. The subject weighs <10 kg at screening.

5. The subject has, in the judgment of the investigator, clinically significant abnormal hematological parameters of hemoglobin, hematocrit, or erythrocytes at screening.
6. The subject has a history of hypersensitivity or allergies to darvadstrocel or any of its excipients.
7. The subject takes or is required to take excluded medications listed in Table 7. a.
8. The subject has concomitant perianal fistula(s) with only internal or external opening(s).
9. The subject has concomitant internal fistula(s) such as ileo-vesical, rectovaginal or ileo-colonic fistula(s).
10. The subject has an abscess >2 cm, unless resolved in the preparation procedure.
11. The subject has rectal and/or anal stenosis, and/or active proctitis, which would restrict the surgical procedure.
12. The subject underwent surgery for the fistula other than drainage or seton placement.
13. The subject has diverting stomas.
14. The subject has ongoing systemic corticosteroid treatment or has been treated with systemic corticosteroids within 4 weeks before screening.
15. The subject requires new treatment with immunosuppressants/anti-TNF agents during the screening period.
16. The subject has known or suspected COVID-19 by the investigator within the past 2 months (additional testing may be performed at the discretion of the investigator). Positive antibody testing for COVID without other evidence of current or recent active infection does not exclude participation.
    - Subjects who were in screening at the time that COVID-19–related factors resulted in discontinuation may also be rescreened with approval of the sponsor or designee.
17. The subject requires surgery in the perianal region for reasons other than fistulas at the time of screening or foreseen either during the study and/or during the 24 weeks after treatment administration.
18. The subject has a serum creatinine ≥2 × upper limit of normal (ULN).
19. The subject has hepatic impairment defined by both of the following laboratory ranges:
    a) Total bilirubin ≥1.5 × ULN.
    b) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥2 × ULN.
20. The subject has known history of abuse of alcohol or other addictive substances in the 6 months before screening.
21. The subject has malignant tumor or a prior history of any malignant tumor, including any type of fistula carcinoma.

22. The subject has current or recent (within 3 months before the screening) history of abnormal, severe, progressive, uncontrolled hepatic, hematologic, gastrointestinal (except CD), endocrine, pulmonary, cardiac, neurological, psychiatric, or cerebral disease.
23. The subject has either congenital or acquired immunodeficiencies, including subjects known to be HIV carriers or subjects with, in the judgment of the investigator, are suspected to have monogenic inflammatory bowel disease.
24. The subject has a known clinically significant chronically active hepatopathy of any origin, including cirrhosis and subjects with persistent positive hepatitis B surface antigen and quantitative hepatitis B virus polymerase chain reaction, or positive serology for hepatitis C virus (IgG) and quantitative hepatitis C virus polymerase chain reaction at the screening visit.
25. The subject has known allergies or hypersensitivity to antibiotics (including benzylpenicillin/streptomycin, gentamicin [used in the darvadstrocel manufacturing process]) human serum albumin; Dulbecco Modified Eagle's Medium, material of bovine origin, or local anesthetics.
26. The subject has previously received a bone marrow transplant.
27. The subject has a contraindication to MRI scan, or other planned study procedures.
28. The subject has a contraindication to the anesthetic procedure.
29. The subject had major surgery or severe trauma within 6 months before the screening visit.
30. A female subject who is pregnant or is lactating or intending to become pregnant before participating in this study or during the study; or intending to donate ova during such time period.
31. If male, the subject intends to donate sperm during the course of this study.
32. The subject does not wish to or cannot comply with study procedures.

### 7.3 Excluded Medications and Treatments

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

The details of allowed/excluded medications or treatments during the period from start of screening period to study product administration, and from the study product administration to Week 52 are summarized in Table 7. a. There are no restrictions for medications and treatments after Week 52. If there are any questionable medications or treatments, the sponsor or its designee should be contacted.

If a subject received any excluded medications or treatments, the subject may continue to participate in the study if the risk is considered acceptable by the investigator and sponsor.

## Table 7. a Allowed/Excluded Medications and Treatments

| Medications/ Treatment | From Start of Screening Period to Darvadstrocel Administration | From Darvadstrocel Administration to Week 52 | Justification |
|---|---|---|---|
| Any investigational drugs or other local investigational treatments for the perianal region | **NOT Allowed**<br>Should be excluded from 84 days before start of screening period. | **NOT Allowed** | These medications/treatments are excluded in consideration of any influences on the efficacy and safety evaluation of darvadstrocel. |
| Antibiotics (including but not limited to ciprofloxacin and/or metronidazole) | **Allowed**<br>Continuous use of antibiotics must be up to a maximum of 4 weeks. | **Allowed**<br>Continuous use of antibiotics must be up to a maximum of 4 weeks, including the period before the study product administration. | These medications are allowed with the restriction following the dosing period because long-term use beyond clinical standards may jeopardize the safety of the subject. |
| 5-aminosalicylic acid | **Allowed** | **Allowed**<br>A stable dose should be given after the study product administration. Only dose reduction from the initial dose will be allowed. | These medications are allowed with the restriction to avoid any influences on the efficacy and safety evaluation of darvadstrocel. |
| Topical steroid (nonrectal)<br>Inhalatory steroids | **Allowed** | **Allowed** | These medications are allowed because they have less effect on the efficacy and safety evaluation of darvadstrocel. |
| Immunosuppressants (eg, azathioprine, 6-mercaptoprine, methotrexate, tacrolimus) | **Allowed**<br>Continuous use of immunosuppressants is allowed if it has been used at stable dose for more than 3 months before start of screening period. | **Allowed**<br>A stable dose should be given after the study product administration. Dose reduction or discontinuation of immunosuppressants will be allowed only if adverse reactions associated with immunosuppressants are observed. | These medications are allowed with the restriction to avoid any influences on the efficacy and safety evaluation of darvadstrocel. |

## Table 7. a Allowed/Excluded Medications and Treatments

| Medications/ Treatment | From Start of Screening Period to Darvadstrocel Administration | From Darvadstrocel Administration to Week 52 | Justification |
|---|---|---|---|
| Biologics (anti-TNF, anti-integrin, anti-IL-12/23) | **Allowed** Continuous use of biologics is allowed if complex perianal fistulas showed no response despite at least 14-week treatment (16 weeks for anti-IL-12/23) before start of screening period, OR complex perianal fistulas recurred after achieving closure of fistulas. | **Allowed** A stable dose should be given after the study product administration. | These medications are allowed with the restriction to avoid any influences on the efficacy and safety evaluation of darvadstrocel. |
| Janus kinase (JAK) inhibitors | **Allowed** Continuous use of JAK inhibitors is allowed if the complex perianal fistula(s) showed no response despite at least 16-week treatment. | **Allowed** A stable dose should be given after the study product administration. | These medications are allowed with the restriction to avoid any influences on the efficacy and safety evaluation of darvadstrocel. |
| Systematic steroids<br>Rectal steroids | **Allowed** These medications should be tapered and discontinued at least 4 weeks before study product administration. | **NOT Allowed** These medications are allowed as a rescue therapy only when CD worsens. | These medications are excluded in consideration of any influences on the efficacy and safety evaluation of darvadstrocel. Use for a rescue therapy is allowed in consideration of the safety of subjects. |
| Enteral nutrition/ exclusive enteral nutrition | **Allowed** No new treatment with total enteral nutrition therapy will be allowed. | **Allowed** Stable therapy allowed. This treatment can be used as a rescue therapy only when CD worsens, see Section 7.4. | This therapy is allowed because it has less effect on the efficacy and safety evaluation of darvadstrocel. |
| Parenteral nutrition | **NOT Allowed** | **NOT Allowed** These treatments can be used as a rescue therapy only when CD worsens, see Section 7.4. | These treatments are excluded in consideration of any influences on the efficacy and safety evaluation of darvadstrocel. Use for a rescue therapy is allowed in consideration of the safety of subjects. |

**Table 7. a Allowed/Excluded Medications and Treatments**

| Medications/ Treatment | From Start of Screening Period to Darvadstrocel Administration | From Darvadstrocel Administration to Week 52 | Justification |
|---|---|---|---|
| Cytapheresis | **NOT Allowed** | **NOT Allowed** | These medications are excluded in consideration of any influences on the efficacy and safety evaluation of darvadstrocel. |
| Oral anticoagulants | **NOT Allowed**<br>If an anticoagulant has been used before screening period and required continuous use, it should be switched to appropriate dose of low molecular weight heparin. | **NOT Allowed**<br>For 2 weeks after study product administration | These medications are restricted in consideration of the safety risk of possible bleeding during/following the preparation surgery and study product administration. |
| Anesthesia/sedation during MRI | **NOT Allowed** | **NOT Allowed** | This therapy is not allowed in consideration of the safety risk associated with anesthesia. |
| NSAIDS | **Allowed** | **Allowed** | These medications are allowed because they have less effect on the efficacy and safety evaluation of darvadstrocel. |

CD: Crohn's disease; IL: interleukin; MRI: magnetic resonance imaging; NSAID: nonsteroidal anti-inflammatory drug; TNF: tumor necrosis factor.

For medications dosed using weight-based dosing: if a subject gains significant weight during the study, the investigator is permitted to adjust the dose to maintain a stable weight-based dose to account for the subject's weight gain.

## 7.4 Rescue Therapy

The need for rescue therapy for complex perianal fistula will be determined, for a safety concern, at the discretion and clinical judgment of the site investigator when the condition of complex perianal fistula deteriorates and requires further treatment immediately. The criteria for rescue medication or interventions are applicable from the time it occurs until Week 52. Examples of subjects that fulfill the need for rescue treatment include (but are not limited to):

- Subject requires add-on treatment for complex perianal fistula with a new immunosuppressant, biologic, or Janus kinase inhibitor, or requires higher doses compared to the baseline therapy documented at screening.

- Subjects starting any other investigational drug for complex perianal fistula or any other local investigational treatment in the perianal region while participating in the study.
- Any new surgical procedure required in the perianal region for the fistula(s) or draining of abscess(es) or established abscess(es).
- Prolonged use of systemic antibiotics (more than 2 weeks) to treat perianal disease after the treatment administration visit.

Rescue therapy, including medications and/or surgical procedures, for complex perianal fistula should follow the local or institutional guidance for standard of care. Subjects requiring any of these rescue medications or interventions for complex perianal fistula during the study will be considered a treatment failure but will not be withdrawn from the study and will attend further visits for safety follow up until Week 52 if the risk is considered acceptable by the investigator.

## 7.5 Criteria for Withdrawal of a Subject

The primary reason for withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories.

1. AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
2. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
3. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (eg, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).
4. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
5. Death.
6. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

For screen failure subjects, refer to Section 9.1.12.

## 7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study withdrawal criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit. Discontinued or withdrawn subjects will not be replaced.

# 8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

## 8.1 Study Drug and Materials

### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

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

#### *8.1.1.1 Darvadstrocel*

Study sites will be supplied by the sponsor with the following medication for local perilesional injection around the internal opening(s) and into the tissue walls along the fistula tract(s):

- Darvadstrocel (code name: Cx601) will be supplied as a white-to-yellowish suspension for local perilesional injection, provided in 4 × 6 mL type I glass vials (suspension of 5 million eASCs per mL [30 million cells per vial and 120 million cells per dose] of Dulbecco Modified Eagle's Medium with human serum albumin). The disposable vials are packaged in a carton box with its corresponding labeling.

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

The packaging material comprises:

- Immediate package: type I glass sterile vials, each of 9 mL volume capacity (filled up to 6 mL each) with chlorobutyl sterile rubber stopper and aluminum seal (not in contact with the product).
- Labels of white polyethylene printed in black ink by thermal transfer printer.
- Secondary packaging: cardboard box with corporate design.

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

Refer to preparation and administration instructions in the pharmacy manual.

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

#### *8.1.1.2 Study drug*

The drug being administered in this study is darvadstrocel.

#### *8.1.1.3 Sponsor-Supplied Drug*

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

**Table 8. a Study Medication**

| | |
|---|---|
| **Drug Name (Identification in the Protocol)** | Darvadstrocel |
| **Product Class** | Stem cell therapies |
| **Designation** | IMP |
| **Marketing Authorization** | Yes (centralized): Alofisel |
| **Used Within Marketing Authorization** | No |
| **ATC Code** | L04AX08 |
| **Route of Administration** | Perilesional injection |
| **Active Substance** | Darvadstrocel |
| **Dosage Level(s)** | 120 million cells (5 million cells/mL) |
| **Dose Regimen** | Single, open-label darvadstrocel dose |
| **Duration** | Single dose |
| **Arm (Subjects Receiving the Medicinal Product)** | Single-arm study |
| **Dose Formulation** | Darvadstrocel (24 mL cell suspension containing 120 million cells of eASCs): 5 million cells/mL |
| **Dose Strength(s)** | 5 million cells/mL |
| **Sourcing** | Provided centrally/locally by the sponsor |

ATC: Anatomical Therapeutic Chemical; eASC: expanded adipose stem cells; IMP: investigational medicinal product.

### 8.1.2 Storage

Study drug must be kept in an appropriate, limited-access, secure place until it is used or ready for destruction. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

Darvadstrocel will be shipped under temperature-controlled conditions, using appropriate transport for biological samples. Shipping material is also duly labelled and has an attached package content list and instructions for use.

Specific instructions will be provided within a separate study manual. The study medication must be stored under the storage conditions specified in the manual.

### 8.1.3 Dose and Regimen

Darvadstrocel will be administered via perilesional injection as a single dose at Day 0/Visit 0 (see Appendix A). The study drug will be administered by the investigator at the study site. A single dose of darvadstrocel (120 million cells of eASCs) is supplied in 4 vials. Each vial contains 30 million cells in 6 mL of suspension. The full content of the 4 vials must be administered for the treatment of up to 2 internal openings and/or up to 3 external openings.

Details on the procedure for study product administration will be specified in the surgical procedure manual.

All subjects will receive the same dose, however if the surgeon is unable to inject the full dose (eg, due to unavoidable resistance at the injection site), a reduced dose (<120 million cells [<24 mL]) will be administered and recorded as a protocol deviation. The adjusted dose (mL) will be recorded in the eCRF and the subject will be able to continue in the study.

Before administration of the study drug, appropriate training will be implemented at each study site. Only personnel who completed the training can administer the study product.

### 8.1.4 Overdose

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

All cases of overdose (with or without associated AEs) will be documented as a medication error on the AESI page of the eCRF and reported to Pharmacovigilance on a paper SSR form. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

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

## 8.2 Study Drug Assignment and Dispensing Procedures

Subjects will receive treatment according to the study schedule. The enrollment number will be entered onto the eCRF.

Subjects will be assigned to receive the next available medication ID number allocated to each study site. The tear-off portion of the medication label will be affixed to the dispensing log. The medication ID Number will be entered onto the eCRF.

## 8.3 Accountability and Destruction of Sponsor-Supplied Drugs

Drug accountability will be performed at the site. The investigator or designee will maintain adequate records of the receipt of study drug shipment to the site. All used and unsed vials of study drug must be recorded and tracked.

All used darvadstrocel vials will be stored at the site until the local monitor has performed the corresponding documented reconciliation and drug accountability. Any dosage deviation should be clearly noted in site source documentation. The corresponding destruction will be documented as per local procedures and regulations (eg, destruction certificate issued and filed in the corresponding study files).

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dosed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, administration to subject, and vial destruction.

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

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

- Continuously monitoring expiration dates.
- Verifying that the log is completed for the drug lot/medication ID/job number/other used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

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

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are available for destruction. The investigator or designee will retain a copy of the

documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

### 8.4 Continued Access to Study Drug After the End of the Study

No aftercare is planned for this study. The study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

## 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/Pediatric Assent Procedure

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

Informed consent/pediatric assent must be obtained before the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent/pediatric assent is obtained/explained; this subject number will be used throughout the study.

#### 9.1.2 Demographics, Medical History, and Surgical History

Demographic information to be obtained will include date of birth or age, sex, race as described by the subject, height, weight, and smoking status of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of informed consent/pediatric assent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 2 years before signing of informed consent/pediatric assent.

Surgical history will be obtained to document any significant procedures performed before the signing of informed consent. In particular, prior surgical procedures related to the fistula will be recorded on the specific eCRF.

### 9.1.3 Physical Examination Procedure

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

All subsequent physical examinations should assess clinically significant changes from the examination prior to study drug administration.

### 9.1.4 Weight, Height and Body Mass Index

A subject should have weight and height measured while wearing indoor clothing and with shoes off.

The body mass index (BMI) is calculated using metric units with the formula provided below: Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.6$ kg/m$^2$

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m$^2$.

### 9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral measurement), blood pressure (systolic and diastolic, resting more than 5 minutes), and heart rate (beats per minute).

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

### 9.1.6 Primary Efficacy Measurements

#### *9.1.6.1 Fistula Clinical Assessment*

Primary efficacy assessments will be based on clinical evaluation of fistula(s) in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification). The fistula(s) must have been draining for at least 6 weeks before screening. The clinical assessment will consist of a physical examination of the fistula(s) by an investigator to evaluate the presence of drainage spontaneously or after gentle finger compression through the external openings. The tracts and external openings must be clearly identified in the eCRF in order to ensure the same tracts are assessed during the study period.

*9.1.6.2 Pelvic MRI*

A pelvic MRI scan will be performed locally at baseline (screening visit), Week 24, and early termination visit before Week 24 to assess for fistula characteristics, fistula location and the presence or absence of abscess(es) >2 cm (in at least 2 dimensions). A quality copy will be sent to the central imaging laboratory for reading as detailed in the specific MRI manual.

At screening, central MRI results reporting fistula characteristics, fistula location and abscess(es), if any will be communicated to the investigator and the surgeon before the preparation visit. The baseline MRI (at screening) can be obtained within a minimum of 4 and a maximum of 5 weeks before the preparation visit before the preparation visit to determine eligibility.

At Week 24 or early termination (if applicable), copies of the MRIs performed locally will be sent to the central imaging laboratory for central MRI reading. MRI assessments at Week 24 will include evaluation of presence of any abscess(es) directly related to the treated fistula tracts, and any new tracts that might appear.

All MRI scans, including MRI scans available from initial treatment, will be assessed centrally by the MRI central reader. The MRI central reader will report fistula characteristics, fistula location, and measurements of any abscess(es) >2 cm (in at least 2 dimensions).

Refer to the specific MRI manual for further details.

### 9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent/pediatric assent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

### 9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent/pediatric assent. This includes clinically significant laboratory or physical examination abnormalities noted at screening examination, according the judgment of the investigator. The condition (ie, diagnosis) should be described.

### 9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single study visit is approximately 7.5 mL, and the approximate total volume of blood for the entire study duration is 30 mL (see Appendix B). Details of these procedures and required safety monitoring will be provided in the laboratory manual. The laboratory manual describes procedures for specimen handling.

Blood samples for central laboratory tests will be collected at the timepoints specified in Appendix A. Table 9. alists the tests that will be obtained for each laboratory specimen.

**Table 9. a Clinical Laboratory Tests**

| Hematology | Serum Chemistry | Urinalysis |
|---|---|---|
| Hemoglobin | ALT | pH |
| Hematocrit | AST | Specific gravity |
| MCV | Albumin | Protein |
| MCH | Total bilirubin | Sugar |
| MCHC | CRP | Ketones |
| Erythrocytes | Creatinine | Bilirubin |
| Leukocytes | Urea | Urobilinogen |
| Lymphocytes | Creatine kinase | Blood (Red blood cells) |
| Monocytes | Potassium | White blood cells |
| Neutrophils | Sodium | Epithelial cells |
| Eosinophils | Chloride | Nitrites/Leukocyte esterase |
| Basophils | | Casts |
| Platelet count | | Crystals |
| ESR [a] | | Bacteria |
| **Serum** | | **Urine** |
| Female subjects who are menstruating or aged ≥11 years, whichever is younger: | | Female subjects only who are menstruating or aged ≥11 years, whichever is younger: |
| Beta hCG (for pregnancy) | | Beta hCG (for pregnancy) |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; hCG: human chorionic gonadotropin; MCH; mean corpuscular hemoglobin; MCHC; mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume.
[a] ESR will be analyzed by a local laboratory.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. In unavoidable circumstances such as the COVID-19 pandemic, laboratory tests may be performed by local laboratories where possible, upon sponsor approval and in compliance with local regulations.

For subjects with treatment-emergent ALT elevations ≥3 × ULN, see Appendix D for additional monitoring, evaluation, and follow-up recommendations.

### 9.1.10 Contraception and Pregnancy Avoidance Procedure

#### *9.1.10.1 Male Subjects and Their Female Partners*

From signing of informed consent/pediatric assent, throughout the duration of the study, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of

childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below.

*9.1.10.2 Female Subjects and Their Male Partners*

From signing of informed consent/pediatric assent, throughout the duration of the study, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective form of contraception (from the list below).

In addition, they must be advised not to donate ova during this period. This will apply to female subjects of childbearing potential who have reached menarche prior to or during the study.

*9.1.10.3 Definitions and Procedures for Contraception and Pregnancy Avoidance*

*The following definitions apply for contraception and pregnancy avoidance procedures.*

* A woman is considered a woman of childbearing potential (WOCBP) as follows: fertile, following menarche or aged ≥11 years, whichever is younger.

** Sterilized males should be at least 1-year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

*The following procedures apply for contraception and pregnancy avoidance.*

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
   - Non-hormonal methods:
     - Intrauterine device.
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success).
     - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from signing of informed consent/pediatric assent.
   - Hormonal methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method.
     - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study

drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;

- Oral.
- Intravaginal (eg, ring).
- Transdermal.

- Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before study drug administration OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
  - Oral.
  - Injectable.
  - Implantable.

2. Unacceptable methods of contraception are:
   - Periodic sexual abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
3. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent/pediatric assent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, ova donation, and sperm donation during the course of the study.
4. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for female subjects following menarche or aged ≥11 years, whichever is younger. All subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study.
   b) Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   c) Assessment of subject compliance through questions such as

i. Have you used the contraception consistently and correctly since the last visit?

ii. Have you forgotten to use contraception since the last visit?

iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")

iv. Is there a chance you could be pregnant?

5. In addition to a negative serum pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative urine hCG pregnancy test before receiving study medication and at the visits specified in Appendix A.

#### *9.1.10.4 General Guidance With Respect to the Avoidance of Pregnancy*

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Reasons for use of barrier methods (ie, condom) in males with female partners with childbearing potential.
- Assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes").
  - Is there a chance you could be pregnant?

### 9.1.11 Pregnancy

Pregnant or breastfeeding women are excluded from study entry. If any subject is found to be pregnant during the study, the pregnancy should be reported immediately using a pregnancy notification form to the contact listed in Section 1.1.

In addition, any pregnancies in the partner of a male subject during the study should also be recorded following authorization from the subject's partner.

See Section 10.3.2 for details on reporting pregnancy.

### 9.1.12 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent/pediatric assent.

If the subject is withdrawn during the screening period, the investigator should complete the eCRF. The primary reason for screen failure is recorded in the eCRF using the following categories:

- AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Pregnancy.
- Death.
- Other (specify reason), including unavoidable circumstances such as the COVID-19 pandemic.

Subject identification numbers assigned to subjects who fail screening should not be reused.

### 9.1.13 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for treatment.

If the subject is found to be not eligible for treatment, the investigator should record the primary reason for failure on the applicable eCRF.

### 9.1.14 Fistula Preparation

Fistula preparation will consist of preparatory surgery (under anesthesia) comprising exploration of fistula anatomy, topography, assessment for potential associated complications, and vigorous curettage, with special emphasis on the internal opening(s). Before scheduling darvadstrocel administration, the surgeon must ensure that no abscesses are present. If there is an abscess present, incision and drainage must be performed in accordance with routine surgical procedures. Loose seton placement will be required for all subjects. Mandatory antibiotic coverage for all subjects will be administered for at least 7 days following the fistula curettage (ciprofloxacin and/or metronidazole are recommended unless there is documented previous intolerance or contraindication to both).

### 9.1.15 Clinical Outcome Assessments

#### *9.1.15.1 Clinician-Reported Outcomes*

**PDAI**

The PDAI score (Appendix E) is a scoring system to evaluate the severity of perianal CD (Sandborn et al. 2003). From the 5-item instrument, discharge and pain will be assessed. Each category is graded on a 5-point Likert scale ranging from no symptoms (score of 0) to severe symptoms (score of 4); a higher score indicates more severe disease.

**PCDAI**

The PCDAI score (Appendix F) was developed and validated as an evaluative multi-item index for disease activity of CD in multicenter studies among children and adolescents (Hyams et al. 1991). The PCDAI score will be evaluated using the subject's/parent's or legal guardian's diary entries and laboratory results collected during screening and then at every scheduled visit during the study as per Appendix A.

ESR as part of the PCDAI assessment will be analyzed by a local laboratory.

#### *9.1.15.2 Patient-Reported Outcomes*

**Perianal Pain VAS**

Pain intensity, recorded using a daily VAS from 0-10 (Appendix G), while standing, sitting, and defecating will be recorded by the subjects at home for 2 weeks (14 days) before each visit (or, for the screening visit only, for 2 weeks [14 days] starting within 7 days after the screening visit) as specified in Appendix A.

## 9.2 Monitoring Subject Treatment Compliance

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

## 9.3 Schedule of Observations and Procedures

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

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

When approval is given for a subject to miss an in-person study visit, a healthcare provider will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact, the study site physician or other qualified site staff should also at minimum conduct the following assessments: AE collection and concomitant medication/procedure documentation and a remote evaluation of the fistula. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Additionally, sites may have study personnel see the subject outside of the on-site clinic to conduct study assessments contingent upon local regulations. Assessments that cannot be completed during the protocol specified window will be considered missing data and such departures will be recorded in the study records. Alternatively, sites may seek approval to extend the visit window in order to conduct an on-site visit.

Visits at screening, preparation, treatment administration, Week 24, and Week 52 must be done with the subject present at the investigative site. Alternative methods of data collection may be considered for visits at Weeks 6, 12, and 36 when it is not possible for the subject to attend the study site. Under such circumstances, a preferred alternative would be for a qualified medical professional delegated by the investigator and authorized to perform assessments for this study to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at subjects' residence should comply with applicable local regulations.

### 9.3.1 Screening Visit

Subjects will be screened within a minimum of 4 weeks and a maximum of 5 weeks before the preparation visit. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.12 for procedures on documenting screening failures.

Procedures to be completed at the screening visit include:

- Informed consent/pediatric assent.
- Inclusion/exclusion criteria check.
- Demographics and medical history.
- Weight, height, and BMI.
- Physical examination covering all body systems.
- Vital signs (body temperature, blood pressure, and heart rate).
- Concomitant medications.
- Concurrent medical conditions.
- CD, fistula and treatment history.
  - Including family history, age at onset, medical and surgical history for any CD-related surgery, and surgeries to treat relapse of treated perianal fistula and new perianal fistula;

preparatory surgery will be completed before darvadstrocel administration at the preparation visit.

- Target fistula(s) information (new fistula or previously treated fistula).
  - Fistula clinical assessment (Appendix C):
    - Clinical characteristics, including age of onset, number of other fistulas, localization, and clock position.
  - The investigator must also complete the FCA eCRF for screening in addition to the anal clock form in Appendix C.
- Screening clinical laboratory tests (refer to Section 9.1.9)
  - Hematology, serum biochemistry and urinalysis.
- Serum pregnancy test for WOCBP. A female subject is considered a WOCBP following menarche or aged ≥11 years, whichever is younger.
- Fistula MRI assessment:
  - Pelvic MRI performed locally.
- PCDAI score.
  - ESR as part of the PCDAI assessment will be analyzed by a local laboratory.
- PDAI subscale scores.
- Perianal pain VAS.
- Luminal disease activity involving the rectum.
  - A colonoscopy or rectoscopy will need to be performed at screening if the subject has not had one within the last 6 months of screening.
- Assessment of AEs/SAEs, AESIs, and SSRs.

### 9.3.2 Potential Rescreening

For any subject not meeting the eligibility criteria, or if there are unavoidable circumstances such as the COVID-19 pandemic, it may be possible to rescreen the subject if they later meet the criteria and based upon the sponsor's approval.

For subjects who require a rescreening, and upon the sponsor's approval, the following procedures will need to be repeated and the preparation visit rescheduled based on protocol timelines:

- Informed consent.
- Inclusion/exclusion criteria check.
- Physical examination.

- Weight, height, and BMI.
- Vital signs.
- Clinical laboratory tests (hematology, biochemistry, and urinalysis).
- Serum pregnancy test for WOCBP. A female subject is considered a WOCBP following menarche or aged ≥ 11 years, whichever is younger.
- Clinical assessment of perianal fistulas and CD (including the presence or absence of proctitis, localization, fistula draining status, and pattern of disease).
  - The investigator must complete the anal clock form in Appendix C in addition to the FCA eCRF for screening.
- Pelvic MRI: The need to repeat the pelvic MRI scan at the rescreening visit will be determined on a case-by-case basis at the investigator's discretion based on the duration between screening and rescreening and the subject's clinical condition.
- PDAI subscale scores.
- Perianal pain VAS.

### 9.3.3 Preparation Visit

The preparation visit will take place within a minimum of 2 weeks and a maximum of 3 weeks before the treatment administration visit. Darvadstrocel will need to be preordered and, thus, this supply request at the preparatory visit will act as a trigger to start the manufacturing process of darvadstrocel for the subject. Subjects must fulfill the eligibility criteria at the preparation visit in order to be enrolled into the study.

The surgeon is to receive the screening MRI to review results before the preparation visit.

- Prior to fistula preparation:
  - Inclusion/exclusion criteria check, including review of central laboratory results and central MRI reading confirmation.
  - Weight, height, and BMI.
  - Physical examination covering all body systems.
  - Vital signs.
  - Review and record concomitant medications.
  - Review and record concurrent medical conditions.
  - Urine pregnancy test for WOCBP. A female subject is considered a WOCBP following menarche or aged ≥11 years, whichever is younger.
- Fistula preparation consisting of examination under anesthesia (including FCA), seton placement, and curettage for ALL subjects by the surgeon according to the surgical

procedure manual (provided as a separate document). This must be done at least 2 weeks and a maximum of 3 weeks before the study treatment administration day. Administration of antibiotics is mandatory, and use should be in accordance with standard clinical care guidelines for perianal fistulas.

  - The FCA eCRF must be completed by the investigator.

- Assessment of AEs/SAEs, AESIs, and SSRs.

### 9.3.4 Treatment Administration Visit (Week 0/Visit 0)

The study treatment administration visit (Visit 0) will take place at a minimum of 2 weeks and a maximum of 3 weeks from the preparation visit. Once the date for treatment administration surgery is set, it cannot be moved due to the darvadstrocel preparation procedure and the limited window of manufacturing, shipment and study drug viability.

- Before treatment administration:
  - Weight, height, and BMI.
  - Physical examination covering all body systems.
  - Vital signs.
  - Concomitant medications taken since last visit.
  - Concurrent medical conditions.
  - Urine pregnancy test for WOCBP.
  - Fistula clinical assessment in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
    - The FCA eCRF must be completed by the investigator. If a new external opening is identified during the assessment, the FCA eCRF for new external openings should be completed.
  - PDAI subscale scores.
  - Perianal pain VAS.
- Study treatment administration:
  - Darvadstrocel administration. To be performed according to the surgery procedure manual. All setons must be withdrawn, fistula curettage should be performed, placing stitches to close each internal opening before treatment administration.
  - Number and location of fistula tracts treated.
- Assessment of AEs/SAEs, AESIs, including AEs concerning surgical procedures and postsurgery complication status (including any CD-related surgery), and SSRs.

At the end of treatment, subjects will be observed after their surgical procedure until full recovery, with special attention to signs and symptoms of potential allergic reactions.

Instructions for the immediate treatment of any acute anaphylaxis according to standard of care will be provided in the surgery procedure manual.

If there is any problem administering darvadstrocel at the administration visit, the visit should be rescheduled within a minimum of 2 weeks and to a maximum of 3 weeks from the date of the original Visit 0. It is not necessary to repeat the preparation visit, the setons will be maintained until the rescheduled repeat administration visit and will be withdrawn just before darvadstrocel administration. All procedures required for repeat administration visit are to be repeated.

### 9.3.5 Follow-up Period

Visits at Week 24 and Week 52 should be performed in person. Alternative methods of data collection may be considered for visits at Weeks 6, 12, and 36 when it is not possible for the subject to attend the study site (see Section 9.3.8).

#### *9.3.5.1 Week 6/Visit 1*

- Weight, height, and BMI.
- Physical examination covering all body systems.
- Vital signs.
- Concomitant medications taken since last visit.
- Concurrent medical conditions.
- Clinical laboratory tests (hematology, biochemistry, and urinalysis).
- Urine pregnancy test for WOCBP. A female subject is considered a WOCBP following menarche or aged ≥11 years, whichever is younger.
- Fistula clinical assessment in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
  - The FCA eCRF must be completed by the investigator. If a new external opening is identified during the assessment, the FCA eCRF for new external openings should be completed.
- PCDAI score.
  - ESR as part of the PCDAI assessment will be analyzed by a local laboratory.
- PDAI subscale scores.
- Perianal pain VAS.
- Assessment of AEs/SAEs, AESIs, and SSRs.

#### *9.3.5.2 Week 12/Visit 2*

- Weight, height, and BMI.

- Physical examination covering all body systems.
- Vital signs.
- Concomitant medications taken since last visit.
- Concurrent medical conditions.
- Urine pregnancy test for WOCBP.
- Fistula clinical assessment in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
  - The FCA eCRF must be completed by the investigator. If a new external opening is identified during the assessment, the FCA eCRF for new external openings should be completed.
- Assessment of AEs/SAEs, AESIs, and SSRs.

*9.3.5.3 Week 24/Visit 3*

- Weight, height, and BMI.
- Physical examination covering all body systems.
- Vital signs.
- Concomitant medications taken since last visit.
- Concurrent medical conditions.
- Clinical laboratory tests (hematology, biochemistry, and urinalysis).
- Urine pregnancy test for WOCBP.
- Fistula clinical assessment in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
  - The FCA eCRF must be completed by the investigator. If a new external opening is identified during the assessment, the FCA eCRF for new external openings should be completed.
- Fistula MRI assessment:
  - Pelvic MRI performed locally.
- Perianal pain VAS.
- PCDAI score.
  - ESR as part of the PCDAI assessment will be analyzed by a local laboratory.
- PDAI subscale scores.
- Assessment of AEs/SAEs, AESIs, and SSRs.

*9.3.5.4 Week 36/Visit 4*

- Weight, height, and BMI.
- Physical examination covering all body systems.
- Vital signs.
- Concomitant medications taken since last visit.
- Concurrent medical conditions.
- Urine pregnancy test for WOCBP.
- Fistula clinical assessment in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
  - The FCA eCRF must be completed by the investigator. If a new external opening is identified during the assessment, the FCA eCRF for new external openings should be completed.
- Assessment of AEs/SAEs, AESIs, and SSRs.

*9.3.5.5 Week 52/Visit 5 (End of Study Visit)*

- Weight, height, and BMI.
- Physical examination covering all body systems.
- Vital signs.
- Concomitant medications taken since last visit.
- Concurrent medical conditions.
- Clinical laboratory tests (hematology, biochemistry, and urinalysis).
- Urine pregnancy test for WOCBP.
- Fistula clinical assessment in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
  - The FCA eCRF must be completed by the investigator. If a new external opening is identified during the assessment, the FCA eCRF for new external openings should be completed.
- Perianal pain VAS.
- PCDAI score.
  - ESR as part of the PCDAI assessment will be analyzed by a local laboratory.
- PDAI subscale scores.
- Assessment of AEs/SAEs, AESIs, and SSRs.

### 9.3.6 Early Termination

The end of study visit will be performed at Week 52 or at the early termination visit. All efforts should be made to keep the subject in the study. If the subject decides to withdraw from the study, the following procedures will be performed and documented ±30 days of the early termination visit:

- Weight, height, and BMI.
- Physical examination covering all body systems.
- Vital signs.
- Concomitant medications taken since last visit.
- Concurrent medical conditions.
- Clinical laboratory tests (hematology, biochemistry, and urinalysis).
- Urine pregnancy test for WOCBP.
- Fistula clinical assessment in terms of drainage at the external opening(s) after gentle finger compression, anal pain, suspicion of perianal abscess (fistula identification).
  - The FCA eCRF must be completed by the investigator. If a new external opening is identified during the assessment, the FCA eCRF for new external openings should be completed.
- Fistula MRI assessment (only if the early termination visit takes place before the Week 24 visit).
  - Pelvic MRI performed locally.
- Perianal pain VAS.
- PCDAI score.
  - ESR as part of the PCDAI assessment will be analyzed by a local laboratory.
- PDAI subscale scores.
- Assessment of AEs/SAEs, AESIs, and SSRs.

For all subjects receiving study drug, the investigator must complete the end of study eCRF page.

### 9.3.7 Unscheduled Telephone Follow-up Calls

Unscheduled telephone-calls are proposed for safety follow-up for any contact requested by the subject between scheduled visits. The following information needs to be recorded:

- Unscheduled phone-call follow-up date and reason.
- Concomitant medications and procedures.

- Concurrent medical conditions.
- Remote evaluation of the fistula(s).
  - The items of the FCA form will be assessed by the investigator via telephone call.
- Review of PDAI and PCDAI questionnaires since last visit by the investigator.
- Assessment of AEs/SAEs, AESIs, and SSRs.

### 9.3.8 Remote Visit due to COVID-19

The following assessments are to be performed if the subject cannot attend any interim visits (Weeks 6, 12, and 36) due to COVID-19 restrictions:

- Date of remote visit.
- Concomitant medications and procedures.
- Concurrent medical conditions.
- Remote evaluation of the fistula(s): The items in the FCA form will be assessed by the investigator via telephone call.
- Review of PDAI and PCDAI questionnaires by the site investigator.
- Clinical laboratory tests (hematology, biochemistry, urinalysis). Tests will be performed at a local laboratory if possible.
- Urine pregnancy test for WOCBP: Test will be performed at a local laboratory if possible.
- Assessment of AEs/SAEs, AESIs, and SSRs.

# 10.0 ADVERSE EVENTS

## 10.1 Definitions

### 10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

### 10.1.2 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 AEs).
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- 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 an AE.

For the purpose of this study, drainage of the treated fistula and abscesses will not be captured as an AE unless there is evidence suggesting a causal relationship between the study drug or the administration procedure. New fistula(s) identified during the course of the study, that are not treated and evaluated by the study drug, will be captured as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) 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:

- Changes in laboratory values 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 re-test 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 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/pediatric assent) are considered concurrent medical conditions and should NOT be recorded as AEs. The first evaluations after signing of informed consent/pediatric assent (eg, laboratory tests, electrocardiogram, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition after informed consent/pediatric assent has been signed, the worsening or complication should be recorded appropriately as an AE. 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 (e.g. "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 an AE 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 condition (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/pediatric assent 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.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF. See Section 10.3.1 for reporting overdose to the Takeda Pharmacovigilance Department.

### 10.1.3 SAEs

An SAE is defined as any untoward medical occurrence in a subject who has signed informed consent/pediatric assent to participate in a study that:

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.

### 10.1.4 AEs of Special Interest

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 in order 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.

AESIs must be recorded as AEs in the eCRF.

See Section 10.2.1.3 for information on AESI reporting and a list of known AESIs.

### 10.1.5 Special Situation Reports

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

Definitions:

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

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

### 10.1.6 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

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

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

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

### 10.1.8 Relationship to Study Procedures

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

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

### 10.1.9 Start Date

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

### 10.1.10 Stop Date

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

### 10.1.11 Frequency

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

### 10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital

anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".

- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

## 10.2 Procedures

### 10.2.1 Collection and Reporting of AEs

#### *10.2.1.1 AE Collection Period*

Collection of AEs will commence from the time that the subject first signs informed consent/pediatric assent. Routine collection of AEs will continue until Visit 6 (Week 52) or the early termination visit.

#### *10.2.1.2 AE Reporting*

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious AE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious AEs that occur before the first exposure to study drug, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

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

1. Event term.
2. Start and stop date.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug.

6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

*10.2.1.3 AESIs*

AESIs should be recorded as AEs in the eCRF.

If the AESI occurs during the treatment period or follow-up period and is considered to meet the seriousness criteria listed in Section 10.2.2, the SAE form should be completed. The completed SAE form should be reported to the pharmacovigilance department of the sponsor or sponsor designee as listed in Section 1.1 within 24 hours of awareness. The investigator should submit the original copy of the SAE form to the sponsor.

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

AESI/abnormality criteria include:

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

### 10.2.2 Collection and Reporting of SAEs

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

SAEs should be reported via the SAE eCRF page in electronic data capture (EDC) (RAVE) by the investigator immediately or within 24 hours of awareness of the event. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.
- Investigator's name.
- Name of the study drug
- Causality assessment.

SAEs should be reported via the SAE eCRF page in electronic data capture (EDC) (RAVE), which is the preferred method of reporting SAEs.

If access to EDC/RAVE is not feasible within 24 hours of awareness of the event, the paper SAE forms should be submitted via fax or email to the attention of the contact listed in Section 1.1.

- In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day.

E-mail submission of SAE forms with a PDF attachment should only be used in the case where fax is not possible and EDC is not feasible within 24 hours of receiving the event.

- In case of e-mail, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day.

If SAEs are reported via fax or by email, EDC/RAVE must be updated as soon as possible with the appropriate information.

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

For any subject with ALT ≥3 × ULN **AND** total bilirubin >2 × ULN **OR** INR >1.5 × ULN for which an alternative etiology has not been found, report the event as an SAE, contact the sponsor's medical monitor within 24 hours immediately and follow the additional monitoring,

## 10.3 Follow-up of SAEs

If information that was not available at the time of the initial report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation. This form should be faxed or emailed 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 Collecting and Reporting of SSRs

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

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

### 10.3.2 Collecting and Reporting of Pregnancies

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

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

### 10.3.3 Summary of Safety Reporting

| Safety Event | How to Report Event to Sponsor Pharmacovigilance | Reporting Timeline to Sponsor (From Time of Awareness) |
|---|---|---|
| SAE | Complete eCRF page in EDC to Sponsor Pharmacovigilance.<br>Use the paper SAE form only if EDC is not available. | Within 24 hours |
| AESI | Complete AE eCRF for all AESIs.<br>Submit the SAE form to Sponsor if AESI meets seriousness criteria in Section 10.2.2. | Within 24 hours |
| Pregnancy | Complete and submit paper pregnancy form. | Within 24 hours |
| SSR | Complete and submit paper SSR form. If the SSR is associated with an SAE, a separate SAE form must also be submitted to the sponsor. | Within 7 calendar days<br>SSR associated with SAE: report within 24 hours of awareness |

AE: adverse event; AESI: adverse event of special interest; eCRF: electronic case report form; EDC: electronic data capture; SAE: serious adverse event; SSR: special situation report.

Contacts for SAE, pregnancy, and SSR reporting can be found in Section 1.1.

### 10.3.4 Safety Reporting to Investigators, IRBs, IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions and any other applicable SAEs to regulatory authorities, including the EMA, investigators and IRBs/the head of the study site 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, suspected unexpected serious adverse reactions will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor

supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the study. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

## 11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data and safety monitoring board (DSMB), or clinical endpoint committee will be used in this study.

A DSMB is not planned for this open-label study, given the safety data available from adult studies and the tolerability of darvadstrocel for the single administration. Takeda's standards and processes, which include continuous review and evaluation of safety data reported from all participating sites through the conduct of the study, are appropriate for the ongoing monitoring of subject safety and data integrity. The decision to convene a DSMB could be made at any time during the conduct of study.

## 12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions 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/pediatric assent.

The sponsor or its designee will supply study 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. eCRFs must be completed in English, if needed. Data are transcribed directly onto 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 Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

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

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the 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 informed consent/pediatric assent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent/pediatric assent forms), 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, International Conference for Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the 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 study SAP will be prepared and finalized prior to database lock. The final analysis for this study will be performed after database lock, which will occur when all subjects have completed the Week 52 visit.

### 13.1.1 Analysis Sets

The following analysis sets will be defined:

- Intent-to-treat (ITT) analysis set: Includes all subjects who undergo the fistula preparation procedure regardless of being treated or not.

[redacted]

- Safety analysis set: Includes all subjects who received the study treatment.

The main population for the primary and secondary efficacy analysis will be the ITT analysis set.

### 13.1.2 Analysis of Demographics and Other Baseline Characteristics

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

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

### 13.1.3 Efficacy Analysis

The analyses the primary and secondary endpoints will be performed on the ITT [redacted], with the ITT as the primary analysis set.

#### *13.1.3.1 Primary Efficacy Analysis*

The primary efficacy endpoint will be summarized at Week 24. The proportion of subjects who achieve combined remission at Week 24 along with 95% 2-sided Clopper-Pearson CIs will be provided at Week 24.

[redacted]

*13.1.3.2 Secondary Efficacy Endpoints*

The proportion of subjects along with 2-sided 95% Clopper-Pearson CIs will be provided by visit for the following proportion-based efficacy endpoints:

- Clinical remission at Weeks 24 and 52.
- Clinical response at Weeks 24 and 52.
- Relapse by Week 52 in subjects who achieve combined remission at Week 24.

[redacted]

Time-to-event variables will be assessed [redacted]

Subjects without documented time-to-event of interest by the end of study (Week 52), will be censored at the date of last assessment. [redacted]

*13.1.3.3* [redacted]

[redacted]

### 13.1.4 Safety Analysis

Safety analysis will be performed on the safety analysis set.

Counts and percentages for subjects with treatment emergent AEs, SAEs (defined as any SAE, regardless of relationship to study drug), and AESIs (immunogenicity/alloimmune reactions, hypersensitivity, ectopic tissue formation, medication errors, tumorigenicity, and transmission of infectious agents) will be summarized descriptively by System Organ Class and Preferred Term using MedDRA terminology. [redacted] Change from baseline in vital signs will also be summarized.

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

### 13.1.5 Exploratory Analyses

The following continuous endpoints will be summarized using descriptive statistics: changes in PDAI discharge and pain subscale scores, PCDAI score, and perianal pain VAS.

## 13.2 Interim Analysis and Criteria for Early Termination

An interim analysis (IA) will be conducted to evaluate the safety and efficacy of darvadstrocel. The IA will include safety and efficacy endpoints in enrolled subjects.

Additional details of the IA will be provided in the SAP.

## 13.3 CCI

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# 14.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 14.1 Study-Site Monitoring

Monitoring will be completed 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 and the study site guarantee access to source documents by the sponsor or its designee (clinical research organization) 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 (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent/pediatric assent documentation, documentation of subject authorization to use personal health information, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during monitoring and that sufficient time is devoted to the process.

## 14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

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 EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

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

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

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

### 14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the 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 and study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

## 15.0 ETHICAL ASPECTS OF THE STUDY

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

### 15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local 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. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services (for studies including TDC Americas).

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 investigator's brochure, a copy of the informed consent/pediatric assent form, 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/pediatric assent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent/pediatric assent form) reviewed; and state the approval date. The sponsor will ship drug 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.

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 informed consent/pediatric assent form, 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/pediatric assent 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 informed consent/pediatric assent form, 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 informed consent/pediatric assent form 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/pediatric assent is given. The informed consent/pediatric assent form 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 informed consent/pediatric assent form and if applicable, the subject authorization form. The informed consent/pediatric assent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent/pediatric assent form, 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 informed consent/pediatric assent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject and to the subject's parent or legal representative. 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/pediatric assent, 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 informed consent/pediatric assent form 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 informed consent/pediatric assent form and subject authorization (if applicable) at the time of consent and before the 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 informed consent/pediatric assent form, 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/pediatric assent in the subject's medical record. Copies of the signed informed consent/pediatric assent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) will be given to the subject.

All revised informed consent/pediatric assent forms 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/pediatric assent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject will receive a copy of the revised informed consent/pediatric assent form.

### 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, and subject initials 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, Food and Drug Administration, 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, 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/pediatric assent 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).

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

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

## 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.

### 15.4.2 Clinical Trial Registration

In order 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.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

### 15.4.3 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.

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## Appendix A Schedule of Study Procedures

| Visit (Week) | Screening Visit (-4 to -5 weeks) [a] | Preparation Visit (-2 to -3 weeks) [b] | V0 | V1 (W6) [r] | V2 (W12) [r] | V3 (W24) | V4 (W36) [r] | V5 (W52) End of Study | Unscheduled Phone Call Follow-up [q] | Early Termination |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (Window)** | **NA** | **NA** | **D0** | **D42 (±8)** | **D84 (±8)** | **D168 (±8)** | **D252 (±15)** | **D364 (±15)** | | **NA (±15)** |
| Enrollment | | X | | | | | | | | |
| ICF/pediatric assent | X | | | | | | | | | |
| Inclusion/exclusion criteria check | X | X | | | | | | | | |
| Demographics, medical and surgical history | X | | | | | | | | | |
| Weight, height, and BMI | X | X | X | X | X | X | X | X | | X |
| Physical examination | X | X | X | X | X | X | X | X | | X |
| Vital signs [c] | X | X | X | X | X | X | X | X | | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Concurrent medical conditions | X | X | X | X | X | X | X | X | X | X |
| CD, fistula, and treatment history [d] | X | | | | | | | | | |
| Target fistula(s) information (new fistula or previously treated fistula) [e] | X | | | | | | | | | |
| Hematology & biochemistry [f] | X | | | X | | X | | X | | X |
| Urinalysis [f] | X | | | X | | X | | X | | X |
| Serum pregnancy | X | | | | | | | | | |
| Urine pregnancy [g] | | X | X | X | X | X | X | X | | X |
| Fistula clinical assessment | X [h] | X | X | X | X | X | X | X | | X |
| Remote fistula clinical assessment | | | | | | | | | X | |
| Fistula MRI assessment [j] | X | | | | | X | | | | X [i] |
| Fistula preparation [k] | | X | | | | | | | | |
| Perianal pain VAS [l] | X | | X | X | | X | | X | X | X |
| PCDAI score [m] | X | | | X | | X | | X | X | X |

| Visit (Week) | Screening Visit (-4 to -5 weeks) [a] | Preparation Visit (-2 to -3 weeks) [b] | V0 | V1 (W6) [r] | V2 (W12) [r] | V3 (W24) | V4 (W36) [r] | V5 (W52) End of Study | Unscheduled Phone Call Follow-up [q] | Early Termination |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (Window)** | **NA** | **NA** | **D0** | **D42 (±8)** | **D84 (±8)** | **D168 (±8)** | **D252 (±15)** | **D364 (±15)** | | **NA (±15)** |
| PDAI subscores [n] | X | | X | X | | X | | X | X | X |
| Luminal disease activity involving the rectum [o] | X | | | | | | | | | |
| Treatment administration [p] | | | X | | | | | | | |
| Number and location of fistula tracts treated | | | X | | | | | | | |
| Assessment of AEs/SAEs/AESIs/SSRs | X | X | X | X | X | X | X | X | X | X |

AE: adverse event; AESI: adverse event of special interest; ALT; alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CD: Crohn's disease; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; D: day; eCRF: electronic case report form; ESR: erythrocyte sedimentation rate; ICF: informed consent form; MCH; mean corpuscular hemoglobin; MCHC; mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MRI: magnetic resonance imaging; NA: not applicable; PCDAI: Pediatric Crohn's Disease Activity Index; PDAI: Perianal Disease Activity Index; SAE: serious adverse event; SSR: special situation report; ULN: upper limit of normal; V: visit; VAS: visual analog scale; W: week.

[a] The screening visit will take place within a minimum of 4 weeks and a maximum of 5 weeks of the preparation visit. For any subject not meeting the eligibility criteria, or if there are unavoidable circumstances such as the COVID-19 pandemic, it may be possible to rescreen the subject if they later meet the criteria and based upon the sponsor's approval. The procedures listed in Section 9.3.2 will need to be repeated and the preparation visit rescheduled based on the protocol timelines.

[b] From the preparation visit to the treatment administration visit (Visit 0) there will be a minimum of 2 weeks and a maximum of 3 weeks (necessary to have darvadstrocel treatment ready for administration). Once the date for treatment administration surgery is set it cannot be moved due to the darvadstrocel preparation procedure and the limited window of manufacturing, shipment and study drug viability.

[c] Temperature, heart rate, and blood pressure will be recorded.

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

[e] Clinical characteristics including age of onset, number of other fistulas, localization, and clock position (Appendix C).

[f] Refer to Section 9.1.9 for clinical laboratory parameters.

[g] If the urine pregnancy test is positive, a serum pregnancy test will also be performed.

[h] Fistula must have been draining for at least 6 weeks before the screening visit.

[i] An MRI will be performed at the early termination visit only if this visit occurs before the Week 24 visit.

[j] A pelvic MRI will be performed at baseline (screening visit), Week 24, and early termination visit. An MRI will be obtained at the early termination visit only if the early termination visit occurs before Week 24. See Section 9.1.6.2 and the MRI manual for further details.

| Visit (Week) | Screening Visit (-4 to -5 weeks) [a] | Preparation Visit (-2 to -3 weeks) [b] | V0 | V1 (W6) [r] | V2 (W12) [r] | V3 (W24) | V4 (W36) [r] | V5 (W52) End of Study | Unscheduled Phone Call Follow-up [q] | Early Termination |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (Window)** | **NA** | **NA** | **D0** | **D42 (±8)** | **D84 (±8)** | **D168 (±8)** | **D252 (±15)** | **D364 (±15)** | | **NA (±15)** |

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

[l] The screening perianal pain VAS will be recorded daily by the subjects at home for a 2-week (14-day) period starting within 7 days after the screening visit. For all other visits, perianal pain VAS will be recorded daily by the subjects at home for 2 weeks (14 days) before each visit.

[m] ESR as part of the PCDAI assessment will be analyzed by a local laboratory.

[n] Change in subscale scores for discharge and pain domains.

[o] Luminal disease activity involving the rectum, as determined by the presence or absence of proctitis as measured by colonoscopy, flexible sigmoidoscopy or rectoscopy performed within 6 months of the screening visit showing absence of rectal ulcers larger than 0.5 cm. A colonoscopy or rectoscopy will need to be performed at screening if the subject has not had one within the last 6 months of screening.

[p] All study procedures should be performed before darvadstrocel administration. Darvadstrocel administration is to be performed according to the surgery procedure manual. If there is any problem administering darvadstrocel on the day of administration, the visit should be rescheduled within a minimum of 2 weeks and a maximum of 3 weeks of Visit 0. It is not necessary to repeat the preparation visit, the setons will be maintained until the rescheduled treatment visit and will be withdrawn just before darvadstrocel administration. All procedures which take place on the day of darvadstrocel administration are to be repeated. If the surgeon is unable to inject the full dose of darvadstrocel (120 million cells [24 mL]) due to resistance at the injection site, the adjusted dose (mL) will be recorded in the eCRF and the subject will be able to continue in the study.

[q] Unscheduled phone-calls are proposed for safety follow-up for any contact requested by the subject between scheduled visits.

[r] The assessments listed in Section 9.3.8 are to be performed if the subject cannot attend any interim visits (Weeks 6, 12, and 36) due to COVID restrictions.

## Appendix B Blood Volume Table

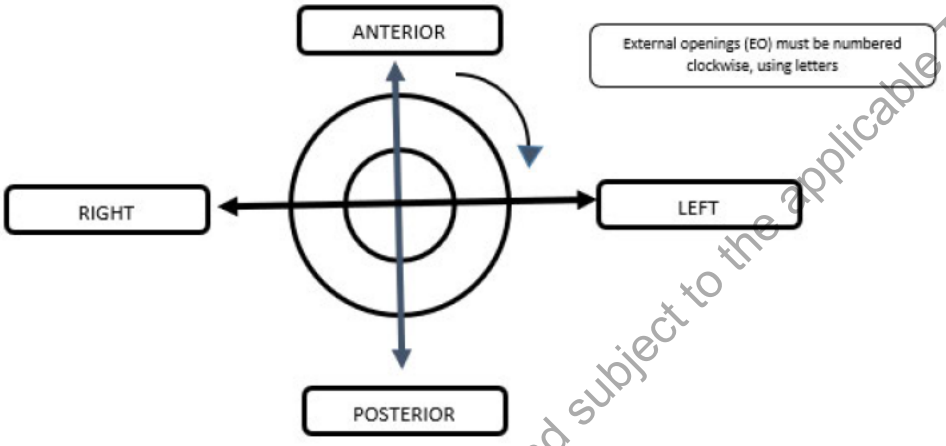
| Sample Type | Sample Volume (ml) | Number of Samples | | | | | | | | | | Total Volume (ml) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Screening Visit (up to 5 weeks) | Preparation Visit (≥2 weeks to ≤3 weeks) | Day 0 | Week 6 | Week 12 | Week 24 | Week 36 | Week 52 | Unscheduled Phone Call Follow-up | Early Termination | |
| | | | | Visit 0 | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | | | |
| Clinical laboratory tests [a] | 7.5 | X | | | X | | X | | X | | X | **30** |
| **Total Approximate Blood Sampling Volume (ml)** | | | | | | | | | | | | **30** |

[a] Hematology and biochemistry.

## Appendix C Anal Clock

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

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




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

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

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

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

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

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

**Investigator Name** _____

**Signature:** _____

## Appendix D Guidance on Liver Test Abnormality Monitoring, Evaluation, and Follow-up

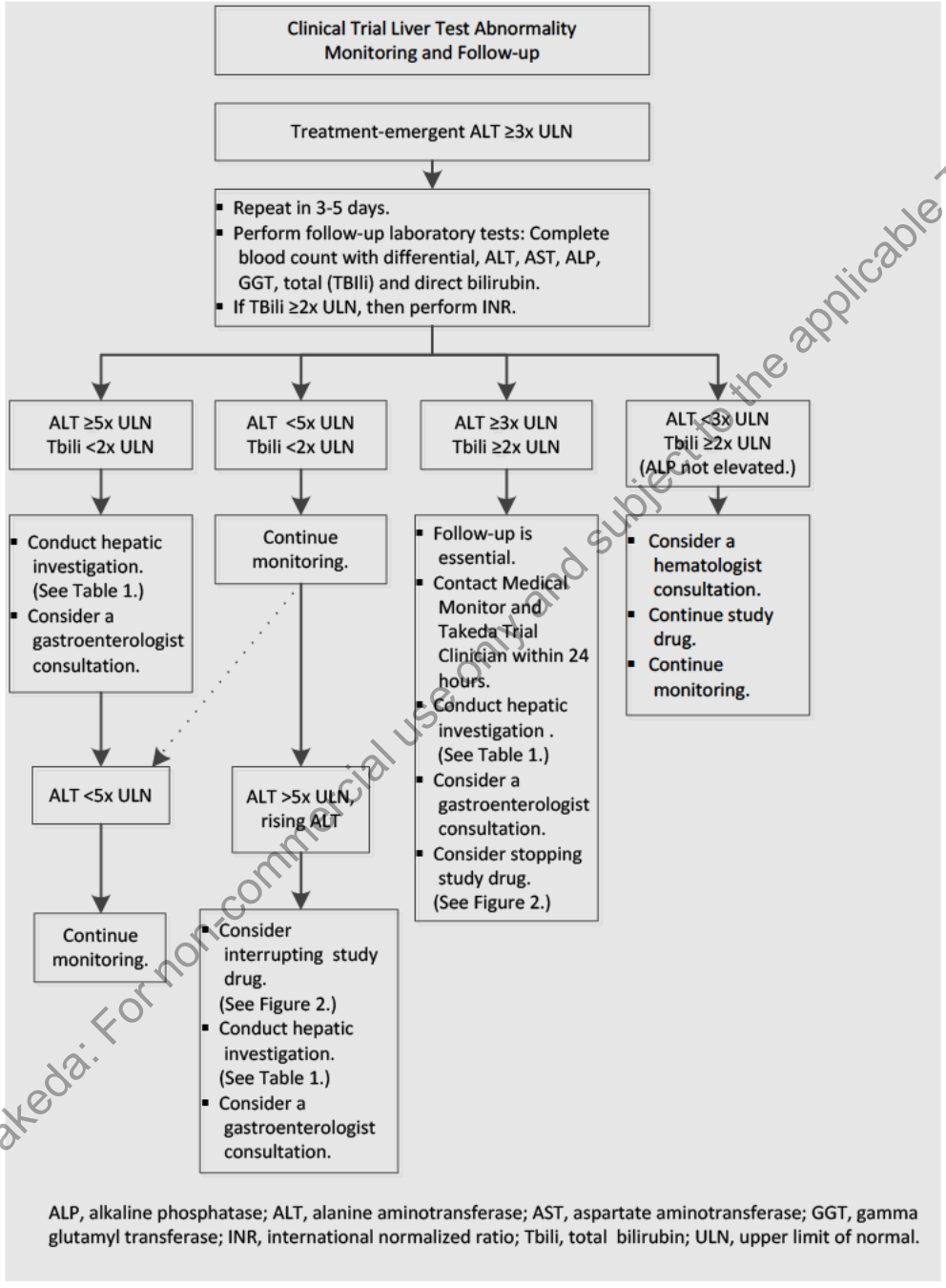
Investigators must be vigilant for abnormal liver test results in subjects during the clinical study. Transient fluctuations in serum aminotransferases occur commonly in clinical study subjects, but it is crucial that the investigator identifies and evaluates subjects with possible hepatic injury. This guidance is intended to aid investigations of abnormal liver tests in clinical study subjects who had no known liver disease and had either normal or near normal baseline liver test results (ie, ALT <2 × ULN, total bilirubin <1.5 × ULN, and alkaline phosphatase <1.5 × ULN) at the time of enrollment).

In evaluating study subjects with abnormal liver test results, the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the subject. If the abnormal liver test results are confirmed, then the subject should be monitored and, if necessary, additional diagnostic tests should be performed as shown in Figure 1. Suggested hepatic investigations are listed in Table 1. Criteria for considering discontinuation of study drug are shown in Figure 2.

### Subjects with Combined Elevations in Aminotransferase and Bilirubin

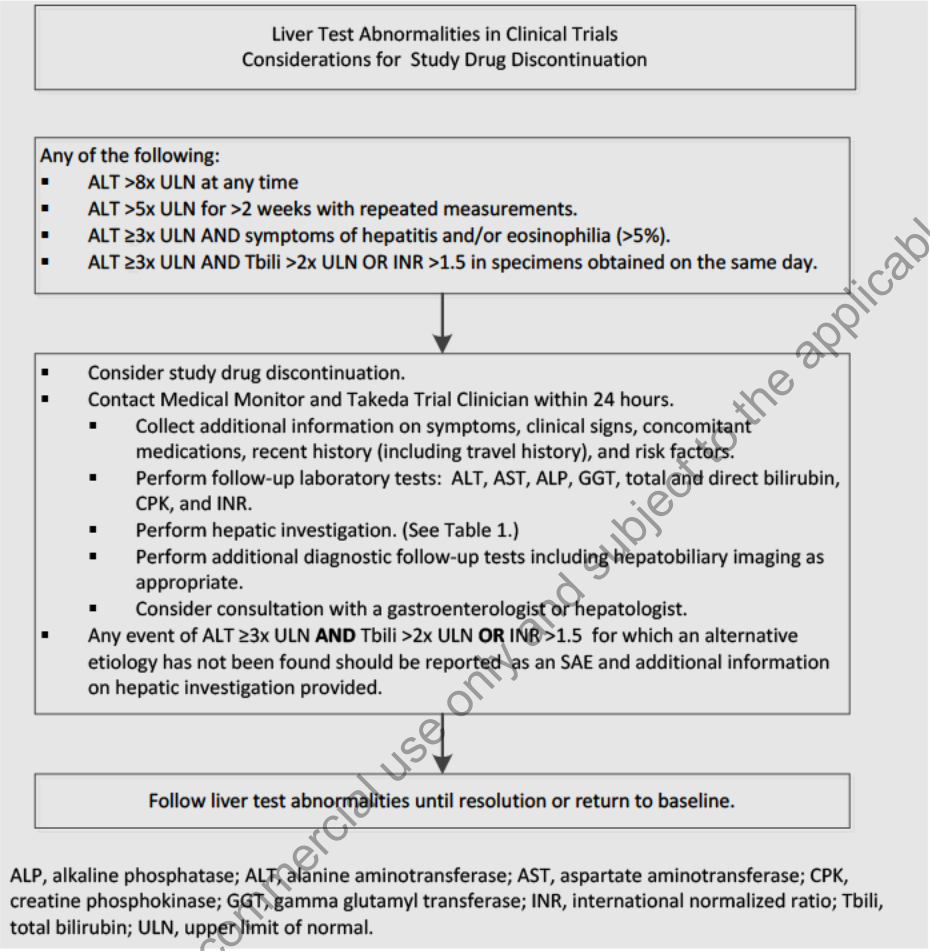
If a subject has elevated ALT ≥3 × ULN with concurrent elevated total bilirubin >2 × ULN ***or*** elevated INR >1.5, the investigator must contact the sponsor's medical monitor within 24 hours. Hepatic investigations as suggested in Table 1 should be initiated. Any event of elevated ALT ≥3 × ULN with concurrent elevated total bilirubin >2 × ULN ***or*** elevated INR >1.5 for which an alternative etiology has not been identified must be reported as an SAE.

**Figure 1 Liver Test Abnormality Monitoring and Follow-up**




ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin; ULN, upper limit of normal.

**Figure 2 Liver Test Abnormalities: Considerations for Study Drug Discontinuation**




ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin; ULN, upper limit of normal.

## Table 1 Hepatic Investigation

| | |
|---|---|
| Medical history | • Concomitant medications (including over-the-counter medications, such as acetaminophen, and herbal supplements).<br>• Medical conditions (eg, ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis).<br>• Alcohol intake.<br>• Hepatobiliary disorder.<br>• Previous liver disease or metabolic syndrome (eg, obesity, insulin resistance, diabetes, or dyslipidemia).<br>• Travel history. |
| Physical examination (symptoms, signs, and laboratory results) | • General malaise, fatigue, nausea, or vomiting.<br>• Right upper quadrant pain or tenderness, fever, jaundice, rash.<br>• Eosinophilia >5%. |
| Hepatic/hepatobiliary imaging | Perform as appropriate (eg, abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging). |
| Viral hepatitis serology | • Hepatitis A antibody (total and IgM).<br>• Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (IgM anti-HBc), hepatitis C antibodies (anti-HCV).<br>• Hepatitis E (IgG and IgM).<br>• Consider polymerase chain reaction for hepatitis B, C, and E.<br>• Consider Epstein-Barr virus serology (viral capsid antigen [VCA] nuclear antigen [EBNA], early antigen [EA]).<br>• Consider cytomegalovirus serology (IgG and IgM). |
| Autoimmune hepatitis serology | • Antinuclear antibody (ANA).<br>• Antismooth muscle antibody (ASMA).<br>• Anti–liver-kidney microsomal antibody (anti-LKM). |

## Appendix E PDAI

| Categories affected by fistulas | Score |
|---|---|
| Discharge | |
| No discharge | 0 |
| Minimal mucous discharge | 1 |
| Moderate mucous or purulent discharge | 2 |
| Substantial discharge | 3 |
| Gross fecal soiling | 4 |
| Pain/restriction of activities | |
| No activity restriction | 0 |
| Mild discomfort, no restriction | 1 |
| Moderate discomfort, some limitation activities | 2 |
| Marked discomfort, marked limitation | 3 |
| Severe pain, severe limitation | 4 |
| Restriction of sexual activity | |
| No restriction in sexual activity | 0 |
| Slight restriction in sexual activity | 1 |
| Moderate limitation in sexual activity | 2 |
| Marked limitation in sexual activity | 3 |
| Unable to engage in sexual activity | 4 |
| Type of perianal disease | |
| No perianal disease/skin tags | 0 |
| Anal fissure or mucosal tear | 1 |
| <3 Perianal fistulae | 2 |
| ≥3 Perianal fistulae | 3 |
| Anal sphincter ulceration or fistulae with significant undermining of skin | 4 |
| Degree of induration | |
| No induration | 0 |
| Minimal induration | 1 |
| Moderate induration | 2 |
| Substantial induration | 3 |
| Gross fluctuance/abscess | 4 |

Source: Irvine E.J, 1999 (Irvine 1999).

# Appendix F PCDAI

**Table 4. PCDAI[11]**

| History (Recall, 1 week) | | | |
|---|---|---|---|
| **Abdominal Pain** | | | **Score** |
| **0** = None | **5** = Mild: Brief, does not interfere with activities | **10** = Moderate/ Severe: Daily, longer lasting, affects activities, nocturnal | |
| **Patient Functioning, General Well-Being** | | | **Score** |
| **0** = No limitation of activities, well | **5** = Occasional difficulty in maintaining age-appropriate activities, below par | **10** = Frequent limitation of activity, very poor | |
| **Stools (per day)** | | | **Score** |
| **0** = 0-1 liquid stools, no blood | **5** = Up to 2 semiformed with small blood, or 2-5 liquid | **10** = Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea | |

| Laboratory | | | | | | |
|---|---|---|---|---|---|---|
| **HCT** | | | | | | **Score** |
| < 10 years (Male and Female): | | | 11-14 years (Male): | | | |
| **0** = > 33% | **2.5** = 28%-32% | **5**= <28% | **0** = ≥ 35% | **2.5** = 30%-34% | **5**=<30% | |
| 11-19 years (Female): | | | 15-19 years (Male): | | | |
| **0** = ≥ 34% | **2.5** = 29%-33% | **5**= <29% | **0** = ≥ 37% | **2.5** = 32%-36% | **5**=<32% | |
| **ESR** | | | | | | **Score** |
| **0** = < 20 mm/hr | **2.5** = 20-50 mm/hr | | **5** = > 50 mm/hr | | | |
| **Albumin** | | | | | | **Score** |
| **0** = ≥ 3.5 g/dL | **5** = 3.1-3.4 g/dL | | **10** = ≤ 3.0 g/dL | | | |

| Examination | | | |
|---|---|---|---|
| **Weight** | | | **Score** |
| **0** = Weight gain or voluntary weight stable/loss | **5** = Involuntary weight stable, weight loss 1%-9% | **10** = Weight loss ≥ 10% | |
| **Height at Diagnosis** | | | **Score** |
| **0** = < 1 channel decrease | **5** = ≥ 1, < 2 channel decrease | **10** = > 2 channel decrease | |
| **Height at Follow-Up** | | | **Score** |
| 0 = Height velocity ≥ -1 SD | **5** = Height velocity < -1 SD, > -2 SD | **10** = Height velocity ≤ -2 SD | |
| **Abdomen** | | | **Score** |
| **0** = No tenderness, no mass | **5** = Tenderness or mass without tenderness | **10** = Tenderness, involuntary guarding, definite mass | |
| **Perirectal Disease** | | | **Score** |
| **0** = None, asymptomatic tags | **5** = 1-2 indolent fistula, scant drainage, no tenderness | **10** = Active fistula, drainage, tenderness, or abscess | |
| **Extraintestinal Manifestations** | | | **Score** |
| (Fever ≥ 38.5°C for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*) | | | |
| **0** = None | **5** = 1 | **10** = ≥ 2 | |
| | | **Total Score:** | |

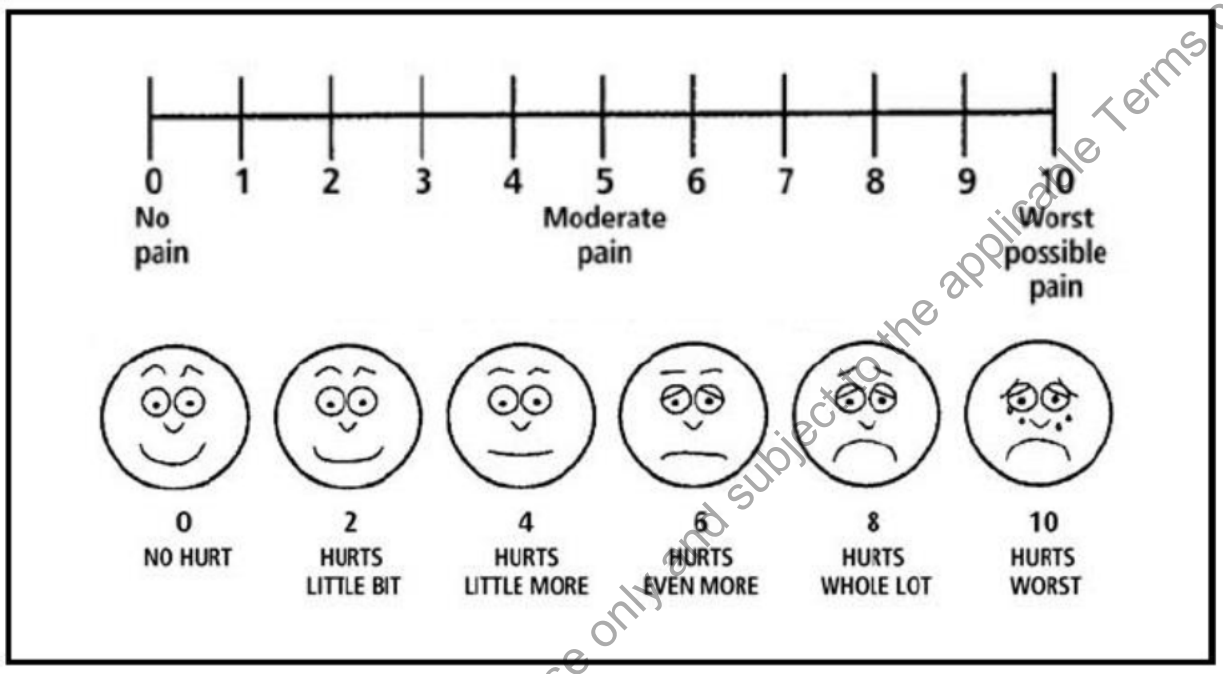
| Score | Decoding |
|---|---|
| ≤ 10 | Inactive disease |
| 11-30 | mild disease |
| > 30 | Moderate-to-severe disease |
| A decrease of 12.5 | Evidence of improvement |

Gastroenterology. 1999 Mar;116(3):527-31.

J Pediatr Gastroenterol Nutr, 2005 Oct;41(4):416-21.

Am J Gastroenterol. 2010 Sep;105(9):2085-92.

## Appendix G Perianal Pain VAS




Source: C.L. Baeyer, 2006 (von Baeyer 2006), D.S. Tsze et al, 2013 (Tsze et al. 2013).

## Appendix H 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, prior to 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/pediatric assent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent/pediatric assent from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent/pediatric assent is the most current version approved by the IRB/IEC. Each informed consent/pediatric assent form 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 informed consent/pediatric assent form 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. *This responsibility lies on the appropriate individual, designated by the site in Japan.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

## Appendix I Elements of the Subject Informed Consent/Pediatric Assent

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

## Appendix J Investigator Consent to Use of Personal Information

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

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

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

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

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

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

## Appendix K Protocol History

### Amendment History:

| Date | Amendment Number | Region |
|---|---|---|
| 22 May 2024 | Amendment 3 | Global |
| 12 February 2024 | Amendment 2 | Global |
| 01 February 2021 | Amendment 1 | Global |
| 24 June 2020 | Initial protocol | Global |

### Protocol Amendment 2 Summary and Rationale:

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

- Revise the age of subject eligibility to 4 to <18 years at the time of study treatment administration.
- Update the protocol to align with the guidelines and requirements of the European Union Clinical Trials Regulations (EU CTR).

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

| **Protocol Amendment 2** | | | |
|---|---|---|---|
| **Summary of Changes Since the Last Version of the Approved Protocol** | | | |
| **Change Number** | **Sections Affected by Change** | **Description of Each Change and Rationale** | |
| | ***Location*** | ***Description*** | ***Rationale*** |
| 1. | Title page<br>Section 2.0 STUDY SUMARY | Replaced EudraCT number with Abbreviated EU CT number. | To comply with new European Union Clinical Trials Regulations (EU CTR) guidelines and requirements. |
| 2. | Section 2.0 STUDY SUMMARY<br>Section 7.1 Inclusion Criteria, inclusion criterion 3 | Revised inclusion criterion to require subjects to be aged 4 to <18 years at the time of study treatment administration. | To align with pediatric age limits in the EU, United Kingdom, and Japan. |
| 3. | Section 2.0 STUDY SUMMARY<br>Section 5.2.2 Secondary Endpoints | Removed the phrase "incidence of" from the safety endpoints of adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs). | To update the endpoint language for consistency with other studies in the darvadstrocel program. |

| **Protocol Amendment 2** | | | |
|---|---|---|---|
| **Summary of Changes Since the Last Version of the Approved Protocol** | | | |
| **Change Number** | **Sections Affected by Change** | **Description of Each Change and Rationale** | |
| | ***Location*** | ***Description*** | ***Rationale*** |
| 4. | Section 2.0 STUDY SUMMARY | Added new section in the Study Summary to include the description of the benefit-risk profile present in Section 4.3. | To comply with new EU CTR guidelines and requirements. |
| 5. | Section 2.0 STUDY SUMMARY<br>Section 13.1.4 Safety Analysis | Corrected the list of AESIs in the description of planned safety analyses. | Correction. |
| 6. | Section 4.2 Rationale for the Proposed Study | Updated information on study status and results from Studies Darvadstrocel-3002 and Cx601-0303. | To provide updated background information on clinical studies of darvadstrocel in adults. |
| 7. | Section 4.3 Benefit-Risk Profile | Updated the section with safety details. | To update the language with details on the known adverse drug reactions since the previous version of the protocol. |
| 8. | Section 5.2.3 Exploratory Endpoint | Removed "at Week 24 and Week 52" from the first 2 exploratory endpoints. | To ensure consistency across the exploratory endpoints and to reflect that analysis of change from baseline will be conducted for all visits at which the assessments are performed (ie, Week 6, Week 24, and Week 52). |
| 9. | Section 6.2 Justification for Study Design, Dose, and Endpoints | Updated text to reflect that Studies Darvadstrocel-3002 and Cx601-0303 are completed. | To update justification for study design with current study status information. |
| 10. | Section 6.3 Definition of Study Start<br>Section 6.4 Definition of End of Study | Added new sections to include definitions of study start and end of study. | To comply with new EU CTR guidelines and requirements. |
| 11. | Section 8.1.1.1 Darvardstrocel | Removed "sterile" and "clear" from the description of darvadstrocel drug product. | Correction. |
| 12. | Section 8.1.1.3 Sponsor-Supplied Drug | Added new table with details of the study medication. | To comply with new EU CTR guidelines and requirements. |

| **Protocol Amendment 2** | | | |
|---|---|---|---|
| **Summary of Changes Since the Last Version of the Approved Protocol** | | | |
| **Change Number** | **Sections Affected by Change** | **Description of Each Change and Rationale** | |
| | ***Location*** | ***Description*** | ***Rationale*** |
| 13. | Section 8.1.4 Overdose | Added details for overdose to be reported in the electronic case report form (eCRF) as a medication error and reported to safety on a paper special situation report (SSR) form. | To align with new EU CTR guidelines. |
| 14. | Section 8.4 Continued Access to Study Drug After the End of the Study | Added new section to state that no aftercare is planned for this study and that the subject should be returned to the care of a physician and standard therapies as required. | To align with new EU CTR guidelines requiring clarification of whether participation in the study will lead to requirements for additional care after the study, or care that differs from that normally expected for their medical condition. |
| 15. | Section 9.1.11 Pregnancy | Removed details of pregnancy reporting and added reference to the new location of these details in newly added Section 10.3.2. | To consolidate the description of procedures for reporting pregnancies in the study. |
| 16. | Section 9.1.15.2 Patient-Reported Outcomes<br>Appendix A Schedule of Study Procedures, new footnote l | Added clarification that the perianal pain visual analog scale at the screening visit should be collected by the subjects at home for 2 weeks (14 days) starting within 7 days after the screening visit. | Clarification |
| 17. | Section 9.3 Schedule of Observations and Procedures<br>Appendix A Schedule of Study Procedures | Added assessment of SSRs to all study visits. | To comply with new EU CTR guidelines and requirements. |
| 18. | Section 10.1.4 AEs of Special Interest<br>Section 10.2.1.3 AESIs | Removed statement regarding an AESI evaluation form. | To comply with new EU CTR guidelines and requirements. |
| 19. | Section 10.1.5 Special Situation Reports | Added new section to define SSRs. | To comply with new EU CTR guidelines and requirements. |
| 20. | Section 10.2.1.3 AESIs | Added a statement for a medication error to be both captured as an AESI and reported as an SSR. | To clarify how to handle reports of medications errors defined as an AESI as well as an SSR. |

| Protocol Amendment 2 | | | |
|---|---|---|---|
| **Summary of Changes Since the Last Version of the Approved Protocol** | | | |
| **Change Number** | **Sections Affected by Change** | **Description of Each Change and Rationale** | |
| | ***Location*** | ***Description*** | ***Rationale*** |
| 21. | Section 10.2.2 Collection and Reporting of SAEs | Clarified that SAEs should be reported via the SAE eCRF page in electronic data capture.<br>Updated the SAE reporting to start from "awareness" instead of "first onset or notification." | To clarify the procedures for SAE reporting. |
| 22. | Section 10.3.1 Collection and Reporting of SSRs | Added new section with details about SSR reporting. | To comply with new EU CTR guidelines and requirements. |
| 23. | Section 10.3.2 Collection and Reporting of Pregnancies | Added new section with details about pregnancy reporting. | To comply with new EU CTR guidelines and requirements. |
| 24. | Section 10.3.3 Summary of Safety Reporting | Added new section summarizing safety reporting timelines and methods. | To comply with new EU CTR guidelines and requirements. |
| 25. | Section 14.2 Protocol Deviations | Updated section to include information on reporting requirements in the event of any serious breach of EU CTR regulations. | To comply with new EU CTR guidelines and requirements. |
| 26. | Section 15.3 Subject Confidentiality | Updated section to include information on reporting requirements in the event of a serious breach of personal data. | To comply with new EU CTR guidelines and requirements. |



## Protocol Amendment 1 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 1. The primary reasons for this amendment are to:

- Remove magnetic resonance imaging (MRI) contrast due to the risks associated in the pediatric population.
- Remove anesthesia for MRI due to the risks associated in the pediatric population.
- Inclusion of erythrocyte sedimentation rate (ESR) as part of the clinical laboratory tests in order to complete the Pediatric Crohn's Disease Activity Index (PCDAI) assessment.
- Provide improved clarity to the eligibility criteria and study assessments.

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 1** | | | |
|---|---|---|---|
| **Summary of Changes Since the Last Version of the Approved Protocol** | | | |
| **Change Number** | **Sections Affected by Change** | **Description of Each Change and Rationale** | |
| | ***Location*** | ***Description*** | ***Rationale*** |
| 1. | Section 4.2 Rationale for the Proposed Study | Update to the number of subjects who have received double-blind treatment in the Cx601-0303 study. | To be in line with recent update to the Cx601 Investigator's Brochure. |
| 2. | Section 6.0 Study Design and Description, Figure 6.a<br>Section 9.3.4 Treatment Administration Visit (Week 0/Visit 0)<br>Section 2.0 STUDY SUMMARY<br>Appendix A Schedule of Study Procedures | Editorial updates to align the study schematic with Appendix A and to include details on the timing of the screening visit in relation to the preparation visit and study drug administration. | For improved clarity on the timing for study drug administration. |
| 3. | Section 7.1 Inclusion Criteria<br>Section 7.2 Exclusion Criteria<br>Section 2.0 STUDY SUMMARY<br>Appendix A Schedule of Study Procedures | Update to inclusion criterion 6.<br>Update to exclusion criterion 27. | The use of magnetic resonance imaging (MRI) contrast has been removed in recognition of the risks associated with the pediatric population. In addition, updates have been made to clarify assessments to be assessed by MRI or by clinical examination. |
| 4. | Section 7.3 Excluded Medications and Treatments<br>Table 7.a | Update to allowed/excluded medications and treatments table. | Anesthesia/sedation during MRI is not allowed in the study in consideration of the safety risk associated with anesthesia in the pediatric population. |
| 5. | Section 8.1.3 Dose and Regimen<br>Section 8.1.4 Overdose | Editorial updates to dose administration. | Since the drug is administered by the investigator/surgeon, the text has been updated to reflect this. |
| 6. | Section 8.3 Accountability and Destruction of Sponsor-Supplied Drugs | Editorial updates to correctly reflect study procedures. | Due to the nature of the drug, there will be no drug supply stored at the site; therefore, there will be no inventory at the site. This section has been updated to reflect the procedures applicable to this study. |
| 7. | Section 9.1.6.2 Pelvic MRI | Inclusion of additional details surrounding the pelvic MRI assessments. | This section has been updated to improve clarity on the timings and assessments related to the MRI scan. |

| **Protocol Amendment 1** | | | |
|---|---|---|---|
| **Summary of Changes Since the Last Version of the Approved Protocol** | | | |
| **Change Number** | **Sections Affected by Change** | **Description of Each Change and Rationale** | |
| | ***Location*** | ***Description*** | ***Rationale*** |
| 8. | Section 9.1.9 Procedures for Clinical Laboratory Samples<br>Section 9.1.15 Clinical Outcome Assessments<br>Section 9.3.1 Screening Visit<br>Section 9.3.5 Follow-up Period<br>Section 9.3.6 Early Termination<br>Appendix A Schedule of Study Procedures | Erythrocyte sedimentation rate (ESR) added as part of the hematology clinical laboratory tests for Pediatric Crohn's Disease Activity Index (PCDAI) assessment. | Analysis of ESR is required as part of the PCDAI assessment. Text added to clarify that ESR will be analyzed by a local laboratory. |
| 9. | Section 9.1.9 Procedures for Clinical Laboratory Samples<br>Section 10.2.3 Reporting of Abnormal Liver Function Tests | Editorial update to monitoring requirements for alanine aminotransferase elevations. | Text has been replaced with reference to Appendix D, which includes guidance on liver test abnormality monitoring, evaluation, and follow-up. |
| 10. | Section 9.1.15 Clinical Outcome Assessments | Heading updated to Clinical Outcome Assessments. | To encompass the clinician (Perianal Disease Activity Index [PDAI] and PCDAI) and patient (Perianal Pain visual analog scale [VAS]) reported outcomes. |
| 11. | Section 9.1.15.1 Clinician-Reported Outcomes | New subheading of Clinician-Reported Outcomes. | Updated since PDAI and PCDAI assessments are clinician-reported outcomes. |
| 12. | Section 9.1.15.2 Patient-Reported Outcomes | New subheading of Patient-Reported Outcomes. | Perianal Pain VAS is reported by the patient; therefore, the subheading has been updated to reflect this. |
| 13. | Section 9.3 Schedule of Observations and Procedures | Update to wording. | To clarify that visits at screening, preparation, treatment administration, Week 24, and Week 52 must be done with the subject present at the investigative site. |
| 14. | Section 9.3.1 Screening Visit to Section 9.3.6 Early Termination | Editorial update to the fistula clinical assessment (FCA). | To provide clarity on which electronic case report forms need to be completed by the investigator at each visit when performing the FCA. |

| **Protocol Amendment 1** | | | |
|---|---|---|---|
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| **Change Number** | **Sections Affected by Change** | **Description of Each Change and Rationale** | |
| | ***Location*** | ***Description*** | ***Rationale*** |
| 15. | Section 9.3.1 Screening Visit<br>Appendix A Schedule of Study Procedures | Editorial update to clarify colonoscopy or rectoscopy requirements at the screening visit. | A colonoscopy or rectoscopy will need to be performed at screening if the subject has not had one within the last 6 months of screening. |
| 16. | Section 9.3.2 Potential Rescreening | Editorial update to clarify requirements for repeat MRI at the rescreening visit. | For completeness to study procedures at the rescreening visit. |
| 17. | Section 9.3.4 Treatment Administration Visit (Week 0/Visit 0)<br>Appendix A Schedule of Study Procedures | Removal of PCDAI assessment from the treatment administration visit. | Since there will be no clinical laboratory tests at the treatment administration visit, PCDAI has been removed from this visit. |
| 18. | Section 9.3.7 Unscheduled Telephone Follow-up Calls<br>Appendix A Schedule of Study Procedures | Editorial update to provide clarity on the unscheduled telephone follow-up calls. | To clarify that subjects will be able to contact the investigator between scheduled visits or if the subject cannot attend an interim visit. |
| 19. | Section 9.3.8 Remote Visit due to COVID-19 | New section added. | To allow remote visits in the event a subject cannot attend an interim visit due to coronavirus disease 2019. |
| 20. | Section 10.1.3 SAEs | Removal of the Takeda Medically Significant AE list. | In line with updated internal process, the EudraVigilance Expert Working Group Important Medical Event Terms list will now be implemented. |
| 21. | Section 13.0 STATISTICAL Methods<br>Section 2.0 STUDY SUMMARY | Editorial updates made. | For improved clarity and completeness to the statistical methodology. |
| 22. | Appendix D Guidance on Liver Test Abnormality Monitoring, Evaluation, and Follow-up | Addition of new appendix. | In line with internal process, this appendix has been included to provide guidance on reporting liver test abnormalities. |
| 23. | Appendix G Perianal Pain VAS | Addition of new appendix. | Added for completeness to protocol. |

Signature Page for Darvadstrocel-3004 Protocol Amend 3 2024-05-22
Title: A Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy and Saf

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