EMA/598555/2024
Committee for Advanced Therapies (CAT)
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alofisel

International non-proprietary name: Darvadstrocel

Procedure No. EMEA/H/C/004258/II/0051/G

Note

Variation assessment report as adopted by the CAT and CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 May 2024	27 May 2024	☐
☐	CAT Rapporteur Assessment Report	25 Jun 2024	18 Jun 2024	☐
☐	PRAC Rapporteur Assessment Report	28 Jun 2024	18 Jun 2024	☐
☐	PRAC members comments	03 Jul 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	04 Jul 2024	n/a	☐
☐	CAT and CHMP members comments	10 Jul 2024	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	11 Jul 2024	11 Jul 2024	☐
☐	Updated CAT Rapporteur Assessment Report	15 Jul 2024	15 Jul 2024	☐
☒	CAT Request for supplementary information (RSI)	19 Jul 2024	19 Jul 2024	☐
☒	CHMP endorsement	25 Jul 2024	25 Jul 2024	☐

LIST OF ABBREVIATIONS

Term	Definition
ADR	adverse drug reaction
AESI	adverse event of special interest
AGA	American Gastroenterological Association
ASC	adipose stem cell
AZA	azathioprine
CD	Crohn's disease
CHMP	Committee for Medicinal Products for Human Use
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CPF	Crohn's perianal fistula
CSR	clinical study report
DDI	drug-drug interaction
DSA	donor-specific antibodies
eASC	expanded adipose-derived stem cell
ECCO	European Crohn's and Colitis Organisation
eCRF	electronic case report form
EMA	European Medicines Agency
FDA	Food and Drug Administration
HLA	human leukocyte antigen
IA	interim analysis
IL	interleukin
IMP	investigational medicinal product
IS	immunosuppressant(s)
ISS	integrated summary of safety
ITT	intent-to-treat
LTE	long-term extension
MAA	marketing authorisation application
mAb	monoclonal antibody(ies)
MAH	marketing authorisation holder
MC	million cells (ISS treatment groups)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTX	methotrexate
PBRER	Periodic Benefit-Risk Evaluation Report
PT	Preferred Term
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNF	tumor necrosis factor
US	United States

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 30 April 2024 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
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C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

A grouped application comprised of 4 Type II Variations, as follows:

(C.I.4): Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information, based on pooled safety data from the two phase 3 controlled studies (ADMIRE-CD & ADMIRE-CD II) and to update efficacy information based on final results from study ADMIRE-CD II, listed as an obligation in the Annex II. ADMIRE-CD II (Cx601-0303) is a Phase III randomised double blind, placebo controlled study to assess efficacy and safety of Cx601, adult allogeneic expanded adipose-derived stem cells (eASC) for the treatment of complex perianal fistula(s) in patients with Crohn's disease. The Annex II is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes to the PI, including to section 4.2 of the SmPC and to the Package Leaflet.

3 x (C.I.13): Submission of interim results from studies Darvadstrocel-3003 and Alofisel-5003 (INSPIRE) and final results from study Darvadstrocel-3002 to support the benefit-risk assessment of darvadstrocel based on all new available clinical data.

The RMP version 8.0 has also been submitted.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

Darvadstrocel is a dispersion of expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue approved in the EU in 2018 (EMEA/H/C/004258) for the treatment of complex perianal fistula(s) in adult patients with nonactive or mildly active luminal Crohn's disease (CD), when fistulas have shown an inadequate response to at least 1 conventional or biologic therapy. Darvadstrocel is administered as a single dose of 120 million cells per patient via perilesional injection to treat up to 3 fistula tracts that open to the perianal area. The mechanism of action proposed involves immunomodulation through reduction of T cell proliferation and release of pro-inflammatory cytokines, decrease of proliferation, expression of activating receptors and cytotoxic activity of NK

cells, decrease of immune cells migrating to inflamed tissues, induction of anti-inflammatory suppressor cells such as Treg cells and M2 macrophages, and increase of phagocytosis by macrophages and neutrophils (Alofisel, INN-darvadstrocel (europa.eu)). Although mesenchymal stromal cells (MSCs) have been promising for regenerative medicine based on their ability to proliferate, differentiate, and secrete a range of growth, angiogenic, and immune regulating factors, a major disadvantage with MSC-based therapies is the occurrence of massive MSC death post-implantation and their limited long-term survival. In the original application, neither clinical data on cell survival in the fistulas nor clinical data on local pharmacological actions of these cells possibly contributing to healing of the fistulas was presented. This is important information for the integrated understanding of the potential efficacy of darvadstrocel in treatment of perianal fistulas. The MAH is asked to provide any new internal data on this matter as well as updated literature data that could shed light on this question.

Cumulative worldwide exposure until September 2023 is estimated to be 1506 patients.

The marketing authorisation application (MAA) was based on one pivotal phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter Study Cx601-0302 (ADMIRE-CD). The study population (n=212) included were patients with mild to moderate luminal Crohn's disease and with perianal fistulas. Fistulas had previously shown an inadequate response to antibiotics (73.6%), immunosuppressants (78.3%) or anti-TNF agents (78.8%).

Although the effect compared to placebo appeared modest, it was considered to be of clinical relevance if other treatment options for fistula have failed. However, given the single pivotal trial setting, the CHMP required (as an Annex II condition) the submission of the final results of another phase 3, placebo-controlled study of darvadstrocel that was ongoing at the time of marketing authorisation (Study Cx601-0303, ADMIRE-CD II). This Type II variation provides the final results of ADMIRE-CD II.

ADMIRE-CD II was a phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of darvadstrocel for the treatment of complex CPF in subjects with nonactive or mildly active CD over a period of 24 weeks and a follow-up period up to 52 weeks. The study followed an add-on design in which subjects receiving any ongoing concomitant medical treatment for CD at stable doses at the time of the screening visit were allowed to continue it throughout the study. The study population included subjects whose perianal fistula(s) were previously treated and had shown an inadequate response or a loss of response, intolerance, or contraindication to immunosuppressants (IS) or mAbs.

The primary endpoint was combined remission at Week 24, defined as

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

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

A total of 568 patients were included and randomised to darvadstrocel (n=283) or placebo (n=285). The study subjects were primarily male (55.8%) with a mean (SD) age of 38.1 (11.35) years; most subjects were aged <65 years (98.1%) and only 1.9% of subjects were aged ≥65 years. The majority of the subjects were white (87.5%). There were no important differences in patient characteristics. Almost all patients had concomitant use of either immunosuppressives or monoclonal antibodies (59.3%), or a combination of both (36.4%).

Effect

The primary endpoint, combined remission at week 24, was achieved by 138/283 patients (48.76%) in the darvadstrocel group and 132/285 patients (46.32) in the placebo group. The difference was not statistically significant (p=0.571), and thus the study failed to meet its primary endpoint.

According to the MAH, ADMIRE-CD and ADMIRE-CD II should be considered 2 distinct studies, mainly because of differences in inclusion/exclusion criteria for the subject population and the distribution of concomitant treatment for CD and perianal fistulas at randomization, which limit the interpretability of pooled analyses of the full subject populations from both studies. To demonstrate the overall efficacy of darvadstrocel treatment among the subject population that is most similar to the population for which darvadstrocel is indicated for use (ie, ADMIRE-CD), a post hoc pooled analysis of efficacy results was performed for the ADMIRE-CD population (212 randomized subjects) and a subsample from ADMIRE-CD II (85 subjects; 39 who received darvadstrocel treatment and 46 who received placebo), which was identified by using profile matching methodology to be similar to the ADMIRE-CD population according to baseline characteristics and concomitant medications at randomization. The MAH states that this post hoc analysis provide supportive evidence of clinical benefit of darvadstrocel compared with placebo for the patient population for which darvadstrocel is indicated for use in the EU. This approach is not agreed with. The studies should be interpreted according to the predefined analysis plans.

According to the MAH, differences between the studies include differences in inclusion/exclusion criteria for the subject population, mandatory seton placement, handling of missing data, and rescue medication (treatment failure). Subjects in both studies had complex CPF that had shown an inadequate response to IS or anti-TNF therapies (or other biologics, in the case of ADMIRE-CD II), while eligible subjects in ADMIRE-CD also could have been eligible if they had CPF(s) that had shown an inadequate response to antibiotic treatment only. Missing data were imputed using the LOCF method in ADMIRE-CD, while nonresponder imputation was used in ADMIRE-CD II. In addition, subjects in both studies underwent exploration under anesthesia and fistula curettage at the preparation visit 2 to 3 weeks before darvadstrocel was administered; however, seton placement at the preparation visit was mandatory in ADMIRE-CD II but was performed only if clinically indicated in ADMIRE-CD.

This is not agreed with. Overall, the study designs and study populations were very similar. The MAH states that one of the main differences was that in ADMIRE-CD, subjects were eligible if they had shown an inadequate response to antibiotic treatment only, while immunosuppressive of biologic therapy was mandatory in ADMIRE-CD II. According to the EPAR, Alofisel, INN-darvadstrocel (europa.eu), almost 80% had prior immunosuppressive therapy and almost 80% had prior anti-TNF treatment. Therefore, it is questionable whether this can be considered as a major difference between the study populations. The MAH is asked to clarify how many patients enrolled in ADMIRE-CD that had prior therapy with antibiotics only.

Another argument for the important differences between the studies is the handling of missing data. Missing data were imputed using the LOCF method in ADMIRE-CD, while nonresponder imputation was used in ADMIRE-CD II. The Applicant has not provided a comprehensive analysis of the impact of missing data in the two studies. However, a sensitivity analysis for the ADMIRE-CD II study based on multiple imputation for missing data was presented and showed similar results as the primary analysis based on non-responder imputation. This indicates that the negative outcome is robust to the handling of missing data and hence, the treatment differences in the ADMIRE-CD II trial is not expected to be underestimated to a large extent due to the missing data handling.

Finally, the differences in surgical procedure and withdrawal criteria are not considered of such importance that they would preclude a comparison the study results.

The post-hoc analyses are significantly influenced by the results of ADMIRE-CD, and of limited value for the overall efficacy conclusions. The post-hoc analyses cannot disregard the fact that ADMIRE-CD II was a failed study.

Supportive efficacy data was submitted; however these studies are of minor importance due to deficiencies in the study designs. These studies are briefly summarised below:

Study Darvadstrocel-3003 is an ongoing long-term extension study of ADMIRE-CD II aiming to evaluate the long-term safety and efficacy of darvadstrocel. After unblinding of ADMIRE-CD II, the study was open-label. This was primarily a safety study and efficacy outcomes are presented descriptively. A total of 37/76 patients (48.68%) in the darvadstrocel arm and 27/74 patients (36.49%) in the placebo arm were in clinical remission at week 104, and 22/76 patients (40.74%) in the darvadostrocel arm and 18/74 patients (30.51%) in the placebo arm were in clinical remission at week 156.

According to the MAH, the study demonstrated that darvadstrocel maintained an acceptable safety profile and that caution must be exercised when interpreting the efficacy results presented in this interim report as this is an ongoing study. Because subjects were not randomized into 2 groups and no formal statistical comparison was conducted, meaningful comparisons with regards to efficacy cannot be made between the 2 groups.

Study Alofisel-5003 (INSPIRE) is an ongoing, multicenter, observational postapproval study in patients with CD with complex CPFs treated with darvadstrocel followed up to 36 months. Patients were invited to participate in the study only after their treating healthcare professional and the patient had opted to proceed with darvadstrocel treatment. The primary outcomes are clinical response and clinical remission. Clinical response was achieved in 75.9% (198 of 261) of patients at Month 6 and in 79.9% (107 of 134) of patients at Month 12.

Clinical remission was achieved at 6 months in 69.7% (182 of 261) of patients. Clinical remission was achieved at 12 months in 102 of 134 patients (76.1%).

The MAH concludes that the results support the effectiveness of darvadstrocel as a treatment for complex CPFs in the real-world setting. The MAH believes that clinical response and clinical remission rates achieved in interim results from this study support the benefit profile of darvadstrocel in adult patients with CD and complex CPF. The MAH considers that treatment with darvadstrocel was well tolerated, that no new safety signals were observed during this study and that the overall safety profile remains consistent with the known safety profile of darvadstrocel. However, in the CHMP's opinion, given its observational design, the study is of limited value for the efficacy assessment.

Study Darvadstrocel-3002 was a phase 3, open-label, uncontrolled study to evaluate the efficacy and safety of darvadstrocel in the treatment of complex perianal fistulas in Japanese adult subjects with CD. The study included subjects with nonactive or mildly active CD (defined by CDAI ≤220) with complex perianal fistulas who had been previously failed other treatments. The study was conducted as an add-on study in which continuation of baseline treatments for CD (eg, IS, biologics) was permitted. A total of 22 patients were included. Given the small sample size and the open-label uncontrolled study design, it is of limited value for the overall efficacy assessment.

There are some data to support that among patients who responded to treatment with darvadstrocel, the effect was maintained over time. However, the response rates over time are not convincingly higher than the response rates for placebo and since the overall effect of darvadstrocel is questioned, the potential long-term effect is of minor importance.

To conclude, the single pivotal study ADMIRE-CD that was the basis for the MAA showed a modest difference in effect between darvadstrocel and placebo, and a confirmatory phase 3 study was included

as an annex II condition (ADMIRE-CD II). The study data now available shows no statistically significant effect for darvadstrocel compared to placebo. This questions the efficacy of the product. (**MO**)

Safety

From a safety perspective, data is presented separately from the respective study, as well as pooled using the following 2 pools: (1) the populations in the phase 3 randomized, placebo-controlled studies (ADMIRE-CD and ADMIRE-CD II) and (2) the populations in the adult phase 1-3 studies (Cx601-0101, ADMIRE-CD, ADMIRE-CD II, Darvadstrocel-3002, and Darvadstrocel-3003). Cumulative postmarketing data as of 22 September 2023 are also presented.

Overall, in the "adult phase 1-3 studies pool" (ADMIRE-CD, ADMIRE-CD II, Study Cx601-0101, Study Darvadstrocel-3002, and Study Darvadstrocel-3003), a total of 427 subjects received darvadstrocel. In the current study ADMIRE-CD II, 278 subjects in the darvadstrocel group and 274 subjects in the placebo group were dosed with study treatment.

ADMIRE-CD II

Any TEAE occurred in 73% of darvadstrocel-treated patients, and 73.4% of placebo-treated patients. SAEs occurred in 14.7% of darvadstrocel-treated patients, and 12.8% of placebo-treated patients. The most common TEAE was within gastrointestinal disorder, with proctalgia being the most frequent AE (15.5% in the darvadstrocel arm and 14.6% in the placebo arm). Also, anal fistula, anal abscess and fistula discharge were numerically more frequent in the darvadstrocel arm although the differences are small.

Serious adverse events were more frequent in the darvadstrocel arm (41/278 patients, 14.7%) than in the placebo arm (35/274 patients, 12.8%). The differences were observed within the SOCs cardiac disorders, gastrointestinal disorders and infections/infestations. The most prominent difference is a higher frequency of proctalgia in the darvadstrocel arm (5/278, 1.8%) than in the placebo arm (1/274, 0.4%). For a treatment with a modest effect, this indicates that treatment is associated with some discomfort for the patients which needs to be taken into account in the overall B/R assessment.

There was 1 fatal event of hepatocellular carcinoma in a subject in the darvadstrocel group. Tumorigenicity is an important potential risk in the Alofisel RMP. Although the most apparent concern (given the local administration of the product in fistulas) is anal canal and local colorectal malignancy, this finding with a reasonable timely relationship with Alofisel treatment is of some concern. The concomitant medication with infliximab and azathioprine is acknowledged, and causality with Alofisel cannot be concluded.

Among adverse events of special interest, there were no cases of ectopic tissue formation, transmission of infectious agents or medication errors reported.

The frequency of tumourogenicity up to week 52 was lower in the Alofisel group (2/278 patients, 0.7%) than in the placebo group (8/274 patients, 2.9%).

Up to Week 52, 24 subjects (8.6%) in the darvadstrocel group and 18 subjects (6.6%) in the placebo group experienced treatment-emergent hypersensitivity reaction AESIs. This indicates that although the safety profile of the product per se seems to be favourable, there are certain non-negligible risks associated with the treatment procedure.

Up to Week 52, 39 subjects (14.0%) in the darvadstrocel group and 29 subjects (10.6%) in the placebo group experienced treatment-emergent fistula or abscess AESIs. This finding is quite remarkable, since the aim of treatment with Alofisel is to treat perianal fistulas. The MAH is asked to further discuss this finding, and the potential impact on the benefit-risk.

Post-marketing data

Cumulative worldwide exposure by sales volume from initial launch on 01 March 2018 to 30 September 2023 for darvadstrocel was estimated to be 1506 patients (PSUSA/00010676/202309). The most frequently reported ADRs of anal abscess, anal fistula, and proctalgia align with the clinical safety findings observed in clinical studies.

There has been 1 fatal case of signet-ring cell carcinoma, which was assessed as not related to darvadstrocel by the reporter. This was a female patient with a medical history of ovarian cancer since, gastrointestinal adenocarcinoma with findings histologically confirmed and anal carcinoma. No concomitant medications were reported. The patient received darvadstrocel. On an unknown date, the patient experienced a medically significant event of anal fistula and signet-ring carcinoma. On the patient died from signet-ring carcinoma after receiving darvadstrocel. It was unknown if an autopsy was performed. No further details surrounding the carcinoma were provided. According to the MAH, this event is confounded by the patient's pre-existing medical history of cancer.

This is not agreed with. Although the patient had a history of ovarian cancer since 2009, it should be acknowledged that there is a possible timely relationship between the Alofisel treatment and the anal carcinoma/gastrointestinal adenocarcinoma.

Pooled safety data

Pooled data were presented for phase 3 placebo-controlled studies (Alofisel n=381, placebo n=376) and adult phase 1-3 studies (Alofisel n=403, placebo n=376).

In phase placebo-controlled studies up to week 24, the most common TEAEs were proctalgia (darvadstrocel: 13.9%, placebo: 12.8%), anal abscess (darvadstrocel: 7.3%, placebo: 6.9%), COVID-19 (darvadstrocel: 3.1%, placebo: 5.1%), and Crohn's disease (darvadstrocel: 2.9%, placebo: 5.1%. Up to week 52, the most common TEAEs were proctalgia (darvadstrocel: 15.2%, placebo: 14.4%), anal abscess (darvadstrocel: 10.2%, placebo: 8.2%), COVID-19 (darvadstrocel: 6.3%, placebo: 6.4%), anal fistula (darvadstrocel: 6.0%, placebo: 6.1%), diarrhoea (darvadstrocel: 5.0%, placebo: 4.0%), Crohn's disease (darvadstrocel: 4.7%, placebo: 6.9%), and abdominal pain (darvadstrocel: 2.9%, placebo: 5.6%).

It is noted that the frequency of proctalgia and anal abscess is higher in the Alofisel arm than in the placebo arm, although it is acknowledged that the differences are small. Nonetheless, this indicates that treatment with Alofisel might be associated with a certain degree of discomfort for the patients.

In the adult phase 1-3 studies pool up to week 156, the frequency of neoplasms was lower in the Alofisel arm (3/403 patients, 0.7%) than in the placebo arm (6/376 patients, 1.6%).

Overall, the safety data presented seems to be in line with current knowledge of the safety profile of Alofisel. Among the most common adverse events observed are pain and abscess formation, occurring with a slightly higher frequency in Alofisel-treated patients than in placebo-treated patients. Whether these are related to Alofisel treatment or rather reflects a lack of efficacy in some patients is difficult to conclude on. Hypersensitivity reactions were also observed, including a case of anaphylactic shock in an Alofisel-treated patient. This indicates that although the safety profile of the product per se seems to be favourable, there are certain non-negligible risks associated with the treatment procedure. Some further clarifications are needed, in particular to a case of anal cancer observed after Alofisel treatment.

To conclude, the efficacy of Alofisel in treatment of perinala fistulas in Crohn's disease and the benefit-risk balance needs further justification. First, the single pivotal study ADMIRE-CD (n=212) that was the basis for the approval showed only a modest difference in achievement of combined remission between darvadstrocel and placebo (49.5% vs 34.5%, difference 15.2%). Confirmatory efficacy data

was considered of importance for the benefit-risk of the product leading to an annex II condition (PAES). The study data now available from study ADMIRE-CD II (n=568) shows no statistically significant effect in terms of achieving combined remission for darvadstrocel compared to placebo (48.86% vs 46.32%, difference 2.37%). Second, there are certain non-negligible risks associated with the treatment procedure such as a higher frequency of hypersensitivity reactions (including anaphylactic shock) and anal fistula or abscess observed for darvadostreocel than for placebo. The latter is remarkable for a treatment aimed for treatment of fistulas. Further, there have been one case of anal cancer observed in a patient treated with Alofisel two years earlier.

Based on above, the MAH is asked to further justify a clinically relevant effect of the product, and that its potential benefit outweighs the observed risks associated with the treatment. (**MO**)

The benefit-risk balance of Alofisel, is currently undetermined since major objections with impact on the benefit-risk is raised.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

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The RMP version 8.0 has also been submitted.

☒is subject to a request for supplementary information

Annex: Rapporteur’s assessment comments on the type II variation

4. Introduction

CD is a chronic inflammatory bowel disease characterized by transmural inflammation and fistula formation. Perianal fistulas are a common complication of CD, particularly in patients with colonic disease and rectal involvement. A perianal fistula is an abnormal connection or passageway that develops between the rectum and the skin of the perianal area. The presence of a perianal fistula results in abnormal discharge of faeces, pus, and blood through a skin opening other than the anus. Perianal fistulas are associated with disabling symptoms and complications that are distinct from the luminal CD symptoms. The main symptoms associated with perianal fistulas are pain associated with perianal swelling, fever in case of abscess formation, and the continuous drainage of pus, stool, or blood from cutaneous fistula openings (Marzo et al. 2015; Molendijk et al. 2014).

Perianal fistulas due to CD in adults are classified by the Parks' classification into 2 main categories: simple and complex (Amil-Dias et al. 2017; Sandborn et al. 2003). The definition of "complex" fistula in darvadstrocel studies conducted by Takeda is based on at least 1 of 3 conditions: (1) high intersphincteric/transsphincteric type; (2) more than 1 external opening; and (3) linked to an abscess. In addition, complex perianal fistulas may have multiple external openings and are characterized by local inflammation that is exacerbated by bacterial infections and faecal contamination. Inflammation leads to cellular infiltration, which causes the release of proinflammatory cytokines, both locally and from the bloodstream into the inflamed region. Continued uncontrolled cytokine secretion results in chronic inflammation at the site of the fistula. Complex perianal fistulas cause severe impairment in the affected patient's quality of life and result in considerable morbidity, including chronic pain, anal swelling, discharge, bleeding, abscess development, scarring, faecal incontinence, and restriction of lifestyle and sexual activity. They are associated with depression and may constitute a risk for anorectal carcinoma.

The aim of therapy for CPF is to achieve fistula healing, alleviate symptoms, prevent recurrence, and treat or prevent complications to improve quality of life. While durable fistula closure is ideal, it is uncommon with current medical or medical/surgical interventions, especially for complex CPF. Surgical options are limited and the surgical treatments available, such as advancement flaps or ligation of the intersphincteric fistula tract, are rarely performed because of the risk of faecal incontinence and nonhealing wounds (Adamina et al. 2020; Lightner 2019). Long-term success rates of surgical treatments remain moderate, at less than 60% in most cases, and are even worse in patients with complex CPF (Lopez et al. 2019; Marzo et al. 2015). Postoperative complications (eg, incontinence, sphincter dysfunction) are common, with an overall complication rate up to 40% (Gaertner et al. 2022), and recurrence rates are reported to be 45% after surgical intervention (Loffler et al. 2009). Given the high recurrence and complication rates associated with currently available surgical treatments (McKay et al. 2023), there remains a significant unmet need for therapies capable of achieving durable fistula healing.

Clinical guidelines from the American Gastroenterological Association (AGA) (Feuerstein et al. 2021), the American College of Gastroenterology (Lichtenstein et al. 2018), ECCO (Torres et al. 2020), and the Toronto Consensus (Steinhart et al. 2019) recommend the use of infliximab for the induction and maintenance of CPF remission. Overall, infliximab is often considered the current standard therapy for patients with fistulizing CD. Infliximab is the only anti–tumor necrosis factor (TNF) monoclonal antibody (mAb) treatment that has evidence from a randomized controlled clinical study (ACCENT II) demonstrating efficacy (ie, closure of at least 50% of treated fistulas), with an induction rate of healing fistulas of 56% versus 26% and a maintenance rate of 36% versus 19% comparing infliximab versus placebo (Present et al. 1999; Sands et al. 2004). However, the ACCENT II study included patients with simple or complex perianal fistulas, and 42% of patients relapsed while on infliximab therapy, suggesting an unmet medical need for patients with complex CPF.

Besides infliximab, the recommendation for the use of other anti-TNF agents or biologics varies across guidelines because of a lack of evidence from randomized controlled studies. For example, the guidelines from AGA recommend the use of adalimumab, ustekinumab, or vedolizumab for the induction or maintenance of fistula remission, whereas the ECCO guidelines do not recommend these therapies, reflecting the different priorities for drug of choice across regions. Although adalimumab is recommended by some clinical guidelines, the level of evidence of efficacy is low. Newly available biologic agents to treat patients with complex CPF who have failed to respond to anti-TNF agents, or those who may not tolerate or have contraindications to receive them, include anti-integrins (eg, vedolizumab) and IL-12/IL-23 antagonists (eg, ustekinumab). However, prospective data to address their efficacy, specifically in patients with perianal fistulas, are currently lacking, and further dedicated studies are needed (Feagan et al. 2018; Yzet et al. 2022). Thus, patients with complex CPFs may undergo several lines of treatment, including invasive surgical procedures and/or biologic therapy, and still experience inadequate response before they achieve sufficient fistula closure.

Darvadstrocel (Cx601) is a dispersion of expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue (ie, expanded adipose-derived stem cells [eASCs]), which exhibit local immunomodulatory and anti-inflammatory effects at inflammation sites.

Darvadstrocel (tradename: Alofisel) was approved in the EU in 2018 (EMEA/H/C/004258) for the treatment of complex perianal fistula(s) in adult patients with nonactive or mildly active luminal Crohn's disease (CD), when fistulas have shown an inadequate response to at least 1 conventional or biologic therapy.

Darvadstrocel is administered as a single dose of 120 million cells per patient via perilesional injection to treat up to 3 fistula tracts that open to the perianal area.

The marketing authorisation application (MAA) was based on one pivotal phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter Study Cx601-0302 (hereinafter referred to as ADMIRE-CD). The study population (n=212) included were patients with mild to moderate luminal Crohn's disease and with perianal fistulas. Fistulas had previously shown an inadequate response to antibiotics (73.6%), immunosuppressants (78.3%) or anti-TNF agents (78.8%).

The B/R was concluded positive, however the CHMP required (as an Annex II condition of the market auhtorisation) the submission of the final results of another phase 3, placebo-controlled study of darvadstrocel that was ongoing at the time of marketing authorization (Study Cx601-0303, hereinafter referred to as ADMIRE-CD II).

From the EPAR (EMEA/H/C/004258): *"Overall, it is considered that the results from the single, pivotal phase III study provide sufficient evidence of efficacy. The results from the pivotal study showed that there was a statistically significant difference between the numbers of patients in combined remission in the active and placebo groups. The difference between the groups at week 24 for the primary outcome combined remission was 15.2 %. This was supported by the results of the key secondary endpoints clinical remission and clinical response although differences were not statistically significant. Other secondary endpoints i.e. combined remission and clinical remission at week 52 show statistically significant differences between treatment groups of 17 % and for clinical response at week 52 the difference was 10 %. Although the effect compared to control appears modest, is considered to be of clinical relevance as other treatment options for fistula have failed. Considering also the approval setting with a single pivotal study, confirmatory information on efficacy is considered as of importance for the benefit-risk of the product and will be obtained from the ongoing Phase III study Cx601-303 (final CSR expected in 2022). Thus, the approval of Alofisel should be subject to the submission of study Cx601-303 which is similar in design to the pivotal study of this application as an Annex II condition. The safety database of Alofisel is considered limited but provides sufficient characterisation of the safety profile for marketing authorisation. Unfavourable effects and uncertainties are*

appropriately described in SmPC and RMP and post authorisation follow up will be carried out in particular on important potential risks, repeated administration and long term safety by means of a post authorisation safety study".

This type II variation provides the final results of ADMIRE-CD II.

5. Clinical Pharmacology aspects

No new data were submitted. For a summary of immunogenicity, please refer to the clinical safety assessment.

6. Clinical Efficacy aspects

A summary of the clinical studies included in the darvadstrocel clinical development program is provided below.

Table 1. Overview of Completed and Ongoing Darvadstrocel Clinical Studies

Protocol No. Status Country(ies) or Region(s)	Study Description	Design	Population	Darvadstrocel Dose	No. Subjects in Study	No. Subjects Exposed to Darvadstrocel
Cx601-0101 Completed Spain	Safety and efficacy of allogeneic eASC in subjects with complex perianal fistula due to CD over a period of 24 weeks.	Phase 1/2a multicenter, open-label pilot study.	Subjects aged more the 18 years with complex perianal fistulas in perianal CD.	Up to [illegible] doses, 12 weeks apart. First dose: 20 million cells (2 mL with 10 million cells/mL) Second dose (if incomplete fistula closure at Week 12): 40 million cells (4 mL with 10 million cells/mL)	24 enrolled and treated: 20 million cells (1 dose): 9 subjects 40 million cells (2 doses): 1 subject [a] 60 million cells (2 doses): 14 subjects	24
Cx601-0302 (ADMIRE-CD) Completed Europe and Israel	Efficacy and safety of eASC for the treatment of perianal fistulizing CD over a period of 24 weeks and an extended follow-up period up to 104 weeks.	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study.	Subjects aged 18 years or older with nonactive or mildly active luminal CD and complex perianal fistulas refractory to at least 1 of the following treatments: antibiotics, immunosuppressants, or anti-TNFs.	One dose: Cx601 (120 million cells; 24 mL with 5 million cells/mL) or placebo (saline solution; 24 mL)	212 randomized: Cx601: 107 Placebo: 105 205 treated: Cx601: 103 Placebo: 102	103
Cx601-0303 (ADMIRE-CD II) Completed Europe, Israel, North America	Efficacy and safety of Cx601 for the treatment of complex perianal fistula(s) in subjects with nonactive or mildly active CD over a period of 24 weeks and a follow-up period up to 52 weeks.	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study.	Subjects aged ≥18 years and ≤75 years with nonactive or mildly active CD and complex perianal fistulas who have shown an inadequate response, a loss of response, or intolerance to immunosuppressants or monoclonal antibodies.	One dose: Cx601 (120 million cells; 24 mL with 5 million cells/mL) or placebo (saline solution; 24 mL)	568 randomized: Cx601: 283 Placebo: 285 552 treated: Cx601: 278 Placebo: 274	278
Darvadstrocel-3002 Completed Japan	Efficacy and safety of Cx601 in the treatment of complex perianal fistula in adult subjects with CD.	Phase 3, open-label, multicenter, uncontrolled study.	Japanese subjects aged 18 years or older with CD whose complex perianal fistulas were previously treated and refractory (inadequate response, loss of response, or intolerance) to at least 1 of the following treatments: antibiotics, immunosuppressants, or biologics.	One dose: Cx601 (120 million cells; 24 mL with 5 million cells/mL)	22 enrolled 22 treated	22

Darvadstrocel-3003 Ongoing Europe, Israel, and United States	Long-term safety and efficacy of darvadstrocel in the treatment of complex perianal fistula in subjects with CD who have participated in Study Cx601-0303.	Follow-up of a phase 3 study.	Adult subjects who have participated in and completed Study Cx601-0303 for treatment of complex perianal fistulas in CD.	No IMP administration.	Planned ~150 subjects. At DLP, 150 enrolled: Cx601: 76 [b] Placebo: 74	76 [b] (as of interim DLP of 26 Jul 2023)
Darvadstrocel-3004 Ongoing Europe, Israel, and Japan	Safety and efficacy of darvadstrocel in pediatric subjects with complex perianal fistula over a period of 24 weeks and a follow-up period up to 52 weeks.	Phase 3, open-label, multicenter, single-arm study.	Pediatric subjects aged 4 to <18 years with CD and complex perianal fistulas refractory to therapy.	120 million cells (24 mL with 5 million cells/mL)	Planned: at least 20 subjects. At DLP: [c] 7 enrolled 7 treated	7 (as of 22 Sep 2023) [c]
Alofisel-4001 Ongoing Europe and Israel	Postauthorization safety study of the long-term safety and efficacy of repeat administration of darvadstrocel in subjects with CD and complex perianal fistula.	Phase 4, single-arm, open-label study.	Subjects with CD, aged 18 years or older, with complex perianal fistula who have previously received treatment with darvadstrocel and for whom a repeat administration of darvadstrocel for the original fistula tract or for a new fistula tract is planned by their physician.	120 million cells (24 mL with 5 million cells/mL)	Planned sample size: 50 subjects. At DLP: [c,d] 53 enrolled 53 re-treated	53 (as of 22 Sep 2023) [c,d]
Alofisel-5003 (INSPIRE) Ongoing Europe	Observational postapproval study on the effectiveness and safety of darvadstrocel in patients with CD and complex perianal fistulas.	Multicenter, prospective, observational, postapproval study.	Subjects with CD and complex perianal fistulas who were evaluated by an HCP and received at least 1 dose of darvadstrocel.	Commercially available darvadstrocel	Planned sample size: A minimum of 800 subjects. At DLP: [e,f] 652 enrolled 619 treated	619 (as of 03 Apr 2023) [e,f]

According to the MAH, ADMIRE-CD and ADMIRE-CD II should be considered 2 distinct studies, mainly because of differences in inclusion/exclusion criteria for the subject population and the distribution of concomitant treatment for CD and perianal fistulas at randomization, which limit the interpretability of pooled analyses of the full subject populations from both studies. To demonstrate the overall efficacy of darvadstrocel treatment among the subject population that is most similar to the population for which darvadstrocel is indicated for use (ie, ADMIRE-CD), a post hoc pooled analysis of efficacy results was performed for the ADMIRE-CD population (212 randomized subjects) and a subsample from ADMIRE-CD II (85 subjects; 39 who received darvadstrocel treatment and 46 who received placebo), which was identified by using profile matching methodology to be similar to the ADMIRE-CD population according to baseline characteristics and concomitant medications at randomization. The MAH states that this post hoc analysis provide supportive evidence of clinical benefit of darvadstrocel compared with placebo for the patient population for which darvadstrocel is indicated for use in the EU.

Assessor's comment:

This approach is not agreed with. The studies should be interpreted in line with the predefined analysis plans.

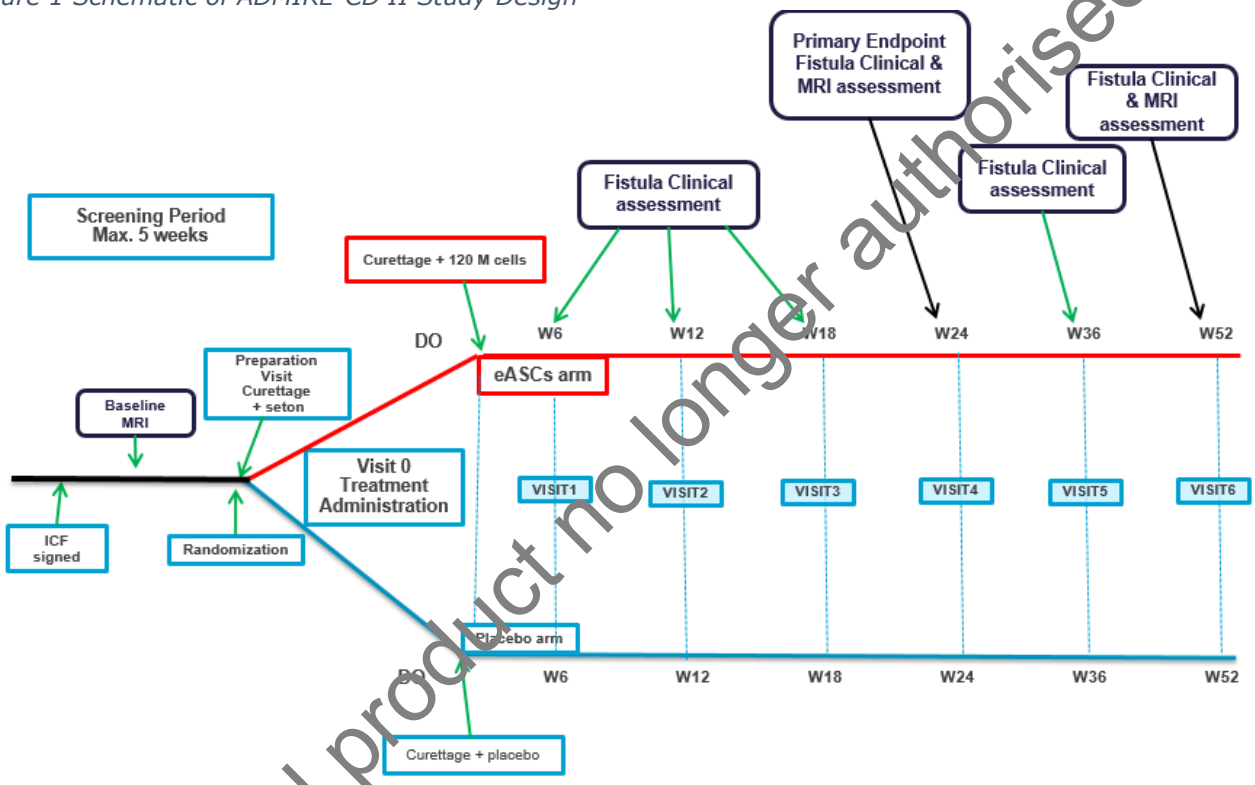
After the granting of marketing authorization, the marketing authorisation holder (MAH) received feedback from the EMA on 3 protocol assistance procedures. In 2018, the MAH received advice on revision of the proposal on long-term safety and effectiveness of single and repeat dosing (Protocol Assistance procedure EMEA/H/SA/654/4/2018/ADT/II). In 2019, the MAH received advice on technology transfer design and the comparability protocol design for an implementation plan of a new manufacturing site (Protocol Assistance procedure EMEA/H/SA/654/5/2019/ADT/I). In 2023, the MAH received advice on a protocol comparability of a pre- and postchange product (Protocol Assistance Procedure EMA/SA/0000101223).

6.1. Main study ADMIRE-CD II

6.1.1. Methods

ADMIRE-CD II was a phase 3, randomized, double-blind, parallel-group, placebo-controlled, global, multicenter study to assess the efficacy and safety of darvadstrocel for the treatment of complex CPF in subjects with nonactive or mildly active CD over a period of 24 weeks and a follow-up period up to 52 weeks. The study followed an add-on design in which subjects receiving any ongoing concomitant medical treatment for CD at stable doses at the time of the screening visit were allowed to continue it throughout the study. An overview of the study design is shown below.

Figure 1 Schematic of ADMIRE-CD II Study Design



Source: Cx601-0303 CSR Figure 1-a.
ADMIRE-CD II: Study Cx601-0303; CSR: clinical study report; D: day; eASC: expanded adipose-derived stem cell; ICF: informed consent form; M: million; MRI: magnetic resonance imaging; W: week.

Study population

The study population included subjects whose perianal fistula(s) were previously treated and had shown an inadequate response or a loss of response, intolerance, or contraindication to immunosuppressants (IS) or mAbs.

The main inclusion criteria were the following:

1. Subjects ≥18 years and ≤75 years of age with CD diagnosed at least 6 months prior to the screening visit in accordance with accepted clinical, endoscopic, histological, and/or radiological criteria.
2. Presence of complex CPF(s) with a maximum of 2 internal openings and a maximum of 3 external openings based on clinical assessment, with a central reading of a locally performed contrast-enhanced (gadolinium-enhanced) pelvic MRI to confirm the location of the fistula and

potential associated perianal abscess(es). The fistula(s) must have been draining for at least 6 weeks prior to the screening visit. Actively draining simple subcutaneous fistula(s), at the time of the screening visit, were not allowed in this study. A complex CPF was defined as a fistula that met 1 or more of the following criteria:

   a. High intersphincteric, high transsphincteric, extrasphincteric, or suprasphincteric.

   b. Presence of ≥2 external openings.

   c. Associated perianal abscess(es). Note: Abscesses that were larger than 2 cm in at least 2 dimensions on MRI must have been confirmed to have been drained adequately by the surgeon during the preparation curettage in order for the individual to be eligible.

3. Nonactive or mildly active CD during the last 6 months prior to the screening visit, with:

   a. A PRO-2 score <14 at screening
   AND

   b. A colonoscopy documenting the absence of ulcers larger than 0.5 cm in the colonic mucosa

4. Previously treated and had shown an inadequate response to:

   a. IS agents: at least 3 months of treatment with azathioprine (2-3 mg/kg/day), 6-mercaptopurine (1-1.5 mg/kg/day), or subcutaneous/intramuscular methotrexate (25 mg/week) prior to the screening for the study

   b. TNF-α antagonists (infliximab, adalimumab, or certolizumab pegol)

   c. Anti-integrin (vedolizumab)

   d. Anti–IL-12/23 (ustekinumab)

5. Women of childbearing potential (WCBPs) must have had a negative serum pregnancy test result at screening (sensitive to 25 IU human chorionic gonadotropin). Both WCBPs or male subjects participating in this study with a WCBP as partner must have agreed to use an adequate method of contraception during the entire duration of the study.

Selected exclusion criteria were:

1. Concomitant rectovaginal or rectovesical fistula(s).
2. Subject naïve to prior specific medical treatment for complex CPF(s) including IS or anti-TNFs.
3. Presence of a perianal collection >2 cm in at least 2 dimensions on the centrally read MRI at the screening visit that was not adequately drained as confirmed by the surgeon during the preparation procedure (Week -3 to Day 0).
4. Severe rectal and/or anal stenosis and/or severe proctitis (defined as the presence of large [>0.5 cm] ulcers in the rectum) that made it impossible to follow the surgical procedure manual.
5. Subject with diverting stomas.
6. Active, uncontrolled infection requiring parenteral antibiotics.
7. Subject with ongoing use of systemic or rectal steroids for CD in the last 2 weeks prior to the preparation visit.

8. Subjects with major alteration of any of the following laboratory test results or with an increased risk for the surgical procedure:
   a) Serum creatinine levels >1.5× ULN.
   b) Total bilirubin >1.5× ULN (unless predominantly nonconjugated due to a documented history of Gilbert syndrome).
   c) Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >3.0× ULN.
   d) Hemoglobin <10.0 g/dL.
   e) Platelets <75.0× 109/L.
   f) Albuminemia <3.0 g/dL.
9. Suspected or documented infectious enterocolitis within 2 weeks prior to the screening visit.
10. Any prior invasive malignancy diagnosed within the last 5 years prior to the screening visit. Subjects with basal cell carcinoma of the skin completely resected outside the perineal region could be included.
11. Current or recent (within 6 months prior to the screening visit) history of severe, progressive, and/or uncontrolled hepatic, hematological, gastrointestinal (other than CD), renal, endocrine, pulmonary, cardiac, neurological, or psychiatric disease that may have resulted in a subject's increased risk from study participation and/or lack of compliance with study procedures.
12. Subjects with primary sclerosing cholangitis.
13. Subjects with known chronically active hepatopathy of any origin (including cirrhosis) and subjects with persistent positive hepatitis B virus (HBV) surface antigen and quantitative HBV polymerase chain reaction (PCR) result, or positive serology for hepatitis C virus (HCV) and quantitative HCV PCR result within 6 months prior to screening.
14. Congenital or acquired immunodeficiencies, including subjects known to be human immunodeficiency virus carriers.
15. Known allergies or hypersensitivity to penicillin or aminoglycosides, Dulbecco's Modified Eagle Medium (DMEM), bovine serum, local anesthetics, or gadolinium (MRI contrast material).
16. Contraindication to MRI (eg, due to the presence of a pacemaker, hip replacement, or severe claustrophobia).
17. Any major surgery of the gastrointestinal tract (including 1 or more segments of the colon or terminal ileum) within 6 months prior to screening or any minor surgery of the gastrointestinal tract within 3 months prior to screening.
18. Subjects who underwent local perianal surgery other than drainage for the fistula within 6 months prior to the screening visit or those who may have needed surgery in the perianal region for reasons other than fistulas at the time of inclusion in the study.

A total of approximately 740 subjects were planned to be screened to randomize 554 subjects in a 1:1 ratio to receive either a local injection of 120 million cells of darvadstrocel or matching placebo.
A 5-week screening period was scheduled to determine subject eligibility for inclusion in the study.

Eligible subjects were stratified by concomitant treatment:

- Current use of concomitant immunosuppressant (IS) or monoclonal antibodies (mAbs) (ie, anti–tumor necrosis
  factor [TNF] or anti-integrin [ie, vedolizumab] or anti–interleukin [IL]-12/23 [ie, ustekinumab] as single agent).
  – Current use of concomitant IS or mAbs (ie, anti-TNF or anti-integrin [ie, vedolizumab] or

anti–IL-12/23 [ie, ustekinumab]) as combination treatment.
– No ongoing concomitant IS or mAbs treatment at time of randomization.

- External opening(s):
  – One external opening.
  – More than 1 external opening.

Assessor's comment:

The study population in the ADMIRE-CD II study was very similar to the study population in ADMIRE-CD I. For a comparison, please refer to Table 13.

Treatment

Subjects received a single dose of darvadstrocel (120 million cells in 24 mL solution) or placebo, locally injected into the tissue around the internal openings and into the walls of the fistula tracts.

Objective

The primary objective was to evaluate the combined remission of complex Crohn's perianal fistula(s) (CPF[s]), defined as the clinical assessment at Week 24 of closure of all treated external openings that were draining at baseline despite gentle finger compression, and absence of collections >2 cm (in at least 2 dimensions) confirmed by blinded central magnetic resonance imaging (MRI) assessment at Week 24. Secondary objectives were

- to evaluate the efficacy of darvadstrocel compared with placebo in clinical remission at Week 24 and in time to clinical remission (weeks).
- To evaluate the efficacy and safety of darvadstrocel compared with placebo in other clinical and time-to-event related endpoints at Weeks 24 and 52.

Endpoints

Efficacy Endpoint	Definition
Primary	
Combined remission at Week 24	a) The closure of all treated external openings that were draining at baseline despite gentle finger compression AND b) Absence of collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by blinded central MRI assessment.
Key Secondary	
Clinical remission at Week 24	Closure of all treated external openings that were draining at baseline despite gentle finger compression.
Time to clinical remission (weeks) assessed at Week 24	Time from treatment start to first visit with closure of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed.
Week 52 Secondary	
Combined remission at Week 52	a) The closure of all treated external openings that were draining at baseline despite gentle finger compression. AND b) Absence of collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by blinded central MRI assessment.

Efficacy Endpoint	Definition
Clinical remission at Week 52	Closure of all treated external openings that were draining at baseline despite gentle finger compression.

Source: Cx601-0303 SAP Version 6.0 Section 5.0 and Section 7.8.2.
ADMIRE-CD II: Study Cx601-0303; MRI: magnetic resonance imaging; SAP: statistical analysis plan.

Assessor's comment:

The primary endpoint in both ADMIRE studies were the same.

Statistical methods

The analyses of the efficacy endpoints were performed on the intent-to-treat (ITT), modified ITT (mITT), per protocol (PP), and randomized and treated (R&T) analysis sets, with the ITT as the primary analysis set. The ITT analysis set included all randomised subjects. The analyses of the secondary endpoints and the exploratory endpoints, were performed on the ITT analysis set, unless otherwise specified.

For multiplicity adjustment of the tested endpoints, the key secondary endpoints and 2 Week 52 secondary endpoints were grouped into the first and second secondary endpoint families (SF1 or SF2, respectively), with 2 null hypotheses in each family. The family-wise type I error rate was controlled at 0.05 for the analyses of the primary, key secondary efficacy endpoints at Week 24, and 2 other secondary endpoints at Week 52 (combined remission at Week 52 and clinical remission at Week 52). The primary endpoint was tested first. Once the null hypothesis for the primary endpoint was rejected, key secondary endpoints and 2 Week 52 endpoints were tested using a modified Hochberg-based gate-keeping approach (Dmitrienko et al. 2003; Hochberg 1988). The primary efficacy endpoint of combined remission at Week 24 served as the gatekeeper for the 2 key secondary endpoints at Week 24. If the p-values of both key secondary endpoint results at Week 24 were significant, the 2 Week 52 endpoints (combined remission at Week 52 and clinical remission at Week 52) were tested.

The primary efficacy analysis of the primary endpoint used a stratified Cochran-Mantel-Haenszel (CMH) method for comparing proportions of combined remission at Week 24, adjusting for the randomization stratification factors. The study was considered positive if the primary efficacy analysis yielded a 2-tailed p-value ≤0.05 (ie, combined remission rate of darvadstrocel was greater than placebo). Unless otherwise specified, a nonresponder imputation rule for the analysis of binary endpoints was applied for each visit as follows: if the value was missing at the visit, then the subject was classified as a nonresponder for the endpoint(s).

The key secondary endpoint of proportion of subjects with clinical remission at Week 24 and all other binary secondary endpoints were analyzed using the same methodology outlined above for the primary efficacy endpoint. The key secondary endpoint of time to clinical remission at Week 24 and all other time-to-event endpoints were analyzed using the stratified log-rank test for comparing darvadstrocel and placebo, adjusting for the randomization stratification factors. Subjects who did not achieve clinical remission by Week 24 were censored at the Week 24 visit. Also, subjects who discontinued without clinical remission before Week 24 were censored at the date of last visit.

The following assumptions were made in the sample size calculations:

- True combined remission rates at Week 24 of 42.2% and 30% in the darvadstrocel and placebo groups, respectively (based on estimates from a similar population in the phase 3 study, ADMIRE-CD).
- The family-wise type I error rate was controlled at 0.05 for the primary and key secondary efficacy endpoints at Week 24.

Given these assumptions, a total sample size of 554 subjects (277 per treatment arm) was expected to provide at least 85% power for the primary efficacy analysis at Week 24.

Post hoc efficacy analyses were conducted for the primary efficacy endpoint, key secondary efficacy endpoints, secondary efficacy endpoints, and other secondary efficacy endpoints of time of clinical remission at Week 52 and relapse at Week 52, to investigate the impact of randomization before the onset of the coronavirus disease 2019 (COVID-19) pandemic as defined by the World Health Organization (WHO) (Cucinotta and Vanelli 2020) on 11 March 2020. Therefore, post hoc analyses were performed for the group of subjects who were randomized before 11 March 2020 and those who were randomized on or after 11 March 2020. The same statistical analysis procedures were followed as outlined above for the primary and secondary efficacy analyses.

Assessor's comment

The primary efficacy analysis of the primary endpoint used a stratified Cochran-Mantel-Haenszel (CMH) method for comparing proportions of combined remission at Week 24, adjusting for the randomization stratification factors. This is a generally accepted method. Primary, key secondary and two week 52 secondary endpoints were included in a multiple testing procedure to control the family wise type I error. Since the study failed on the primary endpoint, no other endpoints could be confirmatory tested. Nevertheless, nominal p-values are presented in the results section below. For missing data a non-responder imputation rule was applied for binary endpoints. A sensitivity analysis was also performed with multiple imputation under MAR assumption.

6.1.2. Results

Disposition

Figure 2. Disposition of Subjects

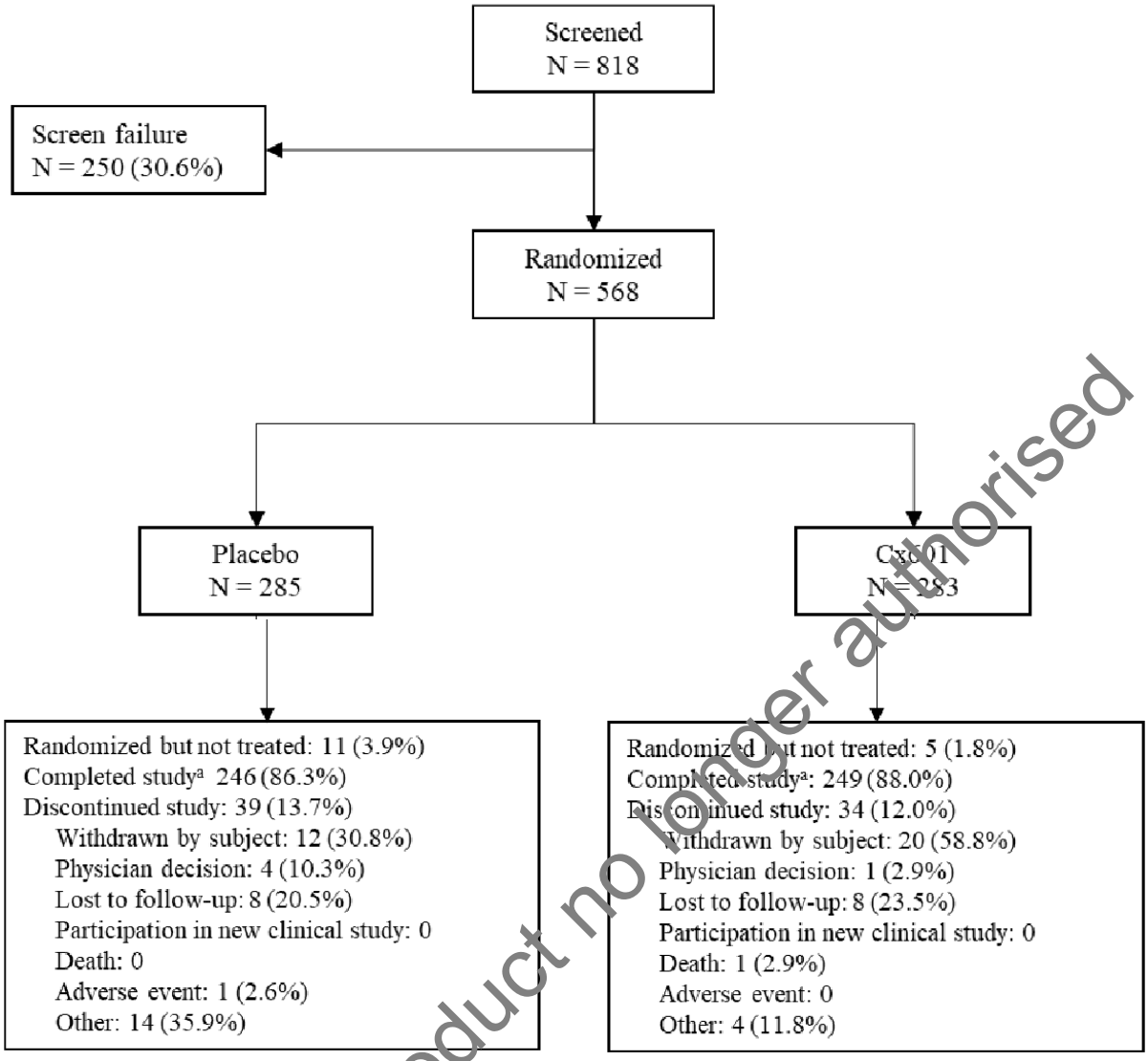


Table 2. Subject Disposition (ITT Analysis Set)

	Number (%) of Subjects		
	Placebo (N = 285)	**Cx601 (N = 283)**	**Total (N = 568)**
Completed the study [a]	246 (86.3)	249 (88.0)	495 (87.1)
Discontinued study	39 (13.7)	34 (12.0)	73 (12.9)
Randomized but not treated	11 (3.9)	5 (1.8)	16 (2.8)
Reasons for discontinuation from the study [b]			
Withdrawal by subject	12 (30.8)	20 (58.8)	32 (43.8)
Physician decision	4 (10.3)	1 (2.9)	5 (6.8)
Lost to follow-up	8 (20.5)	8 (23.5)	16 (21.9)
Participation in a new clinical trial	0	0	0
Death	0	1 (2.9)	1 (1.4)
AE	1 (2.6)	0	1 (1.4)
Other	14 (35.9)	4 (11.8)	18 (24.7)

Source: Table 15.1.1.1.

AE: adverse event; Cx601: darvadstrocel; ITT: intent-to-treat.

The analysis sets are summarised below.

Table 3. Analysis Sets

Analysis Set	Number (%) of Subjects		
	Placebo (N = 285)	Cx601 (N = 283)	Total (N = 568)
ITT [a]	285 (100.0)	283 (100.0)	568 (100.0)
mITT [b]	273 (95.8)	276 (97.5)	549 (96.7)
SAF [c]	274 (96.1)	278 (98.2)	552 (97.2)
PP [d]	262 (91.9)	268 (94.7)	530 (93.3)
R&T [e]	274 (96.1)	278 (98.2)	552 (97.2)

Source: Table 15.1.2.3.

Cx601: darvadstrocel; ITT: intent-to-treat; mITT: modified intent-to-treat; PP: per protocol; SAF: safety; R&T: randomized and treated.

Percentages were based on the number of subjects in the ITT analysis set.

[a] The ITT analysis set included all randomized subjects regardless of their being treated or not and regardless of their having any postbaseline efficacy measurements or not.

[b] The mITT analysis set included all randomized subjects who received the study treatment and for whom 1 postbaseline efficacy value was present, independent of the degree of adherence to the protocol.

[c] The SAF analysis set included all randomized subjects who received the actual study treatment.

[d] The PP analysis set included all randomized and treated subjects, presented according to the actual treatment they received, who adhered to the protocol with no major deviations that might have affected the assessment of the primary endpoint and for whom 1 postbaseline efficacy value was present.

[e] The R&T analysis set included all subjects who were randomized and received the study treatment.

Assessor's comment:

A total of 568 patients were randomised to darvadstrocel (n=283) or placebo (n=285) and constitute the ITT population. Of these, 12% in the darvadstrocel group and 13.7% in the placebo group discontinued the study. The main reason for study discontinuation was subject withdrawal in the darvadstrocel treatment arm and Other in the placebo treatment arm.

Protocol deviations

In total, 185 subjects (32.6%) had ≥ 1 major protocol deviation, including 91 (32.2%) with deviations in the darvadstrocel group and 94 (33.0%) with deviations in the placebo group.

Table 4. Major Protocol Deviations (ITT Analysis Set)

	Number (%) of Subjects		
	Placebo (N = 285)	Cx601 (N = 283)	Total (N = 568)
Subjects with at least 1 major protocol deviation	94 (33.0)	91 (32.2)	185 (32.6)
AE/SAE	0	0	0
Disallowed medications	12 (12.8)	12 (13.2)	24 (13.0)
Inclusion/exclusion criteria	6 (6.4)	3 (3.3)	9 (4.9)
Informed consent	3 (3.2)	6 (6.6)	9 (4.9)
IP administration/study treatment	6 (6.4)	7 (7.7)	13 (7.0)
Procedures/tests	49 (52.1)	54 (59.3)	103 (55.7)
Visit schedule	26 (27.7)	24 (26.4)	50 (27.0)
Withdrawal criteria	0	0	0
Other	4 (4.3)	3 (3.3)	7 (3.8)

Source: Table 15.1.2.1.

AE: adverse event; Cx601: darvadstrocel; IP: investigational product; ITT: intent-to-treat; SAE: serious adverse event.

Major protocol deviations starting between the screening visit and until end of the study (or early termination visit, whichever came first), were included.

The same subject may have had more than 1 major protocol deviation.

Percentages for each type of deviation were based on the total number of subjects with at least 1 major protocol deviation.

MRI unblinding

During routine ongoing medical data quality monitoring, it was identified that, between August 2022 and February 2023, the independent MRI reviewers were unblinded to visit names (either screening or Week 24 time points) during Reading Session 1. This issue was considered a protocol deviation because it impacted blinding of MRI readers to time point sequence for a subset of MRI reads, and impacted to a total of 11 subjects (of 568 randomized subjects). All time point–unblinded MRI reads were re-read in a time point–blinded fashion, and the data from the re-reviewed MRIs were used for the assessment of efficacy for the 11 impacted subjects. The central readers had no access to treatment assignment, and MRI reads remained treatment Darvadstrocel (Cx601) blinded throughout the duration of the study. No changes to the final MRI assessment of responses for these subjects were observed after the re-read (data on file).

Assessor's comment:

Since the MRI reads remained treatment-blinded throughout the duration of the study, this should not have affected the reliability of the study results.

Demographic and Other Baseline Characteristics

The demographic characteristics of subjects are summarized for the ITT analysis set below. There were no notable demographic imbalances between treatment groups. The randomized subjects were primarily male (55.8%) with a mean (SD) age of 38.1 (11.35) years; most subjects were aged <65 years (98.1%) and only 1.9% of subjects were aged ≥65 years. The majority of the subjects were white (87.5%), and 86.3% of subjects were not of Hispanic or Latino ethnicity. The proportion of subjects in the different regions (Europe + Israel vs North America, and US vs non-US) was balanced between treatment groups. Differences among smoking status and number of pack-years between treatment groups were not considered clinically significant.

Table 5. Demographic Characteristics (ITT Analysis Set)

Characteristics	Placebo (N = 285)	Cx601 (N = 283)	Total (N = 568)
Age (years)			
n	285	283	568
Mean (SD)	37.7 (10.78)	38.4 (11.91)	38.1 (11.35)
Median	38.0	37.0	37.0
Q1, Q3	29.0, 45.0	29.0, 46.0	29.0, 46.0
Minimum, maximum	18, 70	18, 71	18, 71
Age group, n (%)			
<65 years	282 (98.9)	275 (97.2)	557 (98.1)
≥65 years	3 (1.1)	8 (2.8)	11 (1.9)
Gender, n (%)			
Male	155 (54.4)	162 (57.2)	317 (55.8)
Female	130 (45.6)	121 (42.8)	251 (44.2)
Ethnicity, n (%)			
Hispanic or Latino	13 (4.6)	13 (4.6)	26 (4.6)
Not Hispanic or Latino	250 (87.7)	240 (84.8)	490 (86.3)
Not applicable	22 (7.7)	30 (10.6)	52 (9.2)
Race, n (%) [a]			
Asian	5 (1.8)	8 (2.8)	13 (2.3)
Black or African American	7 (2.5)	8 (2.8)	15 (2.6)
White	254 (89.1)	243 (85.9)	497 (87.5)
Unknown	18 (6.3)	24 (8.5)	42 (7.4)
Region 1, n (%)			
Europe and Israel	150 (52.6)	170 (60.1)	320 (56.3)
North America	135 (47.4)	113 (39.9)	248 (43.7)

Region 2, n (%)			
US	125 (43.9)	106 (37.5)	231 (40.7)
Non-US	160 (56.1)	177 (62.5)	337 (59.3)
Height (cm)			
n	274	278	552
Mean (SD)	171.78 (9.088)	171.59 (9.429)	171.69 (9.253)
Median	172.00	171.00	171.00
Q1, Q3	165.00, 178.00	165.00, 178.00	165.00, 178.00
Minimum, maximum	150.0, 193.0	152.0, 202.0	150.0, 202.0
Weight (kg)			
n	274	278	552
Mean (SD)	77.69 (16.675)	78.73 (19.620)	78.21 (18.209)
Median	75.28	77.05	76.00
Q1, Q3	65.80, 88.00	64.60, 93.00	65.00, 89.22
Minimum, maximum	45.0, 158.4	44.9, 151.2	44.9, 158.4
BMI (kg/m^2), n (%)			
<18.5	4 (1.4)	9 (3.2)	13 (2.3)
18.5 to <25.0	132 (46.3)	110 (38.9)	242 (42.6)
25.0 to <30.0	81 (28.4)	92 (32.5)	173 (30.5)
≥30.0	57 (20.0)	67 (23.7)	124 (21.8)
Smoking status, n (%)			
Former smoker	70 (24.6)	85 (30.0)	155 (27.3)
Current smoker	42 (14.7)	59 (20.8)	101 (17.8)
Never smoked	173 (60.7)	139 (49.1)	312 (54.9)
Number of pack-years			
n	282	280	562
Mean (SD)	3.7 (8.70)	6.5 (12.59)	5.1 (10.90)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 4.0	0.0, 7.5	0.0, 5.0
Minimum, maximum	0, 82	0, 96	0, 96

Source: Table 15.1.4.1.1.

BMI: body mass index; Cx601: darvadstrocel; ITT: intent-to-treat; Q: quartile; US: United States.

Percentages were based on the number of subjects in the ITT analysis set.

The BMI was calculated as weight (in kg) / (height (in cm)^2 / 10^4).

[a] Race categories with 1 subject or fewer are not presented in this table.

Assessor's comment:

It is agreed with the MAH that there were no important differences in baseline characteristics.

The study subjects were primarily male (55.8%) with a mean (SD) age of 38.1 (11.35) years; most subjects were aged <65 years (98.1%) and only 1.9% of subjects were aged ≥65 years. The majority of the subjects were white (87.5%).

Baseline characteristics is shown below.

Table 6. Baseline Characteristics (ITT Analysis Set)

Characteristics	Number (%) of Subjects		
	Placebo (N = 285)	Cx601 (N = 283)	Total (N = 568)
Colonoscopy status at baseline			
Within the last 6 months prior to screening	100 (35.1)	100 (35.3)	200 (35.2)
New colonoscopy at screening	185 (64.9)	183 (64.7)	368 (64.8)
Concomitant treatment (3 levels) [a]			
Current use of concomitant IS or mAbs as a single agent	164 (57.5)	173 (61.1)	337 (59.3)
Current use of concomitant IS or mAbs as combination treatment	107 (37.5)	100 (35.3)	207 (36.4)
No ongoing concomitant IS or mAbs treatment at time of randomization	14 (4.9)	10 (3.5)	24 (4.2)
Concomitant treatment (4 levels)			
Concomitant IS as a single agent	19 (6.7)	17 (6.0)	36 (6.3)
Concomitant mAbs as a single agent	145 (50.9)	156 (55.1)	301 (53.0)
Concomitant IS or mAbs as combination treatment	107 (37.5)	100 (35.3)	207 (36.4)
No ongoing concomitant IS or mAbs treatment at time of randomization	14 (4.9)	10 (3.5)	24 (4.2)
Anti-HLA and anti-DSA status [b]			
Number of HLA$^+$ at baseline	47 (16.5)	56 (19.8)	–
Number of DSA$^+$ at baseline	–	29 (10.2)	–
Current medication use (at randomization) [c]			
Current IS or mAbs as a single agent	172 (60.4)	173 (61.1)	345 (60.7)
Current combination of IS and mAbs	97 (34.0)	96 (33.9)	193 (34.0)
No ongoing concomitant IS or mAbs treatment	16 (5.6)	14 (4.9)	30 (5.3)
External opening(s)			
1	143 (50.2)	143 (50.5)	286 (50.4)
>1	142 (49.8)	140 (49.5)	282 (49.6)

Assessor's comment:

Almost all patients had concomitant use of either immunosuppressives or monoclonal antibodies (59.3%), or a combination of both (36.4%).

Efficacy results

Results for the primary and key secondary endpoints are shown below.

Table 7 ADMIRE-CD II: Proportion of Subjects Meeting Primary and Key Secondary Efficacy Endpoints at Week 24 and Selected Efficacy Endpoints at Week 52 (ITT Population)

	Placebo N = 285	Cx601 N = 283
Week 24 Primary Endpoint		
Combined Remission		
Number (%) of subjects who achieved combined remission [a, b]	132 (46.32)	138 (48.76)
95% CI	(40.53-52.10)	(42.94-54.59)
Difference in combined remission rate (%) (95% CI) [c]		2.37 (-5.82 to 10.55)

	Placebo N = 285	Cx601 N = 283
P-value [c]		0.571
Relative risk (95% CI) [d]		1.05 (0.89-1.25)
Week 24 Key Secondary Endpoints		
Clinical Remission		
Number (%) of subjects who achieved clinical remission [b, e]	134 (47.02)	141 (49.82)
95% CI	(41.22-52.81)	(44.00-55.65)
Difference in clinical remission rate (%) (95% CI)		2.72 (-5.47 to 10.90)
P-value [c]		0.515
Relative risk (95% CI) [d]		1.06 (0.89-1.25)
Time to Clinical Remission		
Number (%) of subjects who achieved clinical remissions [b, f]	202 (70.88)	211 (74.56)
Number (%) of censored cases [b, g]	83 (29.12)	72 (25.44)
Kaplan-Meier estimate, median (95% CI), weeks		
Median	7.14 (7.00-11.29)	7.00 (6.71-7.29)
P-value (log-rank test, Cx601 vs placebo) [h]		0.374
Hazard ratio (95% CI)		1.09 (0.90-1.32)
P-value [i]		0.386
Week 52 Secondary Endpoints		
Combined Remission		
Number (%) of subjects who achieved combined remission [a, b]	113 (39.65)	116 (40.99)
95% CI	(33.97-45.33)	(35.26-46.72)
Difference in combined remission rate (%) (95% CI) [c]		1.27 (-6.77 to 9.31)
P-value [c]		0.757
Relative risk (95% CI) [d]		1.03 (0.85-1.26)
Clinical Remission		
Number (%) of subjects who achieved clinical remission [b,e]	118 (41.40)	122 (43.11)
95% CI	(35.69-47.12)	(37.34-48.88)
Difference in clinical remission rate (%) (95% CI)		1.60 (-6.46 to 9.66)
P-value [c]		0.697
Relative risk (95% CI) [d]		1.04 (0.86-1.26)

Source: Cx601-0303 Table 15.2.1.1.1 (combined remission at Week 24), Table 15.2.2.1.1 (clinical remission at Week 24), Table 15.2.3.1.1 (time to clinical remission at Week 24), Table 15.2.1.1.2 (combined remission at Week 52), Table 15.2.2.1.2 (clinical remission at Week 52).

CMH: Cochran-Mantel-Haenszel; Cx601: darvadstrocel; ITT: intent-to-treat; IWRS: interactive web response system; MRI: magnetic resonance imaging.

[a] Combined remission was defined as closure of all treated external openings that were draining at baseline despite gentle finger compression and absence of collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by blinded central MRI assessment. Missing values and rescue medication or a rescue procedure were treated as a nonresponse.

[b] Percentages were based on the number of subjects in the ITT analysis set.

[c] For the difference in combined remission rate or clinical remission rate (Cx601 vs placebo), the 95% CI and p-value were based on a stratified CMH test with adjustment for IWRS randomization stratification factors. Except otherwise stated, asymptotic Wald CIs are displayed.

[d] The adjusted relative risk and its 95% CI were based on a stratified CMH test with adjustment for IWRS randomization stratification factors.

[e] Clinical remission was defined as closure of all treated external openings that were draining at baseline despite gentle finger compression. Missing values and rescue medication or a rescue procedure were treated as no response.

[f] Time to clinical remission (weeks) assessed at Week 24 was the time from the start of treatment to the first visit with closure of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed.

	Placebo N = 285	Cx601 N = 283

[g] Subjects who did not achieve clinical remission by Week 24 were censored at Week 24 visit; subjects who discontinued without clinical remission before Week 24 were censored at the date of their last visit.
[h] The p-value was based on a stratified log-rank test with adjustment for IWRS randomization stratification factors.
[i] A Cox proportional hazard model was used to estimate the hazard ratio and 95% CI, with adjustment for IWRS randomization stratification factors.

Assessor's comment:

The primary endpoint, combined remission at week 24, was achieved by 138/283 patients (48.76%) in the darvadstrocel group and 132/285 patients (46.32) in the placebo group. The difference was not statistically significant (p=0.571), and thus the study failed to meet its primary endpoint. The negative result was further supported by all secondary endpoints with very similar outcomes in the two treatment arms.

A sensitivity analysis using multiple imputation was conducted to evaluate the impact of missing data in the ITT analysis set (see Section 7.8.8 of the SAP for additional details). The results of this analysis were consistent with the primary analysis result of clinical remission.

Table 8. Combined Remission of Perianal Fistulizing Crohn's Disease at Week 24 Sensitivity Analysis using Multiple Imputation (ITT Analysis Set)

	Placebo (N=285)	Cx601 (N=283)
Combined Remissions % (95% CI) [a]	53.33 (47.20, 59.33)	56.01 (49.84, 62.19)
No Combined Remissions (%) [b]	46.74	43.99
Difference in Combined Remission Rate (%) (95% CI) [c]		2.60 (-6.01, 11.21)
P-value [c]		0.453

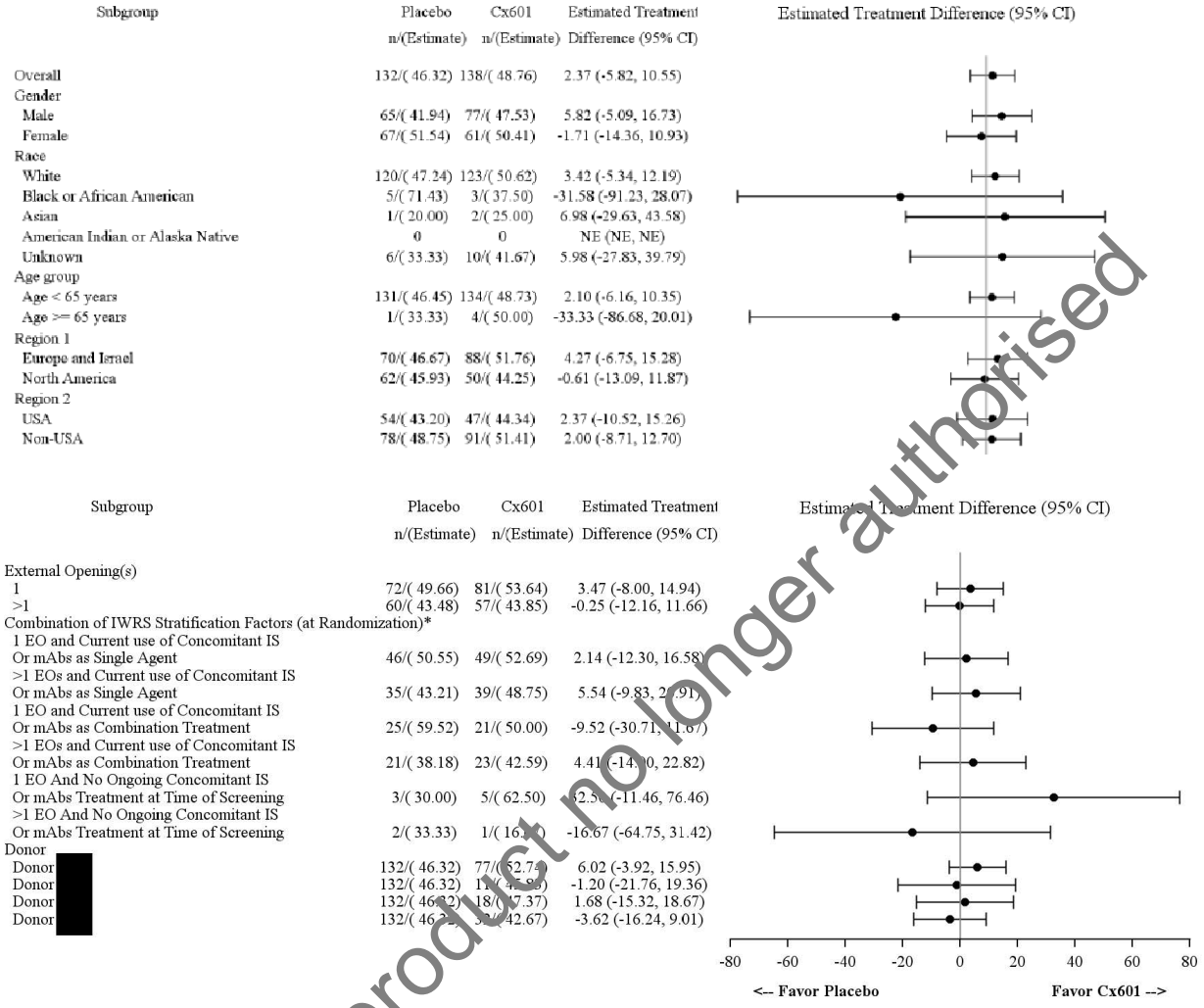
CI = Confidence Interval; CMH = Cochran-Mantel-Haenszel; IWRS = Interactive Web Response System; ITT=Intention to Treat.
[a]Missing efficacy endpoint data is imputed using multiple imputation technique. See SAP section 7.8.8 for details.
[b]No combined remission is considered for subjects taken rescue medication or rescue procedure within week 24 Rescue medication rule will be applied after multiple imputation.
[c]For the difference in combined remission rate (Cx601 vs Placebo), the 95% CI and p-value are based on the CMH test adjusted for IWRS randomization stratification factors. Except otherwise stated, asymptotic Wald's confidence intervals are displayed.

Assessor's comment

A sensitivity analysis using multiple imputation instead of failure imputation for missing data was performed. The results were consistent with the primary analysis. As expected, the responder rates were somewhat higher in both treatment groups, but the treatment difference is similar. This indicates that the negative outcome is robust to the handling of missing data.

A forest plot of combined remission of perianal fistulizing CD at Week 24 is shown below.

Figure 3. Combined Remission of Perianal Fistulizing CD at Week 24 Forest Plot by Subgroup (ITT Analysis Set)



Assessor's comment:

The results were overall similar across subgroups.

Post hoc analyses

According to the MAH, due to an unusual increased efficacy in the placebo group observed during the second half of the study period, post hoc analyses were conducted by 2 periods of study time with the cut-off date of 11 March 2020 (the declaration of COVID-19 pandemic by WHO). Overall, the pre-COVID results showed a greater difference in efficacy benefits in favor of darvadstrocel group than those results during the COVID-19 period, which was attributable to a high placebo response observed during COVID-19.

Potential explanations of the high response rate in the placebo group were explored through subgroup analyses using demographics and baseline characteristics and in post hoc analyses by timing of enrollment in the study relative to the onset of the COVID-19 pandemic; however, no clear factors driving this effect were identified.

Assessor's comment:
These post hoc analyses are of limited value for the overall efficacy conclusions.

6.2. Supportive studies

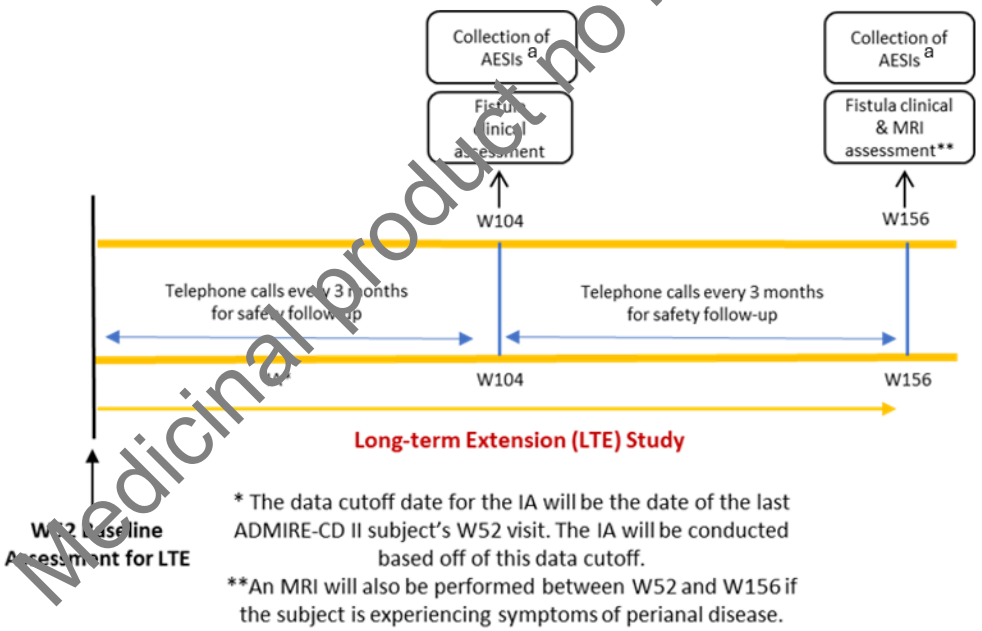
For assessment of darvadstrocel-3003 and Alofisel-5003, please refer also to section 9.

6.2.1. Study Darvadstrocel-3003

Study Design

This LTE study is currently ongoing and is a follow-up of ADMIRE-CD II to evaluate the long-term safety and efficacy of darvadstrocel in the treatment of complex CPFs. To be eligible for the LTE study, subjects must have completed the final Week 52 assessment in ADMIRE-CD II. A schematic of the study design is presented in *Figure **4***. Enrollment into the LTE study after completing ADMIRE-CD II was optional. Subjects are analyzed according to the actual treatment received in the placebo-controlled ADMIRE-CD II study. Although the LTE study included a placebo treatment group, the LTE study itself was not randomized.

Figure 4. Schematic of Darvadstrocel-3003 Study Design



Source: Darvadstrocel-3003 interim CSR Figure 9.a.
AE: adverse event; AESI: adverse event of special interest; CSR: clinical study report; IA: interim analysis; LTE: long-term extension; MRI: magnetic resonance imaging; SAE: serious adverse events; W: week.
[a] AEs, SAEs, and AESIs will be evaluated.

This study is evaluating the long-term safety of darvadstrocel, including adverse events (AEs), serious adverse events (SAEs), and specific adverse events of special interest (AESIs) (immunogenicity/alloimmune reactions, tumorgenicity, and ectopic tissue formation). The study also evaluates the long-term effect of darvadstrocel treatment on fistula remission, major fistula-related events (hospitalizations and surgeries), and health-related quality-of-life measurements.

Study visits occur annually for up to 2 years after enrollment into the LTE study or 3 years following enrollment in ADMIRE-CD II. At these visits, clinical assessment of the fistula is considered for clinical remission. Additional telephone call visits are being conducted every 3 months for safety follow-up.

This LTE study was blinded until unblinding of ADMIRE-CD II occurred after database lock, when all subjects had completed the final Week 52 visit. After unblinding of ADMIRE-CD II, the LTE study is being conducted as an open-label study. Subjects remain in the treatment group assigned in ADMIRE-CD II.

There is no drug administration in this study. A single dose of darvadstrocel (120 million cells) or placebo was administered in ADMIRE-CD II.

The primary endpoint of Study Darvadstrocel-3003 was the long-term safety of darvadstrocel, including AEs, SAEs, and specific AESIs, but the study also evaluates the long-term effect of darvadstrocel treatment.

Key secondary efficacy endpoints for Study Darvadstrocel-3003 are defined below. As of the interim data lock point (26 July 2023), efficacy endpoints involving MRI test results (ie, combined remission, relapse, and new anal abscess in treated fistula) were not included in the efficacy analysis.

Table 9. Study Darvadstrocel-3003: Key Secondary Efficacy Endpoints

Efficacy Endpoint	Definition
Secondary	
Clinical remission at Week 104 and Week 156 after IMP administration	Closure of all treated external fistula openings that were draining at baseline of ADMIRE-CD II despite gentle finger compression.
Clinical response at Week 104 and Week 156 after IMP administration	Closure of at least 50% of all treated external fistula openings that were draining at baseline of ADMIRE-CD II despite gentle finger compression.
Relapse at Week 156	*Defined as subjects who were in combined remission at Week 52 of ADMIRE-CD II, and who had either:* – *Reopening of any of the treated fistula(s) external openings with active drainage as clinically assessed, or* – *The development of a perianal fluid collection >2 cm of the treated perianal fistulas confirmed by centrally read MRI assessment.*
Combined remission at Week 156 after IMP administration	Clinical assessment of closure of all treated external openings that were draining at baseline of ADMIRE-CD II, despite gentle finger compression, and absence of collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by centrally-read, blinded MRI assessment.

Source: Darvadstrocel-3003 interim CSR Section 9.5.3.
ADMIRE-CD II: Study Cx601-0303; CSR: clinical study report; IMP: investigational medicinal product; MRI: magnetic resonance imaging.

Efficacy analyses were performed using the safety analysis set, and 2 sets of baseline values were considered in this study for both efficacy and safety analyses, unless otherwise specified. The ADMIRE-CD II baseline value referred to the baseline from ADMIRE-CD II, and the LTE baseline value referred to the baseline (ie, Week 52 of ADMIRE-CD II) or the re-baseline value collected at entry into the LTE study. For those subjects who had a gap of >4 weeks between the Week 52 visit of ADMIRE-CD II and signing of the informed consent form for the LTE study, a re-baseline visit was scheduled. MRI assessment was not included at the re-baseline visit; MRIs were performed in all subjects at the Week 156 visit of the LTE study. Study visits occur annually for up to 2 years after enrollment into the LTE of ADMIRE-CD II or 3 years following treatment in ADMIRE-CD II. At these visits, clinical assessment of the fistula was considered for clinical remission. In addition, unscheduled visits are performed for safety follow-up and for subjects experiencing any clinically significant symptoms of perianal disease.

Efficacy endpoints were summarized by visit and treatment group starting from the parent study (ADMIRE-CD II), as applicable. The proportions, along with their 95% 2-sided CIs, were provided by visit (whenever applicable) and treatment group for the following endpoints: clinical remission and clinical response.

Continuous endpoints were summarized descriptively by visit and treatment group for change from baseline of ADMIRE-CD II.

Subjects who received surgical and/or biologic treatment for perianal fistulizing disease were considered nonresponders for the analysis of binary endpoints from the next day of "rescue medication" or "rescue procedure" and onward.

Table 10. Study Darvadstrocel-3003: Clinical Remission of Perianal Fistulizing CD at LTE Week 104 and 156 – IA Through 26 July 2023 (Safety Analysis Set)

	Placebo (N = 74)		Cx601 (N = 76)	
	n (%)	95% CI	n (%)	95% CI
LTE Week 104				
Clinical remission [a]	27 (36.49)	(25.52-47.45)	37 (48.68)	(37.45-59.92)
No clinical remission [b]	47 (63.51)	-	39 (51.32)	-
Based on clinical assessment	12 (16.22)	-	10 (13.16)	-
Due to rescue medications/procedure	23 (31.08)	-	18 (23.68)	-
Due to missing data	12 (16.22)	-	11 (14.47)	-
LTE Week 156				
Clinical remission [a, c]	18 (30.51)	(18.76-42.26)	22 (40.74)	(27.64-53.85)
No clinical remission [b, c]	41 (69.49)	-	32 (59.26)	-
Based on clinical assessment	6 (10.17)	-	6 (11.11)	-
Due to rescue medications/procedure	16 (27.12)	-	15 (27.78)	-
Due to missing data	19 (32.20)	-	11 (20.37)	-

Assessor's comment:

This was primarily a safety study and efficacy outcomes are presented descriptively.

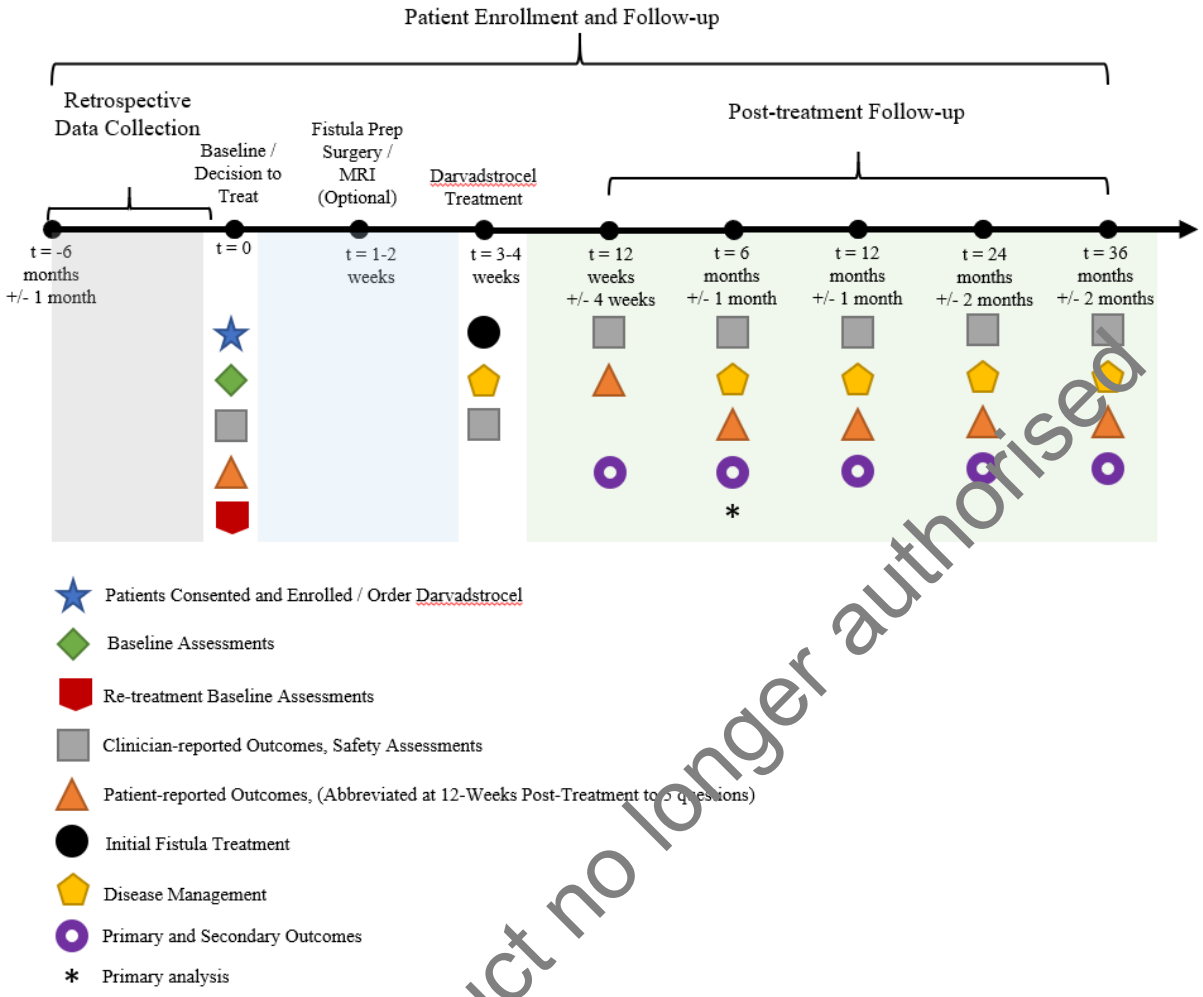
According to the MAH, the study demonstrated that darvadstrocel maintained an acceptable safety profile and that caution must be exercised when interpreting the efficacy results presented in this interim report as this is an ongoing study. Because subjects were not randomized into 2 groups and no formal statistical comparison was conducted, meaningful comparisons cannot be made between the 2 groups.

6.2.2. Study Alofisel-5003 (INSPIRE)

Study Design

Study Alofisel-5003 (INSPIRE; EUPAS24267) is an ongoing, multicenter, observational postapproval study in patients with CD with complex CPFs treated with darvadstrocel. A schematic of the study design is presented below.

Figure 5. Schematic of Darvadstrocel-5003 Study Design



Source: Alofisel-5003 (INSPIRE) interim CSR figure 9.a
CSR: clinical study report; MRI: magnetic resonance imaging; t: timing.

Patients were invited to participate in the study only after their treating healthcare professional and the patient had opted to proceed with darvadstrocel treatment. This postapproval study is being conducted in Europe and is designed to evaluate the real-world clinical effectiveness and safety of darvadstrocel in patients with CD with complex CPFs for up to 36 months after darvadstrocel administration. In this study, the primary outcomes are clinical response and clinical remission. Moreover, additional post hoc analyses are being performed to evaluate the real-world effectiveness of darvadstrocel treatment at 6 months and 12 months by applying additional rules for analysis sets, imputation of missing data, and rescue therapies, which are similar to those in ADMIRE-CD II.

The planned sample size for the study was approximately 800 patients with no quota set for the number of patients to be included from any region or country.

Primary, secondary, and post hoc effectiveness endpoints for Study Alofisel-5003 (INSPIRE) study are defined below.

Table 11. Study Alofisel-5003 (INSPIRE): Primary, Key Secondary, and Post Hoc Effectiveness Outcomes

Effectiveness Outcomes	Definition
Primary	
Clinical response	Closure of fistula despite gentle finger compression of ≥50% of external openings treated with darvadstrocel that were draining at baseline.
Clinical remission	Closure of fistula despite gentle finger compression of all external openings treated with darvadstrocel that were draining at baseline.
Secondary	
Combined remission	Closure of all external fistula openings treated with darvadstrocel that were draining at baseline, as assessed clinically, despite gentle finger compression; and the absence of fluid collections >2 cm in at least 2 dimensions, as confirmed by local pelvic MRI (if conducted) reading at least 6 months after administration of darvadstrocel.
Relapse of perianal fistula treated	Reopening of any of the external fistula openings treated with darvadstrocel with active drainage, as clinically assessed, or the development of a perianal collection >2 cm in at least 2 dimensions of the perianal fistula(s) treated with darvadstrocel confirmed by local MRI assessment (if conducted).
New perianal abscess	Rim-enhancing fluid collection, exhibiting T2 hyperintensity with peripheral rim enhancement on T1 post-gadolinium visualized by pelvic MRI (if performed) in the treated area.
Post hoc	
Clinical remission	Closure of fistula despite gentle finger compression of all external openings treated with darvadstrocel.
Relapse of perianal fistula treated	Reopening of any of the external fistula openings treated with darvadstrocel, as clinically assessed, or the development of a perianal collection >2 cm in at least 2 dimensions of the perianal fistula(s) treated with darvadstrocel confirmed by local MRI assessment (if conducted).

Source: Alofisel-5003 interim CSR Section 10.3.1, Section 10.4.1, and Section 10.4.2.
CSR: clinical study report; MRI: magnetic resonance imaging.

The prespecified primary outcomes of clinical response and clinical remission were assessed at 12 weeks and 6, 12, 24, and 36 months.

In the all-treated population, clinical response was achieved in 75.9% (198 of 261) of patients at Month 6 and in 79.9% (107 of 134) of patients at Month 12 after darvadstrocel treatment.

Clinical remission was achieved at 6 months after darvadstrocel treatment in the all-treated population in 69.7% (182 of 261) of patients with available data. Of those, 54.4% (99 patients) had sustained clinical remission from the prior visit (ie, 12 weeks), and 45.6% (83 patients) had achieved new clinical remission by 6 months. Clinical remission was achieved at 12 months after darvadstrocel treatment in 102 of 134 patients (76.1%) with available data. Of the patients who achieved clinical remission at 12 months, 85.3% (87 patients) had sustained clinical remission from the prior visit (ie, 6 months), and 12.7% (13 patients) had achieved new clinical remission at 12 months.

Assessor's comment:

This was an observational study and all efficacy endpoints are descriptive.

The MAH concludes that the results support the effectiveness of darvadstrocel as a treatment for complex CPFs in the real-world setting. Clinical response and clinical remission rates achieved in interim results from this study support the benefit profile of darvadstrocel in adult patients with CD and complex CPF. Treatment with darvadstrocel was well tolerated, and no new safety signals were observed during this study. The overall safety profile remains consistent with the known safety profile of darvadstrocel.

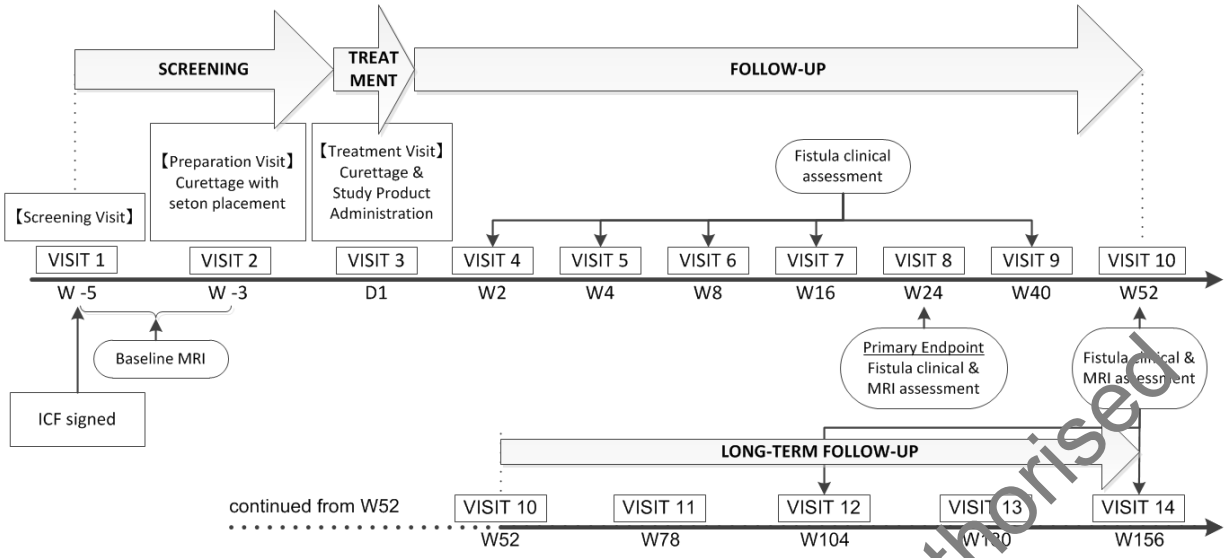
6.2.3. Study Darvadstrocel-3002

Study Design

Study Darvadstrocel-3002 was a phase 3, multicenter, open-label, uncontrolled study to evaluate the efficacy and safety of darvadstrocel in the treatment of complex perianal fistulas in Japanese adult subjects with CD. This study was conducted at 9 sites in Japan.

The study included subjects with nonactive or mildly active CD (defined by CDAI ≤220) with complex perianal fistulas who had been previously treated for complex perianal fistulas and who were refractory (inadequate response, loss of response, or intolerance) to at least 1 of the following treatments: antibiotics, immunomodulators, or biologics. Subjects' refractory to antibiotics only were to be less than 25% of all subjects enrolled. The study was conducted as an add-on study in which continuation of baseline treatments for CD (eg, IS, biologics) was permitted under certain conditions. A schematic of the study design is shown below.

Figure 6. Schematic of Darvadstrocel-3002 Study Design



Source: Darvadstrocel-3002 Week 156 CSR Figure 9.a.
CSR: clinical study report; D: day; ICF: informed consent form; MRI: magnetic resonance imaging; W: week.

Subjects received a perilesionally administered dose of open label darvadstrocel (120 million cells). Following IMP administration, all subjects were to be followed up to Week 52, with a long-term follow-up period up to Week 156. The primary endpoint was evaluated at Week 24. In the 52-week follow-up period after IMP administration, efficacy and safety were evaluated until Week 52, and in the long-term follow-up period after Week 52, safety was followed up every 26 weeks (every 6 months) until Week 156 for all subjects (as much as possible).

The planned sample size was 20 subjects based on feasibility. Given an expected proportion of subjects with combined remission of 50% based on Week 24 results in ADMIRE-CD, a sample size of 20 subjects was expected to provide at least 94% probability of showing a proportion of subjects with combined remission of 35% or more.

The primary, secondary, and additional efficacy endpoints of Study Darvadstrocel-3002 are defined below.

Table 12. Study Darvadstrocel-3002: Primary, Secondary, and Additional Efficacy Endpoints

Efficacy Endpoint	Definition
Primary	
Combined remission at Week 24	Clinically confirmed closure of all treated external openings that were draining at screening despite gentle finger compression, and absence of collections >2 cm in the treated fistulas, which was confirmed by central MRI assessment.
Secondary	
Combined remission at Week 52	Clinically confirmed closure of all treated external openings that were draining at screening despite gentle finger compression, and absence of collections >2 cm in the treated fistulas, which was confirmed by central MRI assessment.
Clinical remission at Week 24 and at Week 52	Clinically confirmed closure of all treated external openings that were draining at screening despite gentle finger compression.
Response at Week 24 and at Week 52	Clinically confirmed closure of at least 50% of all treated external openings that were draining at screening despite gentle finger compression. [a]

Efficacy Endpoint	Definition
Time to combined remission at Week 52	The time from the study treatment administration to the first visit by which combined remission is observed.
Time to clinical remission by Week 24 and by Week 52	Time from study treatment administration to the first visit at which clinical remission is observed.
Time to response by Week 24 and by Week 52	Time from study treatment administration to the first visit at which response is observed.
Relapse at Week 24 and at Week 52	Clinically confirmed reopening of any of the treated external openings with active drainage, or the development of a collection >2 cm in the treated fistulas confirmed by central MRI assessment. (A collection >2 cm was considered as present if at least 2 out of the 3 dimensions centrally assessed were >2 cm in any of fistula tracts.)
Time to relapse by Week 24 and at Week 52	Time from the first visit at which clinical remission was observed to the first visit at which relapse was observed.
Additional	
Combined remission at Week 104 and Week 156	Clinically confirmed closure of all treated external openings that were draining at screening despite gentle finger compression, and absence of collections >2 cm in the treated fistulas confirmed by central MRI assessment.
Clinical remission at Week 104 and Week 156	Clinically confirmed closure of all treated external openings that were draining at screening despite gentle finger compression.
Response at Week 104 and Week 156	Clinically confirmed closure of at least 50% of all treated external openings that were draining at screening despite gentle finger compression. [a]

Source: Darvadstrocel-3002 (Week 156) CSR Section 9.5.3 and Darvadstrocel-3002 SAP (Week 156) Section 7.1.1 and Section 7.8.1.
CSR: clinical study report; MRI: magnetic resonance imaging; SAP: statistical analysis plan.
[a] Clinically confirmed closure of at least 50% was defined as 1 closure for subjects with 1 baseline external opening, 1 or 2 closures for subjects with 2 baseline external openings, and 2 or 3 closures for subjects with 3 baseline external openings.

The analyses of the efficacy endpoints described were performed on the ITT analysis set. In the ITT analysis set, the proportion of subjects achieving combined remission at Week 24 (95% CI) was 59.1% (38.5%-79.6%).

The proportion of subjects achieving clinical remission and response at Week 24 (95% CI) was 59.1% (38.5%-79.6%) and 81.8% (65.7%-97.9%), respectively. The median time to clinical remission and response at Week 24 (95% CI) was 30.0 (14.0-116.0) days and 18.0 (12.0-30.0) days, respectively.

The proportion of subjects achieving combined remission at Week 52 (95% CI) was 68.2% (48.7%-87.6%).

Assessor's comment:

According to the MAH, the results of the primary and secondary efficacy endpoints demonstrated efficacy of darvadstrocel in Japanese subjects. However, due to the open-label, uncontrolled study design no robust efficacy conclusions can be drawn from the study.

6.3. Comparison and analyses of results across studies

According to the MAH, there are distinct differences in inclusion/exclusion criteria for the subject population, mandatory seton placement, handling of missing data, and rescue medication (treatment failure). Subjects in both studies had complex CPF that had shown an inadequate response to IS or anti-TNF therapies (or other biologics, in the case of ADMIRE-CD II), while eligible subjects in ADMIRE-CD also could have been eligible if they had CPF(s) that had shown an inadequate response to

antibiotic treatment only. Missing data were imputed using the LOCF method in ADMIRE-CD, while nonresponder imputation was used in ADMIRE-CD II. In addition, subjects in both studies underwent exploration under anesthesia and fistula curettage at the preparation visit 2 to 3 weeks before darvadstrocel was administered; however, seton placement at the preparation visit was mandatory in ADMIRE-CD II but was performed only if clinically indicated in ADMIRE-CD.

Key study design elements, including differences between the ADMIRE-CD and ADMIRE-CD II studies, are outlined below.

Table 13 Comparison of Study Designs Between Darvadstrocel Phase 3, Placebo-Controlled Efficacy Studies

	ADMIRE-CD (Cx601-0302)	**ADMIRE-CD II (Cx601-0303)**
Target population	Presence of complex CPF and nonactive or mildly active luminal CD (CDAI ≤220). Refractory to at least 1 of the following treatments: antibiotics, immunosuppressants, or antiTNFs.	Presence of complex CPF and clinically controlled nonactive or mildly active CD (confirmed by colonoscopy and PRO-2 score <14). Refractory complex CPF (inadequate response, loss of response, or documented intolerance while receiving immunosuppressants, anti-TNF, or other biologic within specified timeframe).
Study design	Double-blind, placebo-controlled study to assess efficacy and safety of allogeneic eASCs for the treatment of complex CPF in CD over a period of 24 weeks and an extended follow-up period up to Week 104.	Double-blind, placebo-controlled study to assess efficacy and safety of allogeneic eASCs for the treatment of complex CPF in CD over a period of 24 weeks and a follow-up period up to Week 52.
Dose	Single dose of 120 million cells of darvadstrocel.	Single dose of 120 million cells of darvadstrocel.
Primary endpoint	Combined remission of perianal fistulizing CD at Week 24, defined as the clinical assessment of closure of all treated external openings that were draining at baseline despite gentle finger compression at Week 24, and absence of collections >2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment at Week 24.	Proportion of subjects who achieve combined remission at Week 24 after IMP administration, where combined remission is defined as: c) The closure of all treated external openings that were draining at baseline despite gentle finger compression. AND d) Absence of collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by blinded central MRI assessment.
Key secondary endpoint	Clinical remission and response at Week 24.	Clinical remission and time to clinical remission at Week 24.
Other secondary endpoints under family-wise type I error control	Not applicable.	Combined remission at Week 52 and clinical remission at Week 52.
Stratification	Stratification by concomitant treatment.	Stratification by concomitant treatment and also by fistula severity (number of external openings).
Efficacy statistical analysis (handling of missing data)	LOCF	NRI

	ADMIRE-CD (Cx601-0302)	ADMIRE-CD II (Cx601-0303)
Rescue medication (treatment failure)	Continuous use of antibiotics ≥4 weeks was permitted, and then nonresponder status was imputed. Systemic or rectal steroids, new anti-TNF, new immunosuppressant, or surgical procedure after protocol-specified amount of time was imputed as nonresponse.	Addition of any new or increase in dose/frequency of immunosuppressant or biologic; systemic or rectal steroids for CD flare; prolonged use of antibiotics (>2 weeks) or new surgical procedure after protocol-specified amount of time was imputed as nonresponse.
Surgical procedure	Preparation visit: curettage and antibiotic cover were recommended.	Preparation visit: curettage and seton placement and antibiotic cover were mandatory.
Withdrawal criteria	Subjects with treatment failure were to be withdrawn and encouraged to undergo early termination visit.	Subjects were maintained in the study for safety assessment despite treatment failure

Source: Cx601-0302 Protocol Amendment 6, Cx601-0303 Protocol Amendment 3, Cx601-0302 Statistical Analysis Plan Version 3 (Cx601-0302 Appendix 16.1.9) and Cx601-0303 Statistical Analysis Plan Version 6 (Cx601-0303 CSR Appendix 16.1.9.6).
CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CPF: Crohn's perianal fistula; eASC: expanded adipose-derived stem cell; IMP: investigational medicinal product; LOCF: last observation carried forward; MRI: magnetic resonance imaging; NRI: nonresponder imputation; PRO-2: 2-item patient-reported outcome measure; TNF: tumor necrosis factor.

Assessor's comment:

Overall, the study designs and study populations were very similar. The MAH states that one of the main differences was that in ADMIRE-CD, subjects were eligible if they had shown an inadequate response to antibiotic treatment only, while immunosuppressive of biologic therapy was mandatory in ADMIRE-CD II. According to the EPAR, Alofisel, INN-darvadstrocel (europa.eu), almost 80% had prior immunosuppressive therapy and almost 30% had prior anti-TNF treatment. Therefore, it is questionable whether this can be considered as a major difference between the study populations. The MAH is asked to clarify how many patients enrolled in ADMIRE-CD that had prior therapy with antibiotics only.

Another argument for the important differences between the studies is the handling of missing data. Missing data were imputed using the LOCF method in ADMIRE-CD, while nonresponder imputation was used in ADMIRE-CD II.

The Applicant has not provided a comprehensive analysis of the impact of missing data in the two studies. However, a sensitivity analysis for the ADMIRE-CD II study based on multiple imputation for missing data was presented and showed similar results as the primary analysis based on non-responder imputation. This indicates that the negative outcome is robust to the handling of missing data and hence, the treatment differences in the ADMIRE-CD II trial is not expected to be underestimated to a large extent due to the missing data handling.

Finally, the differences in surgical procedure and withdrawal criteria are not considered of such importance that they would preclude a comparison the study results.

Therefore, the MAH has selected a subsample of the ADMIRE-CD population that is similar to the ADMIRE-CD II population using a similar profile matching approach; however, conducting opposite matching is not relevant, given that the marketing EU authorization was based on the ADMIRE-CD population.

The profile matching method selects the largest unweighted subsample from a first sample (ADMIRE-CD II) that matches the "profile" of a second target sample (ADMIRE-CD). This method was applied as a means to combine the results of the 2 phase 3 placebo-controlled studies (ie, ADMIRE-CD and ADMIRE-CD II) because of its simplicity and avoidance of weighted samples, which can complicate subsequent analyses.

Factors used for profile matching included age, gender, external openings (1 vs >1), time of CD diagnosis to screening visit, baseline concomitant medication stratification factors, and prior therapy with IS or mAbs; and the tolerance level (ie, standardized mean differences for all factors selected for matching) was set to 0.20.

Given the substantial representation of ADMIRE-CD subjects in the pooled dataset, a limitation of this post hoc analysis is that the outcomes are significantly influenced by the results of ADMIRE-CD.

Assessor's comment:

The MAH states that they selected a subsample of the ADMIRE-CD population that is similar to the ADMIRE-CD II population, however it seems as if the opposite was made i.e. a subsample of the ADMIRE-CD II population was selected based on the ADMIRE-CD population. This is expected to be a typo since the correct description is provided elsewhere in the documentation.

It is agreed with the MAH that a limitation of this post hoc analysis is that the outcomes are significantly influenced by the results of ADMIRE-CD, where results were available when the post-hoc analysis was designed. This severely impacts the reliability of the post-hoc analysis.

The results are shown below.

Table 14. Post Hoc Pooled Efficacy Analysis of ADMIRE-CD and ADMIRE-CD II: Summary of Efficacy Results at Week 24 (ADMIRE-CD ITT Analysis Set and ADMIRE-CD II Matched Subsample)

	Full ADMIRE-CD (Cx601-0302)		ADMIRE-CD II (Cx601-0303) Matched Subsample		Pooled ADMIRE-CD (Cx601-0302) and ADMIRE-CD II (Cx601-0303) Matched Subsample	
Endpoint Statistic	**Placebo (N = 105)**	**Cx601 (N = 107)**	**Placebo (N = 46)**	**Cx601 (N = 39)**	**Placebo (N = 151)**	**Cx601 (N = 146)**
Combined remission [a]						
n (%)	36 (34.29)	53 (49.53)	22 (47.83)	22 (56.41)	58 (38.41)	75 (51.37)
95% CI	(25.21-43.36)	(40.06-59.01)	(33.39-62.26)	(40.85-71.97)	(30.65-46.17)	(43.26-59.48)
Difference in combined remission rate (95% CI) [b]		15.25 (2.13-28.37)		8.58 (-12.64 to 29.81)		12.96 (1.74-24.18)
Relative risk (95% CI) [c]		1.44(1.04-2.00)		1.18 (0.78-1.78)		1.34 (1.03-1.73)
Clinical remission [d]						
n (%)	43 (40.95)	57 (53.27)	22 (47.83)	23 (58.97)	65 (43.05)	80 (54.79)
95% CI	(31.55-50.36)	(43.82-62.72)	(33.39-62.26)	(43.54-74.41)	(35.15-50.94)	(46.72-62.87)
Difference in clinical remission rate (95% CI) [b]		12.32 (-1.02 to 25.65)		11.15 (-9.99 to 32.28)		11.75 (0.45-23.04)
Relative risk (95% CI) [c]		1.30 (0.97-1.74)		1.23 (0.83-1.84)		1.27 (1.01-1.61)

Table 15. Post Hoc Pooled Efficacy Analysis of ADMIRE-CD and ADMIRE-CD II: Summary of Efficacy Results at Week 52 (ADMIRE-CD ITT Analysis Set and ADMIRE-CD II Matched Subsample)

	Full ADMIRE-CD (Cx601-0302)		ADMIRE-CD II (Cx601-0303) Matched Subsample		Pooled ADMIRE-CD (Cx601-0302) and ADMIRE-CD II (Cx601-0303) Matched Subsample	
Endpoint Statistic	**Placebo (N = 105)**	**Cx601 (N = 107)**	**Placebo (N = 46)**	**Cx601 (N = 39)**	**Placebo (N = 151)**	**Cx601 (N = 146)**
Combined remission [a]						
n (%)	39 (37.14)	58 (54.21)	19 (41.30)	21 (53.85)	58 (38.41)	79 (54.11)
95% CI	(27.90-46.38)	(44.77-63.65)	(27.08-55.53)	(38.20-69.49)	(30.65-46.17)	(46.03-62.19)
Difference in combined remission rate (95% CI) [b]		17.06 (3.85-30.27)		12.54 (-8.61 to 33.69)		15.70 (4.50-26.90)
Relative risk (95% CI) [c]		1.46 (1.08-1.98)		1.30 (0.83, 2.05)		1.41 (1.10-1.81)
Clinical remission [d]						
n (%)	42 (40.0)	61 (57.01)	20 (43.48)	21 (53.85)	62 (41.06)	82 (56.16)
95% CI	(30.63-49.37)	(47.63-66.39)	(29.15-57.80)	(38.20-69.49)	(33.21-48.91)	(48.12-64.21)
Difference in clinical remission rate (95% CI) [b]		17.01 (3.75-30.27)		10.37 (-10.85 to 31.58)		15.10 (3.86-26.35)
Relative risk (95% CI) [c]		1.43 (1.07-1.9)		1.24 (0.80-1.92)		1.37 (1.08-1.74)

Assessor's comment:

The MAH's approach and analyses are acknowledged but not agreed with. The post-hoc analyses are significantly influenced by the results of ADMIRE-CD, and of limited value for the overall efficacy conclusions. The post-hoc analyses cannot disregard the fact that ADMIRE-CD II was a failed study.

Persistence of efficacy

Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy up to Week 52 has been studied in ADMIRE-CD, ADMIRE-CD II, Study Alofisel-5003 (INSPIRE), and Study Darvadstrocel-3002. The persistence of efficacy beyond Week 52 has been studied in ADMIRE-CD, Study Darvadstrocel-3003, and Study Darvadstrocel-3002.

In ADMIRE-CD, the percentages of subjects in the darvadstrocel and placebo groups with combined remission at Week 24 (49.5% and 34.3%, respectively, p = 0.024) were maintained to Week 52 (54.2% and 37.1%, respectively).

In ADMIRE-CD II, the darvadstrocel treatment group had a numerically higher response rate compared with placebo for key efficacy endpoints at Week 24. However, the difference between study groups was not statistically significant or clinically meaningful. At Week 52, a similar proportion of subjects treated with darvadstrocel achieved combined remission compared with subjects treated with placebo (40.99% vs 39.65%, p = 0.757). In addition, the efficacy rate at Week 52 in the darvadstrocel group was unexpectedly lower when compared with the efficacy rate at Week 24.

In Study Alofisel-5003 (INSPIRE), post hoc effectiveness analysis of interim results as of 03 April 2023 showed that the clinical remission rate observed at 6 months after darvadstrocel treatment (60.7%) was sustained at 12 months after darvadstrocel treatment (60.3%) in the safety analysis set.

In Study Darvadstrocel-3002, 84.6% of subjects who achieved combined remission at Week 24 also achieved combined remission at Week 52, and 3 subjects (23.1%) experienced relapse by Week 52. The MAH states that these results suggest that the efficacy of darvadstrocel is maintained from Week 24 to Week 52.

Persistence of Efficacy Beyond 52 Weeks

The persistence of efficacy of darvadstrocel beyond 52 weeks was assessed in ADMIRE-CD up to Week 104, in the ongoing LTE Study Darvadstrocel-3003 up to Week 156, and in the completed Study Darvadstrocel-3002 up to Week 156.

In ADMIRE-CD, interpretation of the efficacy of darvadstrocel beyond Week 52 is limited due to the small number of subjects who continued to be followed up after Week 52 in this study. In addition, per protocol, after Week 52, subjects could receive other treatment for their fistulas (ie, surgery or new medical treatment) with the exception of investigational drugs or other local investigational treatments in the perianal region. Therefore, efficacy results at Week 104 should be interpreted with caution. At Week 104 in ADMIRE-CD, a greater proportion of subjects achieved clinical remission in the darvadstrocel group compared with the placebo group (darvadstrocel: 52.3%; placebo: 39.0%; treatment difference: 13.3% [95% CI: -0.0 to 26.6%]).

Study Darvadstrocel-3003 is currently ongoing and is a follow-up study to evaluate the long-term safety and efficacy of darvadstrocel in subjects who completed the Week 52 visit of ADMIRE-CD II. In data collected as of 26 July 2023, subjects were assessed for clinical remission and clinical response up to Week 104 and up to Week 156 following IMP administration in the ADMIRE-CD II study. In the darvadstrocel group, clinical remission was achieved by 48.68% of subjects at Week 104 and by 40.74% of subjects at Week 156. In the placebo group, clinical remission was achieved by 36.49% of subjects at Week 104 and by 30.51% of subjects at Week 156. Clinical response was achieved in the darvadstrocel group by 56.58% of subjects at Week 104, and by 44.44% of subjects at Week 156. In the placebo group, clinical response was achieved by 40.54% of subjects at Week 104 and by 32.20% of subjects at Week 156.

In Study Darvadstrocel-3002, 55.0% of subjects who entered the long-term follow-up period achieved combined remission at all time points of Week 24, Week 52, and Week 104. In addition, 50.0% of subjects maintained combined remission at Week 24, Week 52, Week 104, and Week 156.

Assessor's comment:

There are some data to support that among patients who responded to treatment with darvadstrocel, the effect was maintained over time. However, the response rates over time are not convincingly higher than the response rates for placebo and since the overall effect of darvadstrocel is questioned, the potential long-term effect is of minor importance.

6.4. Efficacy conclusions as summarized by the MAH

The totality of efficacy data presented in this Type II variation, together with previously submitted results from ADMIRE-CD, has shown a consistent response rate at Week 24 and Week 52 among darvadstrocel-treated subjects.

The primary evidence for efficacy of darvadstrocel in the initial marketing application was derived from ADMIRE-CD, the pivotal, phase 3, randomized, double-blind, placebo-controlled study, which demonstrated the efficacy of darvadstrocel compared with placebo when administered as a single dose of 120 million cells across a range of endpoints, including the primary efficacy endpoint of combined remission at Week 24 (darvadstrocel: 49.5%; placebo: 34.3%; treatment difference: 15.2%; $p = 0.024$).

An additional phase 3 placebo-controlled study of darvadstrocel (ADMIRE-CD II) did not meet its primary efficacy endpoint of combined remission at Week 24. Treatment with a single dose of darvadstrocel suggested numerically higher response rates compared with placebo for key efficacy endpoints in the treatment of complex CPF in adult subjects with CD (combined remission at Week 24: darvadstrocel, 48.76%; placebo, 46.32%); however, the difference between treatment groups was not

clinically meaningful or statistically significant due to an unexpectedly high response in the placebo group (treatment difference: 2.37%; p = 0.571). Although the ADMIRE-CD and ADMIRE-CD II subject populations were different and cross-study comparisons of the full subject populations have limitations, the combined remission rate at Week 24 in the darvadstrocel group of ADMIRE-CD II (48.76%) was consistent with that of ADMIRE-CD (49.5%).

To summarize the overall efficacy results from 2 phase 3 studies (ADMIRE-CD and ADMIRE-CD II) with regard to the approved population from ADMIRE-CD, a post hoc analysis was performed using pooled efficacy data from ADMIRE-CD subjects and a subset of ADMIRE-CD II subjects who were identified through profile matching. Results of this analysis showed nominally favorable rates of combined remission for darvadstrocel compared with placebo at Week 24 (51.4% versus 38.4%) and at Week 52 (54.1% versus 38.4%), with treatment differences (95% CI) of 12.96% (1.74%-24.18%) and 15.70% (4.50%-26.90%), respectively.

Treatment with darvadstrocel demonstrates improvement in remission rates at Week 24 and Week 52 compared with placebo on the basis of the totality of data from these completed phase 3 placebo-controlled clinical studies as well as pooled efficacy analyses from these 2 studies.

Supportive evidence of efficacy of darvadstrocel comes from interim results of the ongoing Study Alofisel-5003 (INSPIRE), the completed phase 3 open-label Study Darvadstrocel-3002, and interim results from the ongoing LTE Study Darvadstrocel-3003, which are summarized as follows:

- Post hoc efficacy analyses of interim results (as of the data lock point of 03 April 2023) for the ongoing observational postapproval Study Alofisel-5003 (INSPIRE) incorporated analysis features similar to those in the phase 3 clinical studies of darvadstrocel (ie, ADMIRE-CD and ADMIRE-CD II). These post hoc analyses showed rates of clinical remission at 6 and 12 months (60.7% and 60.3%, respectively), which support the evidence of efficacy observed in ADMIRE-CD and in the pooled efficacy results.
- In the phase 3 open-label Study Darvadstrocel-3002, the percentage of subjects treated with darvadstrocel who achieved the primary endpoint of combined remission at Week 24 was 59.1%, which was consistent with results of the darvadstrocel treatment group in the ITT populations of ADMIRE-CD study and in the pooled efficacy results.
- Studies Darvadstrocel-3002, and Darvadstrocel-3003 also provide supportive evidence for the persistence of efficacy up to 3 years. In Study Darvadstrocel-3002, combined remission was achieved by 68.2% of subjects at Week 52, 77.3% of subjects at Week 104, and 68.2% of subjects at Week 156. In the interim results from the LTE Study Darvadstrocel-3003, clinical remission rates in the darvadstrocel treatment group were 48.68% at Week 104 and 40.74% at Week 156. Thus, efficacy of darvadstrocel can be observed up to 156 weeks after a single dose.

Together with previously submitted results from ADMIRE-CD, the results of ADMIRE-CD II and the totality of efficacy data submitted in this Type II variation demonstrate that darvadstrocel administered as a single perilesional dose of 120 million cells results in closure of complex perianal fistula(s), which can be maintained for up to 52 weeks and beyond, in adult patients with nonactive or mildly active luminal CD, when fistulas have shown an inadequate response to at least 1 conventional or biologic therapy.

6.5. Discussion

Darvadstrocel is a dispersion of expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue approved in the EU in 2018 (EMEA/H/C/004258) for the treatment of complex

perianal fistula(s) in adult patients with nonactive or mildly active luminal Crohn's disease (CD), when fistulas have shown an inadequate response to at least 1 conventional or biologic therapy. Darvadstrocel is administered as a single dose of 120 million cells per patient via perilesional injection to treat up to 3 fistula tracts that open to the perianal area. The mechanism of action proposed involves immunomodulation through reduction of T cell proliferation and release of pro-inflammatory cytokines, decrease of proliferation, expression of activating receptors and cytotoxic activity of NK cells, decrease of immune cells migrating to inflamed tissues, induction of anti-inflammatory suppressor cells such as Treg cells and M2 macrophages, and increase of phagocytosis by macrophages and neutrophils (Alofisel, INN-darvadstrocel (europa.eu)). Although mesenchymal stromal cells (MSCs) have been promising for regenerative medicine based on their ability to proliferate, differentiate, and secrete a range of growth, angiogenic, and immune regulating factors, a major disadvantage with MSC-based therapies is the occurrence of massive MSC death post-implantation and their limited long-term survival (Denoeud et al. Enzyme-controlled, nutritive hydrogel for mesenchymal stromal cell survival and paracrine functions. Commun Biol 6, 1266 (2023)). In the original application, neither clinical data on cell survival in the fistulas nor clinical data on local pharmacological actions of these cells possibly contributing to healing of the fistulas was presented. The impact of immune rejection of allogeneic cells on cell survival and efficacy should be discussed. This is important information for the integrated understanding of the potential efficacy of darvadstrocel in treatment of perianal fistulas. The MAH is asked to provide any new internal data on this matter as well as updated literature data that could shed light on this question.

Furthermore, the mechanism of action is important for the understanding of the potential effects of mesenchymal stem cells. The MAH should critically review, discuss and / or modify the MoA in light of current data from literature as follows: The proposed mechanism of action represents temporary changes in parameters seen in immune rejection (such as induction of M2 macrophages, etc). A longer duration of effects cannot be expected from cells being acutely rejected. In this respect, the claim of "low levels of HLA class I molecules" on the surface of the cells does not prevent immune rejection, as immune rejection has several different mechanisms, and low HLA expression is also a trigger for immune rejection. In the SmPC it is stated that "Alofisel (darvadstrocel) is expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue". The claim of the product being "mesenchymal stem cells" does not represent the current state of the art nomenclature. For the characterization and nomenclature of the cells, the position statement of the ISCT published in Cytotherapy. 2019 Oct;21(10):1019-1024 may be considered. Based on the provided characterization and the ISCT nomenclature, darvadstrocel seems to be no other but "a mixture of fibroblasts and myofibroblasts". The MoA should be discussed considering further developments in the field since the MAA, aggravated by the recent article retraction of a landmark 22 years old MSC paper in Nature (PMID: 38886620).

The marketing authorisation application (MAA) was based on one pivotal phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter Study Cx601-0302 (ADMIRE-CD). The study population (n=212) included were patients with mild to moderate luminal Crohn's disease and with perianal fistulas. Fistulas had previously shown an inadequate response to antibiotics (73.6%), immunosuppressants (78.3%) or anti-TNF agents (78.8%).

Although the effect compared to placebo appeared modest, it was considered to be of clinical relevance if other treatment options for fistula have failed. However, given the single pivotal trial setting, the CHMP required (as an Annex II condition of the market authorisation) the submission of the final results of another phase 3, placebo-controlled study of darvadstrocel that was ongoing at the time of marketing authorization (Study Cx601-0303, ADMIRE-CD II). This Type II variation provides the final results of ADMIRE-CD II.

ADMIRE-CD II was a phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of darvadstrocel for the treatment of complex CPF in subjects with nonactive or mildly active CD over a period of 24 weeks and a follow-up period up to 52 weeks. The study followed an add-on design in which subjects receiving any ongoing concomitant medical treatment for CD at stable doses at the time of the screening visit were allowed to continue it throughout the study. The study population included subjects whose perianal fistula(s) were previously treated and had shown an inadequate response or a loss of response, intolerance, or contraindication to immunosuppressants (IS) or mAbs.

The primary endpoint was combined remission at Week 24, defined as

c. The closure of all treated external openings that were draining at baseline despite gentle finger compression, AND

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

A total of 568 patients were included and randomised to darvadstrocel (n=283) or placebo (n=285). The study subjects were primarily male (55.8%) with a mean (SD) age of 38.1 (11.35) years; most subjects were aged <65 years (98.1%) and only 1.9% of subjects were aged ≥65 years. The majority of the subjects were white (87.5%). There were no important differences in patient characteristics. Almost all patients had concomitant use of either immunosuppressives or monoclonal antibodies (59.3%), or a combination of both (36.4%).

The primary endpoint, combined remission at week 24, was achieved by 138/283 patients (48.76%) in the darvadstrocel group and 132/285 patients (46.32%) in the placebo group. The difference was not statistically significant (p=0.571), and thus the study failed to meet its primary endpoint.

The high placebo response in the ADMIRE-CD II study is different from what was seen in the ADMIRE-CD study. In fact, the results of the ADMIRE-CD II study might well be lying in the range of placebo responses described in literature, emphasizing the uncertainties about the efficacy of Alofisel.

The initial assessment of ADMIRE-CD data raised concerns considering the small effect size and the history of negative studies with respect to mesenchymal stem cell treatment. The results of ADMIRE-CD-II further add to this concern. It is questioned whether the results of the ADMIRE-CD study should be revisited in the light of the available literature and the failed ADMIRE-CD II study.

Supportive efficacy data was submitted; however these studies are of minor importance due to deficiencies in the study designs. These studies are briefly summarised below:

Study Darvadstrocel-3003 is an ongoing long-term extension study of ADMIRE-CD II aimed to evaluate the long-term safety and efficacy of darvadstrocel. After unblinding of ADMIRE-CD II, the study was open-label. This was primarily a safety study and efficacy outcomes are presented descriptively. A total of 37/76 patients (48.68%) in the darvadstrocel arm and 27/74 patients (36.49%) in the placebo arm were in clinical remission at week 104, and 22/76 patients (40.74%) in the darvadostrocel arm and 18/74 patients (30.51%) in the placebo arm were in clinical remission at week 156. .

According to the MAH, the study demonstrated that darvadstrocel maintained an acceptable safety profile and that caution must be exercised when interpreting the efficacy results presented in this interim report as this is an ongoing study. Because subjects were not randomized into 2 groups and no formal statistical comparison was conducted, meaningful comparisons cannot be made between the 2 groups.

Study Alofisel-5003 (INSPIRE) is an ongoing, multicenter, observational post-approval study in patients with CD with complex CPFs treated with darvadstrocel followed up to 36 months. Patients

were invited to participate in the study only after their treating healthcare professional and the patient had opted to proceed with darvadstrocel treatment. The primary outcomes are clinical response and clinical remission. Clinical response was achieved in 75.9% (198 of 261) of patients at Month 6 and in 79.9% (107 of 134) of patients at Month 12.

Clinical remission was achieved at 6 months in 69.7% (182 of 261) of patients. Clinical remission was achieved at 12 months in 102 of 134 patients (76.1%).

The MAH concludes that the results support the effectiveness of darvadstrocel as a treatment for complex CPFs in the real-world setting. Clinical response and clinical remission rates achieved in interim results from this study support the benefit profile of darvadstrocel in adult patients with CD and complex CPF. Treatment with darvadstrocel was well tolerated, and no new safety signals were observed during this study. The overall safety profile remains consistent with the known safety profile of darvadstrocel. Given its observational design, the study is of limited value for the efficacy assessment.

Study Darvadstrocel-3002 was a phase 3, open-label, uncontrolled study to evaluate the efficacy and safety of darvadstrocel in the treatment of complex perianal fistulas in Japanese adult subjects with CD. The study included subjects with nonactive or mildly active CD (defined by CDAI ≤220) with complex perianal fistulas who had been previously failed other treatments. The study was conducted as an add-on study in which continuation of baseline treatments for CD (eg, IS, biologics) was permitted. A total of 22 patients were included. Given the small sample size and the open-label uncontrolled study design, it is of limited value for the overall efficacy assessment.

According to the MAH, ADMIRE-CD and ADMIRE-CD II should be considered 2 distinct studies, mainly because of differences in inclusion/exclusion criteria for the subject population and the distribution of concomitant treatment for CD and perianal fistulas at randomization, which limit the interpretability of pooled analyses of the full subject populations from both studies. To demonstrate the overall efficacy of darvadstrocel treatment among the subject population that is most similar to the population for which darvadstrocel is indicated for use (ie, ADMIRE-CD), a post hoc pooled analysis of efficacy results was performed for the ADMIRE-CD population (212 randomized subjects) and a subsample from ADMIRE-CD II (85 subjects; 39 who received darvadstrocel treatment and 46 who received placebo), which was identified by using profile matching methodology to be similar to the ADMIRE-CD population according to baseline characteristics and concomitant medications at randomization. The MAH states that this post hoc analysis provide supportive evidence of clinical benefit of darvadstrocel compared with placebo for the patient population for which darvadstrocel is indicated for use in the EU. This approach is not agreed with. The studies should be interpreted according to the predefined analysis plans.

According to the MAH, these differences include differences in inclusion/exclusion criteria for the subject population, mandatory seton placement, handling of missing data, and rescue medication (treatment failure). Subjects in both studies had complex CPF that had shown an inadequate response to IS or anti-TNF therapies (or other biologics, in the case of ADMIRE-CD II), while eligible subjects in ADMIRE-CD also could have been eligible if they had CPF(s) that had shown an inadequate response to antibiotic treatment only. Missing data were imputed using the LOCF method in ADMIRE-CD, while nonresponder imputation was used in ADMIRE-CD II. In addition, subjects in both studies underwent exploration under anesthesia and fistula curettage at the preparation visit 2 to 3 weeks before darvadstrocel was administered; however, seton placement at the preparation visit was mandatory in ADMIRE-CD II but was performed only if clinically indicated in ADMIRE-CD.

This is not agreed with. Overall, the study designs and study populations were very similar. The MAH states that one of the main differences was that in ADMIRE-CD, subjects were eligible if they had shown an inadequate response to antibiotic treatment only, while immunosuppressive of biologic

therapy was mandatory in ADMIRE-CD II. According to the EPAR, Alofisel, INN-darvadstrocel (europa.eu), almost 80% had prior immunosuppressive therapy and almost 80% had prior anti-TNF treatment. Therefore, it is questionable whether this can be considered as a major difference between the study populations. The MAH is asked to clarify how many patients enrolled in ADMIRE-CD that had prior therapy with antibiotics only. Furthermore, the Applicant should clarify the difference in disease severity in both groups (how many patients had non-active CD, how many mild and how many moderate).

Another argument for the important differences between the studies is the handling of missing data. Missing data were imputed using the LOCF method in ADMIRE-CD, while nonresponder imputation was used in ADMIRE-CD II. The Applicant has not provided a comprehensive analysis of the impact of missing data in the two studies. However, a sensitivity analysis for the ADMIRE-CD II study based on multiple imputation for missing data was presented and showed similar results as the primary analysis based on non-responder imputation. This indicates that the negative outcome is robust to the handling of missing data and hence, the treatment differences in the ADMIRE-CD II trial is not expected to be underestimated to a large extent due to the missing data handling.

Finally, the differences in surgical procedure and withdrawal criteria are not considered of such importance that they would preclude a comparison the study results.

The post-hoc analyses are significantly influenced by the results of ADMIRE-CD, and of limited value for the overall efficacy conclusions. The post-hoc analyses cannot disregard the fact that ADMIRE-CD II was a failed study.

There are some data to support that among patients who responded to treatment with darvadstrocel, the effect was maintained over time. However, the response rates over time are not convincingly higher than the response rates for placebo and since the overall effect of darvadstrocel is questioned, the potential long-term effect is of minor importance.

To conclude, the single pivotal study ADMIRE-CD that was the basis for the MAA showed a modest difference in effect between darvadstrocel and placebo, and a confirmatory phase 3 study was included as an annex II condition (ADMIRE-CD II). The study data now available shows no statistically significant effect for darvadstrocel compared to placebo and do not confirm the, modest, effects observed in the ADMIRE-CD study. The positive B/R for darvadstrocel is questioned. The MAH is asked to provide further justification (**MO**).

7. Clinical Safety aspects

The following studies provide clinical safety data for darvadstrocel:

- Four phase 3 studies in adult subjects with CD: ADMIRE-CD, ADMIRE-CD II, Study Darvadstrocel-3002 with the long-term follow-up period, and Study Darvadstrocel-3003 (ongoing LTE study of ADMIRE-CD II).
- One completed phase 1/2a study: Study Cx601-0101. Subjects in this study were administered darvadstrocel at lower multiple doses, and with a different dosing schedule, compared with the phase 3 studies.
- Two additional ongoing studies: Study Darvadstrocel-3004 (a phase 3 open-label, pediatric study) and Study Alofisel-4001 (a phase 4 postauthorization safety study of darvadstrocel). Subjects in Study Darvadstrocel-3004 are from a different study population (ie, pediatric population), and subjects in Study Alofisel-4001 are administered darvadstrocel on a different dosing schedule (ie, repeat administration) compared with subjects in the adult phase 3

studies. Safety data from these ongoing studies are summarized at the study level in a safety snapshot analysis for ongoing studies using a data extract as of 22 September 2023. Data from Study Darvadstrocel-3004 and Study Alofisel-4001 are not included in the integrated safety database.

A summary of the clinical studies is shown in table below.

Safety data for darvadstrocel were pooled into an integrated safety database and analyzed using the following 2 pools: (1) the populations in the phase 3 randomized, placebo-controlled studies (ADMIRE-CD and ADMIRE-CD II) and (2) the populations in the adult phase 1-3 studies (Cx601-0101, ADMIRE-CD, ADMIRE-CD II, Darvadstrocel-3002, and Darvadstrocel-3003).

Table 16. Study Groupings for Pooled Study Data

Analysis Population	Description	Studies	Time Interval Groups in ISS Tables	Treatment Groups in ISS Tables
Phase 3 placebocontrolled studies pool	Phase 3, randomized placebo-controlled studies in subjects with nonactive or mildly active CD up to Week 52	ADMIRE-CD ADMIRE-CD II	0-24 weeks 0-52 weeks	Placebo Cx601 120 MC Overall N = 757
Adult phase 1-3 studies pool	Phase 1-3 studies in treated adult subjects with CD up to Week 156	Cx601-0101 ADMIRE-CD ADMIRE-CD II Darvadstrocel-3002 Darvadstrocel-3003	0-52 weeks 0-104 weeks [a] 0-156 weeks [a]	Placebo [b] Cx601 120 MC [b] Cx601 20 MC Cx601 40/60 MC Cx601 All Overall N = 803

Source: ISS SAP Table 2, ISS SAP Table 6, ISS Table 15.1.1.1.1, ISS Table 15.1.1.1.2.
ADMIRE-CD: Study Cx601-0302; ADMIRE-CD II: Study Cx601-0303; CD: Crohn's disease; Cx601: darvadstrocel; ISS: integrated summary of safety; MC: million cells; N: number of subjects in a group; SAP: statistical analysis plan.
[a] Within this document, analysis of the "adult phase 1-3 studies pool" focuses on these 2 time intervals.
[b] Within this document, analysis of the "adult phase 1-3 studies pool" focuses on these 2 treatment groups.

In addition, the MAH presented unblinded safety data from the individual completed studies (ADMIRE-CD II and Study Darvadstrocel-3002), interim safety data at the time of the data lock point (DLP) (26 July 2023) for the ongoing Study Darvadstrocel-3003, and safety "snapshots" for the other ongoing studies (Study Darvadstrocel-3004 and Study Alofisel-4001) as of 22 September 2023. Data from the individual completed studies, Study Cx601-0101 and ADMIRE-CD, have been previously submitted to the EMA and are not included in this document. Cumulative postmarketing data as of 22 September 2023 are also presented.

7.1.1. Methods – analysis of data submitted

The analysis set consist of all subjects who received at least 1 dose of study treatment (including administration in a previous study) unless otherwise specified. Subjects who inadvertently received study treatment other than the assigned treatment were summarized on the basis of the actual treatment received. While there was no treatment administration in the LTE Study Darvadstrocel-3003, all enrolled subjects were considered part of the safety set, as they received study treatment in ADMIRE-CD II. These subjects were not double counted.

AEs were coded using the MedDRA coding dictionary. AEs from all studies in the ISS were coded to the version of MedDRA used for ADMIRE-CD II (Version 26.0). Thus, some differences in coding may be noted when comparing the ISS to individual CSRs.

TEAEs were defined as AEs whose onset occurred, or severity worsened after initial study treatment up to the study completion date, DLP date (where applicable), or early withdrawal visit, whichever came first. Since Study Darvadstrocel-3003 is an ongoing LTE study of subjects administered treatment in ADMIRE-CD II, all AEs that started during this study are considered as treatment emergent, and a TEAE is defined as any AE starting between the date of informed consent signature for the LTE study and the end of Week 156.

An AE was considered treatment related if the investigator considered the event to be possibly, probably, or definitely related to study treatment. If the relationship to study treatment was missing, then it was considered treatment related.

The following were considered adverse events of special interest (AESI):

- Tumorigenicity.
- Ectopic tissue formation.
- Hypersensitivity reactions.
- Transmission of infectious agents.
- Immunogenicity.
- Medication errors.
- In addition, the AESI category of fistula, abscess was also reviewed.

7.1.2. Results

ADMIRE-CD II

7.1.2.1. Exposure

The overall exposure in ADMIRE-CD II is shown below.

Table 17. ADMIRE-CD II: Summary of Exposure (Safety Analysis Set)

	Treatment		
	Placebo (N = 274)	Cx601 (N = 278)	Total (N = 552)
Number of subjects who received a dose, n (%)	274 (100.0)	278 (100.0)	552 (100.0)
Total exposure (mL)			
n	274	278	552
Mean (SD)	23.9 (1.05)	24.0 (0.24)	23.9 (0.76)
Median	24.0	24.0	24.0
Q1, Q3	24.0, 24.0	24.0, 24.0	24.0, 24.0
Minimum, maximum	12, 24	22, 24	12, 24
Total exposure (mL) for EO			
n	274	278	552
Mean (SD)	12.0 (0.45)	12.0 (0.68)	12.0 (0.58)
Median	12.0	12.0	12.0

	Treatment		
	Placebo (N = 274)	Cx601 (N = 278)	Total (N = 552)
Q1, Q3	12.0, 12.0	12.0, 12.0	12.0, 12.0
Minimum, maximum	6, 16	8, 18	6, 18
Total exposure (mL) for IO			
n	273	278	551
Mean (SD)	11.9 (0.45)	11.9 (0.67)	11.9 (0.57)
Median	12.0	12.0	12.0
Q1, Q3	12.0, 12.0	12.0, 12.0	12.0, 12.0
Minimum, maximum	6, 12	6, 16	6, 16

Source: Cx601-0303 Table 15.3.7.
ADMIRE-CD II: Study Cx601-0303; Cx601: darvadstrocel; EO: external opening(s); IO: internal opening(s); N: number of subjects in a treatment group; n: number of subjects with available data; Q: quartile.

Assessor's comment:

ADMIRE-CD II, 278 subjects in the darvadstrocel group and 274 subjects in the placebo group were dosed with study treatment. Overall, in the "adult phase 1-3 studies pool" (ADMIRE-CD, ADMIRE-CD II, Study Cx601-0101, Study Darvadstrocel-3002, and Study Darvadstrocel-3003), a total of 427 subjects received darvadstrocel.

7.1.2.2. Adverse events

An overview of TEAEs up to Week 52 is presented below.

Table 18. Overview of TEAEs Up to Week 52 (Safety Analysis Set)

	Placebo (N = 274)		Cx601 (N = 278)		Total (N = 552)	
	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events
Any TEAEs	201 (73.4)	598	203 (73.0)	551	404 (73.2)	1149
Treatment-related TEAEs	43 (15.7)	72	49 (17.6)	60	92 (16.7)	132
TESAEs	35 (12.8)	49	41 (14.7)	59	76 (13.8)	108
Treatment-related TESAEs	7 (2.6)	8	6 (2.2)	7	13 (2.4)	15
TEAEs leading to study discontinuation	1 (0.4)	2	1 (0.4)	1	2 (0.4)	3
TESAEs leading to study discontinuation	1 (0.4)	2	1 (0.4)	1	2 (0.4)	3
Fatal TESAEs	0	0	1 (0.4)	1	1 (0.2)	1
Subjects withdrawn from the study due to TEAEs	1 (0.4)	2	1 (0.4)	1	2 (0.4)	3
Intensity						
Mild	95 (34.7)	375	88 (31.7)	333	183 (33.2)	708
Moderate	82 (29.9)	185	88 (31.7)	179	170 (30.8)	364
Severe	24 (8.8)	32	25 (9.0)	32	49 (8.9)	64
Unknown	0	6	2 (0.7)	7	2 (0.4)	13
Relationship to study treatment						
Related	43 (15.7)	72	49 (17.6)	60	92 (16.7)	132
Not related	158 (57.7)	526	154 (55.4)	491	312 (56.5)	1017
Outcome						
Recovered	121 (44.2)	471	119 (42.8)	418	240 (43.5)	889
Recovering/resolving	23 (8.4)	41	29 (10.4)	45	52 (9.4)	86
Recovered with sequelae	10 (3.6)	12	8 (2.9)	12	18 (3.3)	24
Not recovered	41 (15.0)	67	42 (15.1)	71	83 (15.0)	138
Death	0	0	1 (0.4)	1	1 (0.2)	1
Unknown	6 (2.2)	7	4 (1.4)	4	10 (1.8)	11
Concomitant medication given						
Yes	166 (60.6)	412	164 (59.0)	350	330 (59.8)	762
No	35 (12.8)	186	39 (14.0)	201	74 (13.4)	387
Unknown	0	0	0	0	0	0

Source: Table 15.3.1.1.2 and 15.3.1.2.2.

Cx601: darvadstrocel; SAE: serious adverse event; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event.

TEAEs starting between the day of study treatment administration and the end of Week 52 visit were included. If a subject discontinued the study before the Week 52 visit, the discontinuation date was used as the Week 52 end date.

Assessor's comment:

Any TEAE occurred in 73% of darvadstrocel-treated patients, and 73.4% of placebo-treated patients. SAEs occurred in 14.7% of darvadstrocel-treated patients, and 12.8% of placebo-treated patients. Details are provided later in this AR.

The most frequent TEAEs (≥2% subjects in any treatment group) up to Week 52 are presented by SOC and PT below.

Table 19 ADMIRE-CD II: TEAEs Occurring in ≥2% of Subjects in Any Treatment Group Up to Week 52 Sorted by Subjects (Safety Analysis Set)

SOC PT	Placebo (N = 274)		Cx601 (N = 278)		Total (N = 552)	
	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events
Any TEAEs	201 (73.4)	598	203 (73.0)	551	404 (73.2)	1149
Gastrointestinal disorders	105 (38.3)	187	110 (39.6)	176	215 (38.9)	363
Proctalgia	40 (14.6)	53	43 (15.5)	49	83 (15.0)	102
Crohn's disease	18 (6.6)	20	14 (5.0)	19	32 (5.8)	39
Anal fistula	9 (3.3)	10	10 (3.6)	10	19 (3.4)	20
Diarrhoea	12 (4.4)	12	9 (3.2)	9	21 (3.8)	21
Abdominal pain	14 (5.1)	16	6 (2.2)	6	20 (3.6)	22
Constipation	5 (1.8)	5	6 (2.2)	6	11 (2.0)	11
Vomiting	6 (2.2)	6	2 (0.7)	2	8 (1.4)	8
General disorders and administration site conditions	20 (7.3)	22	13 (4.7)	15	33 (6.0)	37
Pyrexia	4 (1.5)	4	6 (2.2)	7	10 (1.8)	11
Infections and infestations	107 (39.1)	162	99 (35.6)	141	206 (37.3)	303
COVID-19	24 (8.8)	25	24 (8.6)	25	48 (8.7)	50
Anal abscess	15 (5.5)	15	18 (6.5)	20	33 (6.0)	35
Gastroenteritis	4 (1.5)	5	7 (2.5)	8	11 (2.0)	13
Nasopharyngitis	8 (2.9)	10	3 (1.1)	3	11 (2.0)	13
Upper respiratory tract infection	13 (4.7)	13	3 (1.1)	3	16 (2.9)	16
Urinary tract infection	11 (4.0)	11	2 (0.7)	3	13 (2.4)	14
Investigations	21 (7.7)	26	20 (7.2)	25	41 (7.4)	51
C-reactive protein increased	8 (2.9)	9	7 (2.5)	7	15 (2.7)	16
Musculoskeletal and connective tissue disorders	27 (9.9)	35	29 (10.4)	34	56 (10.1)	69
Fistula discharge	3 (1.1)	3	6 (2.2)	6	9 (1.6)	9
Arthralgia	9 (3.3)	11	5 (1.8)	8	14 (2.5)	19
Psychiatric disorders	15 (5.5)	19	9 (3.2)	10	24 (4.3)	29
Anxiety	7 (2.6)	8	1 (0.4)	1	8 (1.4)	9

Assessor's comment:

The most common TEAE was within gastrointestinal disorder, with proctalgia being the most frequent AE (15.5% in the darvadstrocel arm and 14.6% in the placebo arm). Also anal fistula, anal abscess and fistula discharge were numerically more frequent in the darvadstrocel arm although the differences are small.

7.1.2.3. Serious adverse events and deaths

Up to Week 52, TESAEs were reported by 41 subjects (14.7%) in the darvadstrocel group and 35 subjects (12.8%) in the placebo group (**Error! Reference source not found.**). The most frequently reported TESAEs (occurring in ≥4 subjects in either treatment group) up to Week 52 were reported in the SOCs of infections and infestations and gastrointestinal disorders, and included the PTs of anal abscess (darvadstrocel: 4.3% of subjects, 14 TESAEs; placebo: 4.4% of subjects, 12 TESAEs), proctalgia (darvadstrocel: 1.8% of subjects, 6 TESAEs; placebo: 0.4% of subjects, 1 TESAE), and anal fistula (darvadstrocel: 1.4% of subjects, 4 TEAEs; placebo: 1.5% of subjects, 4 TEAEs).

Table 20. ADMIRE-CD II: Summary of TESAEs by SOC and PT Occurring in ³2 Subjects Up to Week 52 Sorted by Subjects (Safety Analysis Set)

SOC PT	Placebo (N = 274)		Cx601 (N = 278)		Total (N = 552)	
	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events
Any TESAEs	35 (12.8)	49	41 (14.7)	59	76 (13.8)	108
Cardiac disorders	1 (0.4)	2	2 (0.7)	2	3 (0.5)	4
Cardiomyopathy	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Gastrointestinal disorders	15 (5.5)	19	17 (6.1)	22	32 (5.8)	41
Proctalgia	1 (0.4)	1	5 (1.8)	6	6 (1.1)	7
Anal fistula	4 (1.5)	4	4 (1.4)	4	8 (1.4)	8
Crohn's disease	2 (0.7)	2	2 (0.7)	3	4 (0.7)	5
Small intestinal obstruction	2 (0.7)	2	2 (0.7)	2	4 (0.7)	4
Abdominal pain	2 (0.7)	2	0	0	2 (0.4)	2
Intestinal obstruction	2 (0.7)	3	0	0	2 (0.4)	3
Vomiting	2 (0.7)	2	0	0	2 (0.4)	2
Infections and infestations	18 (6.6)	19	20 (7.2)	23	38 (6.9)	42
Anal abscess	12 (4.4)	12	12 (4.3)	14	24 (4.3)	26
COVID-19	2 (0.7)	2	3 (1.1)	3	5 (0.9)	5
Perirectal abscess	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Reproductive system and breast disorders	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Female genital tract fistula	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2

Assessor's comment:

Serious adverse events were more frequent in the darvadstrocel arm (41/278 patients, 14.7%) than in the placebo arm (35/274 patients, 12.8%). The differences were observed within the SOCs cardiac disorders, gastrointestinal disorders and infections/infestations. The most prominent difference is a higher frequency of proctalgia in the darvadstrocel arm (5/278, 1.8%) than in the placebo arm (1/274, 0.4%). For a treatment with a modest effect, this indicates that treatment is associated with some discomfort for the patients.

Deaths

Up to Week 52, 1 fatal TESAE of hepatocellular carcinoma occurred in a subject in the darvadstrocel group. This was a male with normal liver laboratory findings before entrance in the study. Concomitant medication included infliximab and azathioprine. He was given treatment with Alofisel. In, 11 months after receiving treatment with Alofisel, he was hospitalised due to abdominal pain and weight loss and was diagnosed with hepatocellular carcinoma. He died.

Assessor's comment:

Tumorigenicity is an important potential risk in the Alofisel RMP. Although the most apparent concern (given the local administration of the product in fistulas) is anal canal and local colorectal malignancy, this finding with a reasonable timely relationship with Alofisel treatment is of concern. The concomitant medication with infliximab and azathioprine is acknowledged, and causality with Alofisel cannot be concluded.

The risk for tumourigenocity was discussed in the MAA EPAR, "The risk of tumour formation is a key potential concern in cell based therapies. While nonclinical studies using human eASC in rodents suggest that the tumourigenicity risk of Alofisel is low, the relevance of these data for understanding the risk of tumourigenicity after prolonged engraftment of these cells in human is insufficiently understood*".*

Given this is a key potential concern, this case is of concern. For further discussion on the risk for tumourogenicity, please see below.

7.1.2.4. Adverse events of special interest

Prespecified AESIs included tumorigenicity, ectopic tissue formation, hypersensitivity reactions, transmission of infectious agents, immunogenicity/alloimmune reactions, and medication errors.

Tumorigenicity

Up to Week 52, 2 subjects (0.7%) in the darvadstrocel group and 8 subjects (2.9%) in the placebo group experienced treatment-emergent tumorigenicity AESIs as identified via MedDRA SOC and SMQ search criteria.

Table 21. Treatment-Emergent AESIs: Tumorigenicity by MedDRA Search by SOC and PT Up to Week 52 (Safety Analysis Set)

SOC PT	Placebo (N = 274)		Cx601 (N = 278)		Total (N = 552)	
	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events
Any tumorigenicity AESI	8 (2.9)	11	2 (0.7)	2	10 (1.8)	13
Blood and lymphatic system disorders	1 (0.4)	1	0	0	1 (0.2)	1
Hyperleukocytosis	1 (0.4)	1	0	0	1 (0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.9)	10	2 (0.7)	2	10 (1.8)	12
Hepatocellular carcinoma	0	0	1 (0.4)	1	1 (0.2)	1
Lipoma	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Acrochordon	1 (0.4)	1	0	0	1 (0.2)	1
B-cell lymphoma	1 (0.4)	1	0	0	1 (0.2)	1
Breast cancer	1 (0.4)	1	0	0	1 (0.2)	1
Fallopian tube cancer	1 (0.4)	1	0	0	1 (0.2)	1
Fibroadenoma of breast	1 (0.4)	1	0	0	1 (0.2)	1
Metastases to peritoneum	1 (0.4)	1	0	0	1 (0.2)	1
Ovarian cancer	1 (0.4)	1	0	0	1 (0.2)	1
Skin papilloma	1 (0.4)	1	0	0	1 (0.2)	1
Vaginal neoplasm	1 (0.4)	1	0	0	1 (0.2)	1

Assessor's comment:

Overall, the frequency of tumourogenicity was lower in the Alofisel group than in the placebo group, which is reassuring

Ectopic tissue formation

No cases were reported.

Hypersensitivity reactions

Up to Week 52, 24 subjects (8.6%) in the darvadstrocel group and 18 subjects (6.6%) in the placebo group experienced treatment-emergent hypersensitivity reaction AESIs.

One subject in the darvadstrocel group experienced a serious AESI of anaphylactic shock. The subject had a medical history of postoperative anaphylactic shock after receiving paracetamol, dexketoprofen, and ondansetron during a previous surgical procedure in 2012. Approximately 25 minutes after the surgical procedure with IMP, the subject experienced life-threatening anaphylactic shock. Concomitant medications included dexketoprofen and paracetamol. The subject recovered after receiving corticosteroids, antihistamines, and adrenaline. The investigator assessed the event as related to IMP as it could not be entirely excluded; however, causality was confounded by the coadministration of dexketoprofen and paracetamol given intravenously at the end of IMP administration.

Assessor's comment:

This indicates that although the safety profile of the product per se seems to be favourable, there are certain non-negligible risks associated with the treatment procedure.

Transmission of infectious agents

No cases were reported.

Immunogenicity/alloimmune reactions

Up to Week 52, 25 subjects (9.0%) in the darvadstrocel group and 25 subjects (9.1%) in the placebo group experienced treatment-emergent immunogenicity or alloimmune reaction AESIs.

Medication errors

No cases were reported.

Fistula, Abscess

Up to Week 52, 39 subjects (14.0%) in the darvadstrocel group and 29 subjects (10.6%) in the placebo group experienced treatment-emergent fistula or abscess AESIs.

Table 22. Treatment-Emergent AESIs: Fistula, Abscess by MedDRA Search by SOC and PT Up to Week 52 (Safety Analysis Set)

SOC PT	Placebo (N = 274)		Cx601 (N = 278)		Total (N = 552)	
	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events
Any fistula, abscess AESI	29 (10.6)	40	39 (14.0)	49	68 (12.3)	89
Gastrointestinal disorders	14 (5.1)	19	22 (7.9)	26	36 (6.5)	45
Anal fistula	9 (3.3)	10	10 (3.6)	10	19 (3.4)	20
Anal haemorrhage	1 (0.4)	2	4 (1.4)	5	5 (0.9)	7
Rectal haemorrhage	1 (0.4)	1	5 (1.8)	5	6 (1.1)	6
Small intestinal obstruction	2 (0.7)	2	2 (0.7)	2	4 (0.7)	4
Large intestine perforation	0	0	1 (0.4)	1	1 (0.2)	1
Obstruction gastric	0	0	1 (0.4)	1	1 (0.2)	1
Small intestinal stenosis	0	0	1 (0.4)	1	1 (0.2)	1
Subileus	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Intestinal obstruction	2 (0.7)	3	0	0	2 (0.4)	3
Infections and infestations	20 (7.3)	21	20 (7.2)	23	40 (7.2)	44
Anal abscess	15 (5.5)	15	18 (6.5)	20	33 (6.0)	35
Anal fistula infection	0	0	2 (0.7)	2	2 (0.4)	2
Perirectal abscess	2 (0.7)	2	1 (0.4)	1	3 (0.5)	3
Abdominal wall abscess	1 (0.4)	2	0	0	1 (0.2)	2
Peritonitis	1 (0.4)	1	0	0	1 (0.2)	1
Rectal abscess	1 (0.4)	1	0	0	1 (0.2)	1

Assessor's comment:

This finding, that a higher proportion of patients in the Alofisel group (14%) than compared to the placebo group (10.6%) experienced treatment-emergent fistulas or abscesses is quite remarkable, since the aim of treatment with Alofisel is to treat perianal fistulas. The MAH is asked to further discuss this finding, and the potential impact on the benefit-risk.

7.1.2.5. Laboratory evaluations

According to the MAH, all hematology and serum biochemistry parameters were generally within expected ranges and similar across treatment groups at baseline in individual studies ADMIRE-CD II, and Darvadstrocel-3002, as well as in the "phase 3 placebo-controlled studies pool" and the "adult phase 1-3 studies pool". There were no notable trends in mean changes from baseline at the time points examined.

Assessor's comment:

Since Alofisel is applied locally in the fistula, laboratory derangements are not expected.

7.1.2.6. Special populations

There were no meaningful differences observed across subgoups of age group (<65 years, ≥65 years), gender (male, female), and race (Asian, black or African American, white, other, unknown).

Pregnant and breastfeeding women were excluded from participating in clinical studies of darvadstrocel (except for the LTE Study Darvadstrocel-3003). In ADMIRE-CD II, subjects who were reported to be pregnant during the study were not automatically withdrawn but were followed until study completion.

A total of 20 pregnancies have been reported by subjects participating in the darvadstrocel clinical studies (Argus Global Safety Database).

In ADMIRE-CD II, 10 pregnancies were reported. Overall, no safety signals were identified. Darvadstrocel is not recommended during pregnancy and in women of childbearing potential not using contraception.

The use of darvadstrocel in lactating women has not been evaluated in clinical studies. Darvadstrocel is not recommended for administration during breastfeeding.

7.1.2.7. Immunogenicity

The potential for immunogenicity by darvadstrocel was investigated in the completed Study Darvadstrocel-3002 and ADMIRE-CD II. Immunogenicity data were not pooled because of differences in immunogenicity status definitions between studies.

Adipose stem cells (ASCs) are considered minimally immunogenic due to low expression of human leukocyte antigen (HLA) Class I and costimulatory molecules and absence of HLA Class II expression (Griffin et al. 2013; Le Blanc et al. 2003). However, there is a potential for recognition of "allo" antigens of ASCs by the recipient's immune system. Published clinical study data have demonstrated that, following treatment with ASCs, some patients generate antibodies against HLA Class I molecules expressed by the administered ASCs (Alvaro-Gracia et al. 2017; Garcia-Sancho et al. 2017; Griffin et al. 2013; Hare et al. 2012; Ouboter et al. 2023; Panes et al. 2018). These antibodies are referred to as DSAs. The significance of DSAs generated as a result of ASC administration has been demonstrated by Avivar-Valderas et al., who reported that DSA could bind to the surface of ASCs leading to complement-mediated killing of the cells (Avivar-Valderas et al. 2019). The destruction of cells could mediate their removal from the body, thus rendering treatment ineffective. This is particularly relevant in a situation when DSAs already exist in patients at the time of ASC administration at baseline. Preexisting DSA can arise due to previous exposure to HLA antigens, usually through organ transplantation, pregnancy, or blood transfusion (Filippone and Farber 2015; Lawrence et al. 2013). However, anti-HLA antibodies have also been detected in the absence of any known previous immunizing events (Sicard et al. 2014; Sigle et al. 2013), although the cause for generation of these spontaneous anti-HLA antibodies is unknown. In the kidney post-transplant setting, there is evidence for generation of anti-HLA molecules not expressed by the graft, so-called non–donor-specific antibodies (Briggs et al. 2009). Cross-reactivity of the anti-HLA antibodies against shared epitopes has been proposed as a potential mechanism to explain development of non–donor-specific antibodies (Cai et al. 2006). Regardless of the origin of preexisting DSA, in the field of transplantation there is strong evidence that presence of DSA is associated with higher graft rejection (Lefaucheur et al. 2010).

Therefore, subjects with preexisting DSA at the time of treatment are considered to be "presensitized", while subjects without detectable levels of DSA at baseline are considered to be "naïve" (*Table **23***).

It is important to note that in earlier clinical studies of darvadstrocel (ie, ADMIRE-CD and Darvadstrocel-3002), the definition used to identify presensitized subjects was broader and included subjects with detectable baseline titers to HLA molecules, regardless of donor specificity. However, existence of anti-HLA antibodies that are not able to bind to administered ASCs have no immunological and clinical relevance, as explained above, which prompted the change in the definition for presensitized subjects for the ADMIRE-CD II study to specifically focus on subjects who were DSA-positive at baseline. Subjects who are DSA-negative at baseline are therefore considered "naïve" (regardless of whether they demonstrate positivity for non–donor-specific HLA molecules).

Table 23 Definitions of Key Immunogenicity Terms for Darvadstrocel

Term	Definition
DSA	Anti-HLA antibodies ***specific to the donor administered***.
Anti-HLA antibodies	Anti-HLA antibodies present in the subject **before** darvadstrocel administration (likely due to blood transfusion, pregnancy, or transplantations). Part of subject's immunological history.
Naïve subject	ADMIRE-CD, Darvadstrocel-3002: No detectable anti-HLA antibodies at baseline (HLA^-) by the same methodology. ADMIRE-CD II: No detectable DSAs regardless of anti-HLA status at baseline (DSA^-HLA^- and DSA^-HLA^+).
Presensitized subject	ADMIRE-CD, Darvadstrocel-3002: Detectable anti-HLA antibodies at baseline (HLA^+) with independence of the HLA molecules reactivity against the Darvadstrocel HLA. ADMIRE-CD II: Detectable DSAs at baseline (DSA^+HLA^+).

Source: Cx601-0302 Week 104 CSR, Cx601-0303 CSR, Darvadstrocel-3002 Week 156 CSR, Cx-RD-FSR-1416.
ADMIRE-CD: Study Cx601-0302; ADMIRE-CD II: Study Cx601-0303; CSR: clinical study report; DSA: donor-specific antibody; HLA: human leukocyte antigen.

Generation of DSAs in subjects with complex CPF following administration of darvadstrocel has been investigated using blood samples in Studies Cx601-0101, ADMIRE-CD, ADMIRE-CD II, and Darvadstrocel-3002. In addition, the efficacy and safety data determined the impact of DSA generation on clinical efficacy and adverse events, respectively, for both presensitized and naïve groups in ADMIRE-CD, ADMIRE-CD II, and Darvadstrocel-3002. Results from Studies Cx601-0101 and ADMIRE-CD were summarized in the initial marketing application. The results of ADMIRE-CD suggested that generation of DSA following treatment with darvadstrocel is not associated with a detrimental effect on its efficacy or safety. Immunogenicity results from the recently completed Studies ADMIRE-CD II and Darvadstrocel-3002 are summarized in this module.

In all clinical studies, Luminex technology was used to detect anti-HLA antibodies using the LABScreen Mixed (One Lambda Inc.) and DSAs using the LABScreen Single Antigen (One Lambda Inc.) at a clinical laboratory (University Hospital Ramon y Cajal, Madrid, Spain, and LSI Medience Corporation 3-30-1 Shimura, Itabashi-ku, Tokyo [Darvadstrocel-3002 only]), and the results were interpreted with the HLA Fusion 3.0 software (One Lambda Inc.) (HLA Fusion 4.4 software for Darvadstrocel-3002 only). For the respective antibodies, the unit of outputs was mean fluorescence intensity (MFI) (LABScreen Mixed) or standardized fluorescence intensity (SFI) (LABScreen Single Antigen), and the positive cut-off value (determined based on solid organ transplant experience) was 800 MFI (LABScreen Mixed) or 20,000 SFI (equivalent to 800 MFI) (LABScreen Single Antigen) in ADMIRE-CD and ADMIRE-CD II studies. For Darvadstrocel-3002 the positive cut-of value was Normal value 1.5 (LABScreen Mixed) or Normal value 1000 (LABScreen Single Antigen). For the specificity of antibodies, analysis results were examined using the positive cut-off value in combination with the Matchmaker.

These analysis methods are routinely used to analyze the development of alloantibodies in samples from organ transplant patients (Pei et al. 2003).

ADMIRE-CD II (Study Cx601-0303)

In this study, subjects received a single perilesional dose of cell dispersion containing darvadstrocel (120 million cells) or placebo (saline). Blood samples were collected from a total of 568 subjects (283 in the darvadstrocel group and 285 in the placebo group) at baseline and at Weeks 6, 12, 24, and 52. Subjects were screened for histocompatibility with the donor cells and assigned DSA status at baseline. Subjects who were positive for DSA at baseline were considered presensitized, and subjects who were negative for DSA at baseline were considered naïve.

At baseline, 56 subjects (19.8%) in the darvadstrocel group and 47 subjects (16.5%) in the placebo group were HLA+. Of the 56 subjects (19.8%) in the darvadstrocel group who were HLA+, 29 subjects were DSA+ and thus were included in the presensitized group (10.2% of the darvadstrocel treatment group in the ITT population).

Of the 283 subjects in the darvadstrocel group, 98 non-DSA/naïve subjects (34.6%) and 23 presensitized subjects (8.1%) were DSA+ at any posttreatment visit during the study (DSA incidence by visit is presented in *Table **24***). DSA incidence was highest at Week 6 for both non-DSA/naïve subjects and presensitized subjects (25.1% and 7.1%, respectively). An overall reduction in DSA incidence in both naïve and presensitized groups was observed by Week 52, suggesting clearance of these antibodies over time.

Table 24 ADMIRE-CD II: DSA Incidence by Visit for Subjects in the Darvadstrocel Treatment Group (ITT Analysis Set)

		Cx601 (N = 283) n (%)	
Baseline DSA Status	**Visit**	**DSA–**	**DSA+**
Non-DSA/naïve	Week 6	154 (54.4)	71 (25.1)
	Week 12	162 (57.2)	54 (19.1)
	Week 24	176 (62.2)	39 (13.8)
	Week 52	177 (62.5)	28 (9.9)
	Cumulative	139 (49.1)	98 (34.6)
Presensitized	Week 6	8 (2.8)	20 (7.1)
	Week 12	14 (4.9)	15 (5.3)
	Week 24	14 (4.9)	14 (4.9)
	Week 52	15 (5.3)	14 (4.9)
	Cumulative	6 (2.1)	23 (8.1)

Source: Cx601-0303 Table 15.2.20.
ADMIRE-CD II: Study Cx601-0303: Cx601: darvadstrocel; DSA: donor-specific antibody; ITT: intent-to-treat.
Percentages were based on the number of subjects in the ITT analysis set.
"Non-DSA/naïve" and "presensitized" refer to DSA status at baseline.
Cumulative DSA incidence considers the subjects who have at least 1 DSA+ status after the treatment.
DSA statuses were collected only for subjects with Cx601 treatment.

Impact of DSA on Clinical Efficacy

Combined remission at Week 24 was achieved by 38.89% (35 of 90) of non-DSA/naïve subjects who were DSA+ up to Week 24, and by 52.05% (76 of 146) of non-DSA/naïve subjects who were DSA– up to Week 24.

Among subjects who were presensitized to DSA at baseline, 65.22% (15 of 23 subjects) who were DSA+ up to Week 24 achieved combined remission at Week 24. The number of presensitized subjects in the darvadstrocel group who were DSA– up to Week 24 was small (6 subjects); all 6 (100%) subjects achieved combined remission at Week 24.

Results at Week 52 were similar to those at Week 24. Combined remission at Week 52 was achieved by 35.71% (35 of 98) of non-DSA/naïve subjects who were DSA+ up to Week 52, and by 45.32% (63 of 139) of non-DSA/naïve subjects who were DSA– up to Week 52.

Among subjects who were presensitized to DSA at baseline, 56.52% (13 of 23) of subjects who were DSA+ up to Week 52 achieved combined remission at Week 52. The number of presensitized subjects who were DSA– up to Week 52 was small (6 subjects); 50.00% (3 of 6 subjects) achieved combined remission at Week 52.

Impact of DSA Generation on the Safety of Darvadstrocel

Subjects who were naïve to DSA at baseline did not report onset of any immunogenicity or alloimmune reaction treatment-emergent adverse events (TEAEs) during DSA+ postbaseline periods. No adverse consequences were noted in DSA+ subjects over the course of the study.

MAH's conclusion

Overall, after treatment with darvadstrocel, the cumulative rate of DSA generation in the non-DSA/naïve population was 34.6%. An overall reduction in DSA incidence in both naïve and presensitized groups was observed by Week 52, suggesting clearance of these antibodies over time.

Immunogenicity results indicated no major negative effect of generation of DSAs on clinical efficacy. While combined remission was achieved at lower rates in the non-DSA/naïve subjects who generated DSA (DSA+) compared with those subjects who did not develop DSA (DSA–), subjects in the presensitized group were able to achieve combined remission at a rate comparable with, or even higher than, those subjects who never developed DSA. Overall, there was no observed relationship between preexisting sensitization or DSA status and incidences of TEAEs, and safety data analyzed by DSA status did not reveal any safety concerns.

Assessor's comment:

It is agreed with the MAH that there was no impact of DSA on safety. A lower number of DSA+ patients achieved combined remission; however the differences are small and firm conclusions regarding the impact of DSAs on efficacy cannot be made.

Study Darvadstrocel-3002

In this study, subjects with CPF in CD received a single perilesional dose of cell dispersion containing darvadstrocel (120 million cells). Subjects were screened for HLA antibodies at baseline and retested at Weeks 24 and 52. DSA status was determined in the subjects positive for anti-HLA antibodies at these time points.

In this study the presence of anti-HLA antibodies at baseline defined presensitized or naïve subjects' status, similar to ADMIRE-CD.

Of the 22 subjects in the safety analysis set, 16 subjects were presensitized (defined as presence of anti-HLA antibody at baseline), and 6 subjects were naïve (defined as absence of anti-HLA antibody at baseline).

Of the 16 presensitized subjects:

- 6 subjects were DSA negative during post-baseline by Week 156.
- 10 presensitized subjects were DSA positive at any timepoint during post-baseline by Week 156:
    - 3 subjects were persistently DSA positive by Week 156.
    - 6 subjects with transiently DSA positive by Week 24 became DSA negative by Week 52, and continued DSA negative by Week 156 except for 1 subject who returned to being DSA positive after Week 52 by Week 156.
    - 1 subject became DSA positive after Week 52 by Week 156 for the first time during the post-baseline period.

Of the 6 naïve subjects:

- 3 naïve subjects were DSA negative during postbaseline by Week 156.
- 3 subjects were DSA positive at any timepoint during post-baseline by Week 156:
    - 1 subject with transiently DSA positive by Week 24 became DSA negative by Week 52, and continued DSA negative by Week 156.
    - 2 subjects were those who discontinued the study between Weeks 24 and 52, one was DSA negative, and the other was DSA positive at the time of discontinuation; no DSA status after Week 52 by Week 156 was obtained from these 2 subjects.

Impact of DSA on Clinical Efficacy

In presensitized subjects, combined remission at Week 24 was achieved by 55.6% (5 of 9) of subjects with presence of DSA during postbaseline by Week 24 and by 71.4% (5 of 7) of subjects with absence of DSA during postbaseline by Week 24. In naïve subjects, combined remission at Week 24 was achieved by 33.3% (1 of 3) of subjects with presence of DSA during postbaseline by Week 24 and by 66.7% (2 of 3) of subjects with absence of DSA during postbaseline by Week 24. Similar results were observed for clinical remission and response at Week 24, and also in combined remission, clinical remission, and response at Week 52.

In presensitized subjects, combined remission at Week 156 was achieved by 80.0% (8 of 10) of subjects with presence of DSA during postbaseline by Week 156 and by 83.3% (5 of 6) of subjects with absence of DSA during postbaseline by Week 156. In naïve subjects, combined remission at Week 156 was achieved by 33.3% (1 of 3) of subjects with presence of DSA, and subjects with absence of DSA during postbaseline by Week 156. Similar results were observed for clinical remission and response at Week 156.

Assessor's comment:

In study Darvadstrocel-3002, among presensitized subjects combined remission at Week 24 was achieved by 55.6% (5 of 9) of subjects with presence of DSA during postbaseline by Week 24 and by 71.4% (5 of 7) of subjects with absence of DSA during postbaseline by Week 24. Thus, based on the results from this study, DSAs seems to impair the effect of darvadstrocel.

Impact of DSA Generation on the Safety of Darvadstrocel

According to the MAH, there was likely no clear relationship between pre-existing sensitization or DSA status and incidences of TEAEs, although the interpretation of these results is limited because of a small number of subjects in each subgroup.

MAH's conclusion

Overall, 12 (54.5%) out of 22 darvadstrocel-treated subjects in Study Darvadstrocel-3002 were DSA positive by Week 52, and 13 (45.5%) of 22 subjects were DSA positive by Week 156. There was no apparent relationship between preexisting sensitization or DSA status and darvadstrocel efficacy (ie, clinical remission, combined remission, and response) or safety (ie, TEAEs incidence) at Week 24, Week 52, and Week 156. However, the interpretation of these results is limited because of a small number of subjects in each subgroup.

MAH's immunogenicity Discussion and Conclusions

Taken together, development of DSA occurs in approximately one-third of all treated subjects with the vast majority showing antibody clearance by Week 52. Subjects with preexisting antibodies at baseline specific to the administered ASCs showed sustained or elevated DSA titers throughout the observation period without antibody clearance for up to Week 52. No apparent impact on efficacy or safety was found among subjects with DSA generation after darvadstrocel treatment in clinical studies ADMIRE-CD II and Darvadstrocel-3002.

Assessor's comment:

Development of DSA occurs in approximately one-third of all treated subjects. Although it is agreed with the MAH tat DSAs do not seem to impact safety, there are some signals on an impaired efficacy in DSA+ subjects. However, firm conclusions cannot be made due to the small number of patients in each group.

7.1.2.8. Supportive safety data

Study Darvadstrocel-3002

Safety data was assessed up to Weeks 24, 52, and 156 in Study Darvadstrocel-3002. According to the MAH, for all safety data, data up to Weeks 24 and 52 were consistent with data up to Week 156; therefore, only data up to Week 156 are presented.

The most frequent TEAEs (≥2 subjects) up to Week 156 are presented by SOC and PT below. In total, 21 subjects (95.5%) experienced at least 1 TEAE up to Week 156. TESAEs were reported by 11 subjects (50.0%). The most frequently reported TESAEs (occurring in ≥2 subjects) were reported in the SOCs of infections and infestations and gastrointestinal disorders and included the PTs of COVID-19 (18.2% of subjects) and Crohn's disease (13.6% of subjects). There were no deaths of treatment-emergent AESIs reported in the study.

Table 25 Darvadstrocel-3002: TEAEs Occurring in ≥2 Subjects by SOC and PT Up to Week 156 (Safety Analysis Set)

System Organ Class Preferred Term	Number (%) of Subjects Cx601 (N=22)
Subjects with Any TEAEs	21 (95.5)
Gastrointestinal disorders	18 (81.8)
Anal fistula	7 (31.8)
Proctalgia	7 (31.8)
Crohn's disease	4 (18.2)
Cheilitis	2 (9.1)
Dental caries	2 (9.1)
Nausea	2 (9.1)
General disorders and administration site conditions	3 (13.6)
Pyrexia	2 (9.1)
Infections and infestations	16 (72.7)
Nasopharyngitis	6 (27.3)
COVID-19	4 (18.2)
Pharyngitis	2 (9.1)
Rhinitis	2 (9.1)
Musculoskeletal and connective tissue disorders	8 (36.4)
Back pain	3 (13.6)
Fistula	2 (9.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (9.1)
Acrochordon	2 (9.1)
Renal and urinary disorders	4 (18.2)
Calculus urinary	2 (9.1)

Source: Darvadstrocel-3002 (Week 156) Table 15.3.1.2.1.
COVID-19: coronavirus disease 2019; Cx601: darvadstrocel; MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects in a treatment group; PT: Preferred Term; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
A subject was counted once, even if the subject reported the same event more than once. MedDRA Version 25.0 was used for coding adverse events.

Study Darvadstrocel-3003

This ongoing LTE study includes interim data up to the DLP of 26 July 2023. Unless otherwise specified, the Week 52 visit from ADMIRE-CD II was considered as the baseline visit for all analyses. A TEAE is defined as any AE starting between the date of informed consent signature for the LTE study and the end of Week 156.

In total, 80 subjects (53.3%) experienced 181 TEAEs (*Table **26***).

Table 26. Darvadstrocel-3003: TEAEs Occurring in ≥2% of Subjects in Any Treatment Group – IA (Safety Analysis Set)

SOC	Placebo (N = 74)		Cx601 (N = 76)		Total (N = 150)	
PT	n (%)	E	n (%)	E	n (%)	E
Any TEAE	39 (52.7)	86	41 (53.9)	95	80 (53.3)	181

In the overall population, TEAEs occurred most often in the SOCs of infections and infestations and gastrointestinal disorders. The most common TEAEs by PT (in ≥5 subjects in total) were COVID-19 (darvadstrocel: 13.2% of subjects, placebo: 12.2% of subjects), severe acute respiratory syndrome coronavirus-2 test positive (darvadstrocel: 6.6% of subjects, placebo: 4.1% of subjects), and anal abscess (darvadstrocel: 5.3% of subjects, placebo: 2.7% of subjects).

There were no deaths in the study.

A summary of AESIs is provided below.

Table 27. Summary of adverse events of special interest

SOC	Placebo (N = 74)		Cx601 (N = 76)		Total (N = 150)	
PT	n (%)	E	n (%)	E	n (%)	E
Any AESI by reported in the case report form	1 (1.4)	1	1 (1.3)	1	2 (1.3)	2
Tumorigenicity	1 (1.4)	1	3 (3.9)	3	4 (2.7)	4
Immunogenicity/alloimmunoreactions	3 (4.1)	4	4 (5.3)	5	7 (4.7)	9
Ectopic tissue formation	1 (1.4)	1	0	0	1 (0.7)	1
Fistula, abscess	6 (8.1)	8	7 (9.2)	8	13 (8.7)	16
Hypersensitivity	2 (2.7)	2	3 (3.9)	3	5 (3.3)	5

Assessor's comment:

Tumourogenicity was reported in 3 patients in the darvadstrocel group: 2 basal cell carcinoma and 1 papilloma. These are not considered related to the study drug.

Study Darvadstrocel-3004

In this open-label single-armed study including 7 patients, 5 subjects (71.4%) reported TEAEs. TEAEs occurred most often in the SOC of gastrointestinal disorders, and no PT was reported by more than 1 subject. TESAEs were reported by 2 subjects (28.6%) and included the PTs of proctalgia and anal abscess (14.3% each). No TEAEs or TESAEs were considered by the investigator as related to study treatment.

Study Alofisel-4001

In this open-label single-armed study including 53 patients re-treated with darvadstrocel, 26 subjects (49.1%) experienced 52 TEAEs. TEAEs occurred most often in the SOCs of infections and infestations and gastrointestinal disorders. The most frequently reported TEAEs (≥5% subjects) by PT were proctalgia (8 subjects [15.1%]), COVID-19 (6 subjects [11.3%]), and diarrhoea (3 subjects [5.7%]). TESAEs were reported by 2 subjects (3.8%) and included the PTs of proctalgia and cerebrovascular accident (1.9% each).

A total of 6 subjects (11.3%) experienced 6 TEAEs considered by the investigator as related to study treatment. Treatment-related TEAEs occurred most often in the SOC of gastrointestinal disorders. The most commonly reported treatment-related TEAE was proctalgia (4 subjects [7.5%]), and 1 treatment-related TESAE was proctalgia.

7.1.2.9. Post-marketing data

Cumulative worldwide exposure by sales volume from initial launch on 01 March 2018 to 30 September 2023 for darvadstrocel was estimated to be 1506 patients (PSUSA/00010676/202309).

The most frequently reported ADRs of anal abscess, anal fistula, and proctalgia align with the clinical safety findings observed in clinical studies. There has been 1 fatal case of signet-ring cell carcinoma, which was assessed as not related to darvadstrocel by the reporter.

Assessor's comment:

This was a female patient with a medical history of ovarian cancer, gastrointestinal adenocarcinoma with findings histologically confirmed since, and anal carcinoma since. No concomitant medications were reported. The patient received darvadstrocel. On an unknown date, the patient experienced a medically significant event of anal fistula and signet-ring carcinoma. The patient died from signet-ring carcinoma after receiving darvadstrocel. It was unknown if an autopsy was performed. No further details surrounding the carcinoma were provided. According to the MAH, this event is confounded by the patient's pre-existing medical history of cancer.

This is not agreed with. The case was assessed already in the latest PSUR (PSUSA/00010676/202309) as follows:

While it is known that Crohn disease patients have an increased risk for developing colorectal cancer some ambiguities concerning the patient's medical history of ovarian cancer remain.

From a medical point of view, it seems to be a bit far-fetched to evaluate ovarian cancer as a confounding factor for the development of anal carcinoma and signet ring carcinoma.

Crohn's disease itself and potential concomitant treatment would serve as plausible confounders enough.

Although the patient had a history of ovarian cancer, there is a possible timely relationship with Alofisel treatment. Treatment was given, and the anal carcinoma/gastrointestinal adenocarcinoma was diagnosed.

The MAH is asked to present further details such as whether previous radiotherapy was given, the localisation of the treated fistula and the tumour, and to further discuss a possible causal relation between Alofisel treatment and the tumour.

7.1.2.10. Pooled safety data

Phase 3 Placebo-Controlled Studies Pool (ADMIRE-CD and ADMIRE-CD II)

An overall summary of TEAEs **up to Week 24** in the "phase 3 placebo-controlled studies pool" is presented below. The most common TEAEs (≥5% of subjects in any treatment group) by PT were proctalgia (darvadstrocel: 13.9%, placebo: 12.8%), anal abscess (darvadstrocel: 7.3%, placebo: 6.9%), COVID-19 (darvadstrocel: 3.1%, placebo: 5.1%), and Crohn's disease (darvadstrocel: 2.9%, placebo: 5.1%

Table 28 Phase 3 Placebo-Controlled Studies Pool: Overall Summary of TEAEs Up to Week 24 (Safety Analysis Set)

AE Category	Placebo (N = 376) n (%) E	Cx601 120 MC (N = 381) n (%) E	Overall (N = 757) n (%) E
Any TEAE	252 (67.0) 666	250 (65.6) 541	502 (66.3) 1207
Mild	123 (32.7) 394	115 (30.2) 337	238 (31.4) 731
Moderate	100 (26.6) 221	103 (27.0) 168	203 (26.8) 389

AE Category	Placebo (N = 376) n (%) E	Cx601 120 MC (N = 381) n (%) E	Overall (N = 757) n (%) E
Severe	29 (7.7) 37	29 (7.6) 30	58 (7.7) 67
Unknown severity	0 (0) 14	3 (0.8) 6	3 (0.4) 20
Treatment-related TEAEs	69 (18.4) 113	62 (16.3) 74	131 (17.3) 187
TEAEs leading to study discontinuation	7 (1.9) 8	5 (1.3) 5	12 (1.6) 13
TESAEs	42 (11.2) 52	42 (11.0) 49	84 (11.1) 101
Treatment-related TESAEs	14 (3.7) 16	11 (2.9) 12	25 (3.3) 28
TESAEs leading to study discontinuation	5 (1.3) 6	4 (1.0) 4	9 (1.2) 10
Fatal TESAEs	0	0	0

An overall summary of TEAEs **up to Week 52** in the "phase 3 placebo-controlled studies pool" is presented below. The most common TEAEs (≥5% of subjects in any treatment group) were proctalgia (darvadstrocel: 15.2%, placebo: 14.4%), anal abscess (darvadstrocel: 10.2%, placebo: 8.2%), COVID-19 (darvadstrocel: 6.3%, placebo: 6.4%), anal fistula (darvadstrocel: 5.0%, placebo: 6.1%), diarrhoea (darvadstrocel: 5.0%, placebo: 4.0%), Crohn's disease (darvadstrocel: 4.7%, placebo: 6.9%), and abdominal pain (darvadstrocel: 2.9%, placebo: 5.6%).

Table 29 Phase 3 Placebo-Controlled Studies Pool: Overall Summary of TEAEs Up to Week 52 (Safety Analysis Set)

AE Category	Placebo (N = 376) n (%) E	Cx601 120 MC (N = 381) n (%) E	Overall (N = 757) n (%) E
Any TEAE	277 (73.7) 890	283 (74.3) 804	560 (74.0) 1694
Mild	113 (30.1) 522	107 (28.1) 475	220 (29.1) 997
Moderate	128 (34.0) 303	138 (36.2) 277	266 (35.1) 580
Severe	36 (9.6) 47	35 (9.2) 43	71 (9.4) 90
Unknown severity	0 (0) 18	3 (0.8) 9	3 (0.4) 27
Treatment-related TEAEs	69 (18.4) 121	69 (18.1) 86	138 (18.2) 207
TEAEs leading to study discontinuation	10 (2.7) 11	10 (2.6) 10	20 (2.6) 21
TESAEs	56 (14.9) 81	66 (17.3) 90	122 (16.1) 171
Treatment-related TESAEs	14 (3.7) 17	13 (3.4) 14	27 (3.6) 31
TESAEs leading to study discontinuation	8 (2.1) 9	7 (1.8) 7	15 (2.0) 16
Fatal TESAEs	0	1 (0.3) 1	1 (0.1) 1

Adult Phase 1-3 Studies Pool (Studies Cx601-0101, ADMIRE-CD, ADMIRE-CD II, Darvadstrocel-3002, and Darvadstrocel-3003)

Up to Week 156, 312 subjects (77.4%) in the darvadstrocel 120 MC group and 285 subjects (75.8%) in the placebo group reported at least 1 TEAE. The most common TEAEs (≥5% of subjects in any treatment group) by PT were proctalgia (darvadstrocel: 16.4%, placebo: 14.9%), anal abscess (darvadstrocel: 10.9%, placebo: 8.8%), COVID-19 (darvadstrocel: 9.4%, placebo: 8.8%), anal fistula (darvadstrocel: 7.4%, placebo: 6.6%), Crohn's disease (darvadstrocel: 5.5%, placebo: 7.2%), nasopharyngitis (darvadstrocel: 5.7%, placebo: 3.5%), diarrhoea (darvadstrocel: 5.0%, placebo: 4.0%), and abdominal pain (darvadstrocel: 3.0%, placebo: 5.6%).

Table 30 Adult Phase 1-3 Studies Pool: Overall Summary of TEAEs Up to Week 156 (Safety Analysis Set)

AE Category	Placebo (N = 376) n (%) E	Cx601 120 MC (N = 403) n (%) E
Any TEAE	285 (75.8) 976	312 (77.4) 1024
Mild	109 (29.0) 568	108 (26.8) 612
Moderate	132 (35.1) 329	160 (39.7) 347
Severe	44 (11.7) 60	41 (10.2) 54
Unknown Severity	0 (0) 19	3 (0.7) 11
Treatment-related TEAEs	69 (18.4) 121	72 (17.9) 90
TEAEs leading to study discontinuation	10 (2.7) 11	11 (2.7) 14
TESAEs	67 (17.8) 103	89 (22.1) 129
Treatment-related TESAEs	14 (3.7) 17	15 (3.7) 16
TESAEs leading to study discontinuation	8 (2.1) 9	8 (2.0) 8
Fatal TESAEs	0	1 (0.2) 1

Assessor's comment:

It is noted that the frequency of proctalgia, anal abscess, and anal fistula is higher in the Alofisel arm than in the placebo arm. This indicates that treatment with Alofisel is associated with a certain degree of discomfort for the patients.

In the adult phase 1-3 studies pool up to week 156, the frequency of neoplasms was lower in the Alofisel arm (3/403 patients, 0.7%) than in the placebo arm (6/376 patients, 1.6%).

7.2. Discussion

The following studies provide clinical safety data for darvadstrocel:

- Four phase 3 studies in adult subjects with CD: ADMIRE-CD, ADMIRE-CD II, Study Darvadstrocel-3002 with the long-term follow-up period, and Study Darvadstrocel-3003 (ongoing LTE study of ADMIRE-CD II).
- One completed phase 1/2a study: Study Cx601-0101. Subjects in this study were administered darvadstrocel at lower multiple doses, and with a different dosing schedule, compared with the phase 3 studies.
- Two additional ongoing studies: Study Darvadstrocel-3004 (a phase 3 open-label, pediatric study) and Study Alofisel-4001 (a phase 4 postauthorization safety study of darvadstrocel). Subjects in Study Darvadstrocel-3004 are from a different study population (ie, pediatric population), and subjects in Study Alofisel-4001 are administered darvadstrocel on a different dosing schedule (ie, repeat administration) compared with subjects in the adult phase 3 studies. Safety data from these ongoing studies are summarized at the study level in a safety snapshot analysis for ongoing studies using a data extract as of 22 September 2023. Data from Study Darvadstrocel-3004 and Study Alofisel-4001 are not included in the integrated safety database.

Safety data for darvadstrocel is presented separately from the respective study, as well as pooled using the following 2 pools: (1) the populations in the phase 3 randomized, placebo-controlled studies (ADMIRE-CD and ADMIRE-CD II) and (2) the populations in the adult phase 1-3 studies (Cx601-0101,

ADMIRE-CD, ADMIRE-CD II, Darvadstrocel-3002, and Darvadstrocel-3003). Cumulative postmarketing data as of 22 September 2023 are also presented.

The analysis set consist of all subjects who received at least 1 dose of study treatment (including administration in a previous study) unless otherwise specified. Subjects who inadvertently received study treatment other than the assigned treatment were summarized on the basis of the actual treatment received. While there was no treatment administration in the LTE Study Darvadstrocel-3003, all enrolled subjects were considered part of the safety set, as they received study treatment in ADMIRE-CD II. These subjects were not double counted.

AEs were coded using the MedDRA coding dictionary. AEs from all studies in the ISS were coded to the version of MedDRA used for ADMIRE-CD II (Version 26.0). Thus, some differences in coding may be noted when comparing the ISS to individual CSRs.

TEAEs were defined as AEs whose onset occurred or severity worsened after initial study treatment up to the study completion date, DLP date (where applicable), or early withdrawal visit, whichever came first. Since Study Darvadstrocel-3003 is an ongoing LTE study of subjects administered treatment in ADMIRE-CD II, all AEs that started during this study are considered as treatment emergent, and a TEAE is defined as any AE starting between the date of informed consent signature for the LTE study and the end of Week 156.

An AE was considered treatment related if the investigator considered the event to be possibly, probably, or definitely related to study treatment. If the relationship to study treatment was missing, then it was considered treatment related.

The following were considered adverse events of special interest (AESI):

- Tumorigenicity.
- Ectopic tissue formation.
- Hypersensitivity reactions.
- Transmission of infectious agents.
- Immunogenicity.
- Medication errors.
- In addition, the AFSI category of fistula, abscess was also reviewed.

Results

Cumulative worldwide exposure from initial launch on 01 March 2018 to 30 September 2023 for darvadstrocel is estimated to be 1506 patients PSUSA/00010676/202309).

Overall, in the "adult phase 1-3 studies pool" (ADMIRE-CD, ADMIRE-CD II, Study Cx601-0101, Study Darvadstrocel-3002, and Study Darvadstrocel-3003), a total of 427 subjects received darvadstrocel. In the current study ADMIRE-CD II, 278 subjects in the darvadstrocel group and 274 subjects in the placebo group were dosed with study treatment.

ADMIRE-CD II

Adverse events

Any TEAE occurred in 73% of darvadstrocel-treated patients, and 73.4% of placebo-treated patients. SAEs occurred in 14.7% of darvadstrocel-treated patients, and 12.8% of placebo-treated patients. Details are provided later in this AR.

The most common TEAE was within gastrointestinal disorder, with proctalgia being the most frequent AE (15.5% in the darvadstrocel arm and 14.6% in the placebo arm). Also anal fistula, anal abscess and fistula discharge were numerically more frequent in the darvadstrocel arm although the differences are small.

Serious adverse events and deaths

Serious adverse events were more frequent in the darvadstrocel arm (41/278 patients, 14.7%) than in the placebo arm (35/274 patients, 12.8%). The differences were observed within the SOCs cardiac disorders, gastrointestinal disorders and infections/infestations. The most prominent difference is a higher frequency of proctalgia in the darvadstrocel arm (5/278, 1.8%) than in the placebo arm (1/274, 0.4%). For a treatment with a modest effect, this indicates that treatment is associated with some discomfort for the patients which needs to be taken into account in the overall B/R assessment.

There was 1 fatal event of hepatocellular carcinoma in a subject in the darvadstrocel group. Tumorigenicity is an important potential risk in the Alofisel RMP. Although the most apparent concern (given the local administration of the product in fistulas) is anal canal and local colorectal malignancy, this finding with a reasonable timely relationship with Alofisel treatment is of some concern. The concomitant medication with infliximab and azathioprine is acknowledged, and causality with Alofisel cannot be concluded.

The risk for tumourigenocity was discussed in the MAA EPAR, "The risk of tumour formation is a key potential concern in cell based therapies. While nonclinical studies using human eASC in rodents suggest that the tumourigenicity risk of Alofisel is low, the relevance of these data for understanding the risk of tumourigenicity after prolonged engraftment of these cells in human is insufficiently understood*".*

Adverse events of special interest

There were no cases of ectopic tissue formation, transmission of infectious agents or medication errors reported.

The frequency of tumourogenicity up to week 52 was lower in the Alofisel group (2/278 patients, 0.7%) than in the placebo group (8/274 patients, 2.9%).

Up to Week 52, 24 subjects (8.6%) in the darvadstrocel group and 18 subjects (6.6%) in the placebo group experienced treatment-emergent hypersensitivity reaction AESIs. This indicates that although the safety profile of the product per se seems to be favourable, there are certain non-negligible risks associated with the treatment procedure.

Up to Week 52, 39 subjects (14.0%) in the darvadstrocel group and 29 subjects (10.6%) in the placebo group experienced treatment-emergent fistula or abscess AESIs. This finding is quite remarkable, since the aim of treatment with Alofisel is to treat perianal fistulas. The MAH is asked to further discuss this finding, and the potential impact on the benefit-risk.

Special populations

Darvadstrocel is not recommended during pregnancy and in women of childbearing potential not using contraception. Pregnant and breastfeeding women were excluded from participating in clinical studies of darvadstrocel (except for the LTE Study Darvadstrocel-3003). In ADMIRE-CD II, subjects who were reported to be pregnant during the study were not automatically withdrawn but were followed until study completion.

A total of 20 pregnancies have been reported by subjects participating in the darvadstrocel clinical studies. Overall, no safety signals have been identified.

The use of darvadstrocel in lactating women has not been evaluated in clinical studies. Darvadstrocel is not recommended for administration during breastfeeding.

Post-marketing data

Cumulative worldwide exposure by sales volume from initial launch on 01 March 2018 to 30 September 2023 for darvadstrocel was estimated to be 1506 patients (PSUSA/00010676/202309). The most frequently reported ADRs of anal abscess, anal fistula, and proctalgia align with the clinical safety findings observed in clinical studies. There has been 1 fatal case of signet-ring cell carcinoma, which was assessed as not related to darvadstrocel by the reporter.

This was a female patient with a medical history of ovarian cancer, gastrointestinal adenocarcinoma with findings histologically confirmed, and anal carcinoma since. No concomitant medications were reported. The patient received darvadstrocel. On an unknown date, the patient experienced a medically significant event of anal fistula and signet-ring carcinoma. The patient died from signet-ring carcinoma after receiving darvadstrocel. It was unknown if an autopsy was performed. No further details surrounding the carcinoma were provided. According to the MAH, this event is confounded by the patient's pre-existing medical history of cancer.

This is not agreed with. The case was assessed already in the latest PSUR (PSUSA/00010676/202309) as follows: *While it is known that Crohn disease patients have an increased risk for developing colorectal cancer some ambiguities concerning the patient's medical history of ovarian cancer remain. From a medical point of view it seems to be a bit far-fetched to evaluate ovarian as a confounding factor for the development of anal carcinoma and signet ring carcinoma. Crohn's disease itself and potential concomitant treatment would serve as plausible confounders enough.*

Although the patient had a history of ovarian cancer, there is a possible timely relationship with Alofisel treatment. Treatment was given, and the anal carcinoma/gastrointestinal adenocarcinoma was diagnosed.

The Applicant is asked to present further details such as whether previous radiotherapy was given, the localisation of the treated fistula and the tumour, and to further discuss a possible causal relation between Alofisel treatment and the tumour.

Pooled safety data

Pooled data were presented for phase 3 placebo-controlled studies (Alofisel n=381, placebo n=376) and adult phase 1-3 studies (Alofisel n=403, placebo n=376).

In phase placebo-controlled studies up to week 24, the most common TEAEs were proctalgia (darvadstrocel: 13.9%, placebo: 12.8%), anal abscess (darvadstrocel: 7.3%, placebo: 6.9%), COVID-19 (darvadstrocel: 3.1%, placebo: 5.1%), and Crohn's disease (darvadstrocel: 2.9%, placebo: 5.1%. Up to week 52, the most common TEAEs were proctalgia (darvadstrocel: 15.2%, placebo: 14.4%), anal abscess (darvadstrocel: 10.2%, placebo: 8.2%), COVID-19 (darvadstrocel: 6.3%, placebo: 6.4%), anal fistula (darvadstrocel: 6.0%, placebo: 6.1%), diarrhoea (darvadstrocel: 5.0%, placebo: 4.0%), Crohn's disease (darvadstrocel: 4.7%, placebo: 6.9%), and abdominal pain (darvadstrocel: 2.9%, placebo: 5.6%).

It is noted that the frequency of proctalgia and anal abscess is higher in the Alofisel arm than in the placebo arm, although it is acknowledged that the differences are small. Nonetheless, this indicates that treatment with Alofisel might be associated with a certain degree of discomfort for the patients.

In the adult phase 1-3 studies pool up to week 156, the frequency of neoplasms was lower in the Alofisel arm (3/403 patients, 0.7%) than in the placebo arm (6/376 patients, 1.6%).

The MAH should discuss whether donor specific antibodies (DSA) could have potential negative implications for future therapies (e.g. transfusions, transplantations) and if so, whether a related warning should be included into SmPC Section 4.4.

To conclude, the safety data presented seems to be in line with current knowledge of the safety profile of Alofisel. Among the most common adverse events observed are pain and abscess formation, occurring with a slightly higher frequency in Alofisel-treated patients than in placebo-treated patients. Whether these are related to Alofisel treatment or rather reflects a lack of efficacy in some patients is difficult to conclude on. Hypersensitivity reactions were also observed, including a case of anaphylactic shock in an Alofisel-treated patient. This indicates that although the safety profile of the product per se seems to be favourable, there are certain non-negligible risks associated with the treatment procedure. Some further clarifications are needed, in particular to a case of anal cancer observed after Alofisel treatment.

8. Non-interventional Post-Authorisation Safety Study (PASS) results – assessed by PRAC Rapp

The MAH included interim reports and a final study report of 2 non-interventional PASS:

- interim results of study darvadstrocel-3003, a Follow-up of a Phase 3 Study to Evaluate the Long-term Safety and Efficacy of Darvadstrocel in the Treatment of Complex Perianal Fistula in Subjects with Crohn's Disease Who Have Participated in ADMIRE II Study.
- interim results of study Alofisel-5003 "An observational poSt marketing study on the effectiveness and safety of darvadstrocel in PaTients with CRohn's disease and complex pErianal fistulas (INSPIRE)"

8.1. Analysis of data submitted

8.1.1. Analysis of data submitted in Darvadstrocel-3003

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

In the ADMIRE-CD II study all subjects in active treatment arm received a single dose of darvadstrocel while subjects in the control arm received saline solution (to mask the treatment).

For those subjects who had a gap of more than >4 weeks between the Week 52 visit of the ADMIRE CD II study and signing of the informed consent form (ICF) for the LTE study, a re-baseline visit was scheduled; the re-baseline visit included the same procedures performed at the Week 52/baseline visit, with the addition of obtaining the subject's interval inflammatory bowel disease (IBD) history and completing medical interventions since the Week 52 visit. A magnetic resonance imaging (MRI) assessment was not included at the re-baseline visit. The re-baseline visit was not to be performed any later than 3 months after the Week 52 visit. MRI is performed in all subjects at the Week 156 visit of the LTE study.

Study visits occur annually for up to 2 years after enrollment into the LTE of ADMIRE-CD II or 3 years following treatment in ADMIRE-CD II. At these visits, clinical assessment of the fistula is considered for clinical remission.

Additional telephone call visits are conducted every 3 months for safety follow-up. In addition, unscheduled visits are performed for safety follow-up and, for subjects experiencing any clinically significant symptoms of perianal disease, MRI is performed.

There was no administration of investigational medicinal product (IMP) in this LTE study.

Statistical Methods

The safety analysis set was used for all analyses in this IA report, which included all subjects enrolled in the LTE study, according to the actual treatment they received in the ADMIRE-CD II study.

Safety Analysis

Safety data (including physical examination and vital signs) were summarized by treatment group using descriptive statistics.

8.1.2. Results darvadstrocel-3003

Demographics

The subjects in the overall population were primarily male (58.0%), white (94%) and aged <65 years (98.7%), with a mean (SD) age of 38.1 (11.61) years.

The proportion of subjects with a re-baseline visit in the overall population was 16.7%. The mean (SD) age of subjects was 39.8 (11.69) years, and 2.0% of subjects were aged ≥65 years. The proportion of former or current smokers was 48.7%, and the mean (SD) pack-years was 5.0 (10.03). The mean weight (SD) was 79.86 (19.411) kg, and mean height (SD) was 171.60 (9.675) cm, where 27.3% subjects had a BMI ≥30.0 kg/m2.

The majority of subjects (128 subjects [85.3%]) in the overall population when entering the ADMIRE-CD II study had a fistula location of either transsphincteric high or intersphincteric high, and most of the subjects (149 subjects [99.3%]) had no abscess.

Medical history and other baseline characteristics

IBD history in the LTE study (ie, any new CD- or perianal disease–related condition or event between LTE study enrollment as of 26 July 2023 including those that started before but were ongoing at LTE enrollment) included 20 subjects (13.3%) who experienced new or worsening events related to CD, and 44 subjects (29.3%) experienced new or worsening events related to perianal disease.

Concomitant medication

In the overall population, 149 subjects (99.3%) reported at least 1 concomitant medication as of 26 July 2023. Common concomitant medication included infliximab in the category of tumor necrosis factor- alpha (TNF-α) inhibitors (71 subjects [47.3%]). Other common concomitant medications besides TNF-α inhibitors included azathioprine in the category of other immunosuppressants (48 subjects [32.0%]), and paracetamol in the category of anilides (34 subjects [22.7%]). The most common indication for concomitant medication use was medical history, reported for a total of 143 subjects (95.3%).

A total of 41 subjects (27.3%) reported 87 concomitant CD- or perianal disease–related procedures with the most common being drain placement (22 subjects [14.7%]). Eleven subjects (7.3%) reported

at least 1 concomitant surgery/procedure not related to CD or perianal disease, with the most common being elective surgery (10 subjects [6.7%]). Twelve subjects (8.0%) had a surgical procedure related to CD, and 36 (24.0%) had at least 1 surgical procedure related to that of perianal disease.

Rescue Medications and Procedures

In the overall population, 3 subjects (2.0%) reported use of any rescue medication. This included autologous stem cells not otherwise specified (2 subjects [2.7%] in the placebo group) and infliximab (1 subject [1.3%] in darvadstrocel group). A total of 30 subjects (20.0%) underwent a total of 56 rescue surgery/procedures, all of which were related to perianal disease with the most common being drain placement (18 subjects [12.0%]).

8.1.3. Efficacy Results (summary)Darvadstrocel-3003

In the darvadstrocel group, the proportion of subjects achieving clinical remission was 59.21% at Week 24, 53.95% at Week 52, 48.68% at Week 104, and 40.74% at Week 156. The proportion of subjects achieving clinical response in the darvadstrocel group was 73.68% at Week 24, 68.42% at Week 52, 56.58% at Week 104, and 44.44% at Week156. At Week 104, 2 subjects (2.6%) had >1 new external opening, and 2 subjects (2.6%) had >1 new external opening draining. At Week 156, 3 subjects (3.9%) had >1 new external opening, and 2 subjects (2.6%) had >1 new external opening draining.

In the placebo group, the proportion of subjects achieving clinical remission was 47.30% at Week 24, 56.76% at Week 52, 36.49% at Week 104, and 30.51% at Week 156. The proportion of subjects achieving clinical response was 58.11% at Week 24, 63.51% at Week 52, 40.54% at Week 104, and 32.20% at Week 156. At Week 104, 1 subject (1.4%) had >1 new external opening, and 1 subject (1.4%) had >1 new external opening draining. At Week 156, 2 subjects (2.7%) had >1 new external opening, and 2 subjects (2.7%) had >1 new external opening draining.

8.1.4. Safety results Darvadstrocel-3003

The mean time on study in the darvadstrocel group was 87.66 weeks. The mean time on study in the placebo group was 89.01 weeks.

As of the interim data cut-off date of 26 July 2023, a total of 80 subjects (53.3%) experienced a TEAE during this study. Most events were not related to study treatment.

Of the 80 subjects (53.3%) with any TEAE, most subjects reported TEAEs that were mild (22.0%) or moderate (23.3%) in intensity. Eleven subjects (7.3%) had TEAEs of severe intensity, with severe TEAEs occurring most often in the SOCs of gastrointestinal disorders (4 subjects [2.7%]) and infections and infestations (4 subjects). [2.7%]).

The most common severe TEAEs by PT were anal fistula (2 subjects [1.3%]), CD (2 subjects [1.3%]), and anal abscess (2 subjects [1.3%]). The most frequently reported TEAEs were in the infections and infestations SOC (28.0% of subjects overall). None of these events were considered related to study treatment. By treatment groups in the parent ADMIRE-CD II study, the most frequently reported TEAEs in the darvadstrocel group or placebo group were in the infections and infestations SOC.

As of the data cut-off date for this IA, in the overall population, most TEAEs recovered (49 subjects [32.7%]), were recovering/resolving (9 subjects [6.0%]), or recovered with sequelae (1 subject [0.7%]). A total of 19 subjects (12.7%) had a TEAE that was not recovered at the data cut-off date for this IA. The most common TEAEs that were not resolved were from the SOCs of gastrointestinal disorders (5 subjects [3.3%]), investigations (3 subjects [2.0%]), and musculoskeletal and connective tissue disorders (3 subjects [2.0%]. One subject (in the darvadstrocel group) in the study experienced

a TEAE by PT of fistula; this event was considered moderate in intensity (classified as a TESAE) and was assessed as related to study treatment by the investigator.

No deaths were reported in the study as of the cut-off date (26 July 2023) for this IA.

No subjects were withdrawn or discontinued from the study due to TEAE.

There were 7 pregnancies reported during the study. There were no safety concerns identified from these pregnancy cases.

8.1.5. Discussion Darvadstrocel-3003

The MAH provided interim results of the currently ongoing long-term follow-up study Darvadstrocel-3003 (LTF of Admire-CDII). Approximately 50 % of the 80 participants (of 149), included in the LTF study at DLP (26 Jul 2023) of this report, experienced a treatment emergent adverse event, most of which were assessed as not related to study treatment. Eleven subjects had severe TEAEs (7.3%), most often reported for the SOC Gastrointestinal disorders (4 subjects, 2.7%) and SOC Infections and Infestations (4 subjects, 2.7%). The most common severe TEAEs were anal fistula in 2 subjects, Crohn disease also in 2 subjects and anal abscess also in 2 subjects. TEAEs most frequently reported were in SOC Infections and Infestations which is similar to the reporting in the parent study Admire II. All TEAEs in the SOC were considered not related to study treatment.

It does not surprise that infections are the most frequently reported adverse events in this specific population, with multiple predispositions for infections e.g. localised and disease related infections and/ or treatment related (e.g. concomitant anti-TNF treatments). At DLP of this interim report neither type nor frequency of adverse events raise specific concern.

The above similarly applies to the other more frequently reported adverse event of anal fistula or abscess. Both are characteristics of the underlying disease, and their occurrence or re-occurrence is typical for the disease. Important to note at this stage is that most frequently reported serious and non-serious events concern only 4 subjects each, so that the absolute numbers are very low.

The final study report for Darvadstrocel-3003 is due in Q3/4 2024 and hopefully will provide comprehensive information. At this stage, it can be stated that no new safety concerns have emerged following treatment with darvadstrocel, so that in turn no change of the adverse event table in section 4.8 of the SmPC in terms of frequency or type of the PTs listed is required.

8.2. Analysis of data submitted in interim report for Alofisel-5003

The main goal of this study was to gain a better understanding (from both a country-specific and global perspective) of the following in patients treated with darvadstrocel:

• Disease presentation.

• Patient characteristics, treatment patterns, and clinical outcomes associated with CD with complex CPFs.

• Effectiveness and safety of darvadstrocel treatment, and its impact on HRQoL.

8.2.1. Methods

INSPIRE is a multicenter, prospective, observational postapproval study in CD patients with complex CPFs treated with darvadstrocel. As per the observational nature of the study, procedures and

assessments are not mandatory; investigators do not need to deviate from their current practice if current practice is not in accordance with the protocol schedule of visits and procedures.

Setting

All hospitals or clinics in a country where darvadstrocel was commercially available, providing care for patients with CD and complex CPFs, and met Takeda's qualification process to treat patients with CD and complex CPFs with darvadstrocel.

Subjects and Study Size, Including Dropouts

Planned study size is 800 patients. This interim report presents data on 619 patients who received darvadstrocel from 14 December 2018 to 03 April 2023 and were followed up for up to 36 months post treatment.

Variables and Data Sources

Healthcare professionals (HCPs) enrolled most of the patients before administration of darvadstrocel, and in patients enrolled after, baseline data were collected retrospectively. Baseline demographics, clinical characteristics, history, disease activity and remission, treatment patterns, comorbidities, and PROs were collected and assessed in accordance with routine clinical practice. Safety was assessed by collection of adverse events (AEs), serious AEs (SAEs), AEs leading to discontinuation, adverse events of special interest (AESIs), serious/nonserious adverse drug reactions, and special situation reports at baseline, 12 weeks, and 6, 12, 24, and 36 months posttreatment.

8.2.2. Results Alofisel-5003

As of the interim data cutoff, 619 of 668 consented patients (92.7%) received initial treatment with darvadstrocel and were included in the safety analysis (Safety population). A total of 302 patients (45.2%) have received at least 1 vial of darvadstrocel and have at least 1 available evaluation of the fistula status at the 6-month visit (All Treated population) and were included in the effectiveness analysis. In the All Treated population, 51.0% of patients were male, and the mean (SD) age was 39.9 (12.71) years. In the All Treated population, nearly all patients (96.7%) had historical use of any biologic, with the most common biologic historical treatments being infliximab (74.5%), adalimumab (54.0%), and ustekinumab (20.5%). Concomitant use of a biologic at baseline was common (68.2%). Slightly more than half of patients (52.0%) had at least 1 surgical procedure related to anal fistula/perianal fistula disease in the last 6 months, the most common of which was loose seton placement. Most patients had 1 external opening (EO) treated with darvadstrocel at baseline (68.2%), and 27.2% had 2 EOs treated with darvadstrocel at baseline. In the All Treated population with available data, clinical response (defined as a reduction of at least 50% in the number of treated draining perianal fistulae [where closed fistulae are no longer draining despite gentle finger compression] compared with baseline) was achieved at was achieved in 75.9% (198 of 261 patients) at 6 months after darvadstrocel treatment and in 79.9% (107 of 134 patients) at 12 months after darvadstrocel treatment. The median (95% CI) time to clinical response was 3.6 (3.4-4.0) months.

Clinical remission (defined as a closure of all draining perianal fistulas treated with darvadstrocel [where closed fistulas are no longer draining despite gentle finger compression] compared to baseline) was achieved in 69.7% (182 of 261 patients with available data) at 6 months after darvadstrocel treatment and in 76.1% of patients (102 of 134 patients with available data) at 12 months after darvadstrocel treatment. The median (95% CI) time to clinical remission was 4.1 (3.6-5.5) months. Clinical relapse was defined in this study as the reopening of any of the external fistula openings treated with darvadstrocel with active drainage (as clinically assessed), or the development of a perianal collection >2 cm in at least 2 dimensions of the perianal fistula(s) treated with darvadstrocel

confirmed by local MRI assessment (if conducted). In the All Treated population, clinical relapse was observed in 10.8% of patients by 6 months after darvadstrocel treatment (12 of 111 patients with available data; 95% CI, 5.7-18.1) and in 10.3% of patients by 12 months after darvadstrocel treatment (10 of 97 patients with available data; 95% CI, 5.1-18.1).

The percentage of patients with available data developing new perianal abscess in a treated fistula 6 months after darvadstrocel treatment was low (7.5% [95% CI, 4.8-11.1] in the All Treated population) and remained low at 12 months after darvadstrocel treatment (5.4% [95%CI, 2.4-10.4]).

As of the interim data cut-off of 03 April 2023, darvadstrocel was well tolerated in the 619 exposed patients, and the safety profile did not differ from previously reported accumulated data. No new safety signals were identified.

The most common treatment-related treatment-emergent adverse events (TEAEs) by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) were anal abscess (20 patients, 3.2%) and anal fistula (6 patients, 1.0%). As of 03 April 2023, 63 patients (10.2%) had at least 1 serious TEAE, and the most common serious TEAEs by PT were anal abscess (2.8%, considered related to darvadstrocel for 1.8% of patients) and Crohn's disease (8 patients; 1.3%). The rate of TEAEs leading to study discontinuation was 0.3%, and there have been no reported deaths in the study.

A total of 143 AESIs in 103 patients (16.6%) were identified via MedDRA criteria search, and 6 AESIs in 5 patients (0.8%) were identified in the case report form (CRF)/electronic CRF (eCRF). The overall pattern of AESIs identified was consistent with that of previous clinical studies of darvadstrocel, and no safety concerns were observed. As of 03 April 2023, no events met the MedDRA search criteria for ectopic tissue formation, medication errors, or transmission of infectious agents

8.2.3. Discussion Alofisel-5003

The MAH provided interim data for study Alofisel-5003 with a data cut-off at 03 Apr 2023 including 619 patients 302 of which had received at least 1 vial Alofisel and 1 available fistula for evaluation after 6 months. Approximately 50% of the study participants were male at a mean age of 39.9 years and a mean disease duration of 10.4 years. Almost all patients had a history of treatment with biologics (infliximab, adalimumab, ustekinumab) and in approximately 70 % biologic treatment was continued as concomitant medication during the study. The majority of patients received surgical pre-treatment (curettage) of the fistulas and the target fistula did not have an abscess (92.7%), and the internal openings (IOs) and EOs were clearly identified (98.7%).

The most frequent TEAE reported during the study were anal abscess with is a key feature of the underlying disease and its occurrence is rather expected and cannot be attributed to the Alofisel treatment alone, which also applies to the second frequently reported TEAE, anal fistula. The favourable outcome in terms of clinical remission after 12 months for 76 % of the patients in the all treated population is noteworthy, however, of limited significance due to several factors, two of which are the observational character and the concomitant medication continued during the study, so that it appears difficult to identify the contributory effect of Alofisel against the concomitant medication and intensified surgical procedures and other preparatory measures preceding the treatment.

More importantly in terms of the beneficial effects appear figures on clinical relapse, which was observed in only 10% at month 6 (12 of 111 patients) and at a similar rate at month 12. Clinical relapse was defined as reopening of any of the external fistula openings with active drainage (as clinically assessed), or the development of a perianal collection >2 cm in at least 2 dimensions of the perianal fistula(s) treated with darvadstrocel. However, the relapse figures refer to the part of the all treated population with available data and the 95% confidence interval covers a wide span from 5.7-

18.1. Nevertheless, the overall results of the observational study are encouraging with no new safety concerns emerged until cut-off of the interim report and an overall mild adverse reaction profile of the treatment.

9. PRAC advice

Not applicable.

10. Risk management plan – assessed by PRAC Rapp

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

Version	Approval date Procedure Number	Change
8.0	Procedure number: XX	**Part III. Pharmacovigilance plan** ADMIRE CD II (Cx601-0303) phase III study removed as an ongoing study as it is now a completed study. **Annex 1:** Updated study status and milestone for ADMIRE-CD II (Cx601-0303) phase III study. **Annex 3:** ADMIRE-CD II (Cx601-0303) phase III study removed as an ongoing study as it is now a completed study. **Other updates:** Clinical trial exposure and post-marketing details were updated as of DLP 22-September-2023.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: Tumorigenicity Medical Dictionary for Regulatory Activities (MedDRA) terms: System Organ Class (SOC) - Neoplasms benign, malignant, and unspecified (including cysts and polyps) and Standardised MedDRA Query (SMQ) Malignancies (Broad & Narrow)	
Potential mechanisms:	Paracrine signalling and cell-to-cell signalling, as well as differentiation into cancer-associated myofibroblasts or incorporation into newly formed vessels, may lead to morphological and functional alterations of cancer cells.
Evidence source(s) and strength of evidence:	Evidence from clinical development and post-marketing (PM) data.

Important Potential Risk: Tumorigenicity Medical Dictionary for Regulatory Activities (MedDRA) terms: System Organ Class (SOC) - Neoplasms benign, malignant, and unspecified (including cysts and polyps) and Standardised MedDRA Query (SMQ) Malignancies (Broad & Narrow)	
Characterisation of the risk:	Based on the broad scope of the global safety database (GSDB) search criteria: Clinical trials: Cumulatively, 12 SAEs were reported: Cx601-0302 (n=4), Cx601-0303 (n=5), Darvadstrocel-3003 (n=2), and Alofisel-4001 (n=1). For Cx601-0302 study, 3 of the 4 events were reported as pretreatment events or with placebo. Therefore, the remaining 9 SAEs by Preferred Term (PT) included: B-cell lymphoma, Basal cell carcinoma, Breast cancer, Chronic myeloid leukaemia, Fallopian tube cancer, Hepatocellular carcinoma, Leiomyoma, Ovarian cancer, and Uterine leiomyoma. The causality was assessed as not related by the investigator in all 9 SAEs. PM data: Cumulatively, 14 events were received from PM sources, two of which were invalid reports of Lymphoma and Neoplasm malignant. Five events that resulted from the broad search criteria do not represent tumorigenicity events: Anogenital warts, Benign neoplasm of prostate, Hyperleukocytosis, Pyoderma gangrenosum, and Tumour pain. Therefore, the remaining 7 serious events by PT included: Invasive ductal breast carcinoma, Metastases to lymph nodes, Ovarian dysgerminoma stage unspecified, Ovarian epithelial cancer, Pancreatic carcinoma, Signet-ring cell carcinoma, and Testis cancer. All 7 events were assessed as not related to darvadstrocel by the reporter.
Risk factors and risk groups:	CD patients with persistent inflammation, long-standing disease, extensive disease, young age at diagnosis, family history of colorectal cancer and co-existing primary sclerosing cholangitis.
Preventability:	Unknown
Impact on the risk-benefit balance of the product:	The currently available information regarding this risk has not impacted the positive benefit-risk balance for Alofisel. Further data will continue to be collected in the PM setting to evaluate the potential impact on the benefit-risk balance.
Public health impact:	Considering the rarity of tumorigenicity in CD patients, the potential public impact is very limited.

Important Potential Risk: Ectopic tissue formation MedDRA terms: High Level Group Term (HLGT): Benign neoplasms gastrointestinal	
Potential mechanisms:	Unknown
Evidence source(s) and strength of evidence:	Evidence from published scientific literature, clinical development and PM data.

Important Potential Risk: Ectopic tissue formation MedDRA terms: High Level Group Term (HLGT): Benign neoplasms gastrointestinal	
Characterisation of the risk:	In non-clinical studies, the differentiation potential of eASC (PD16) has been characterised as low. However, data on the incidence or prevalence of ectopic tissue formation after perilesional injection of Alofisel are not available. *Clinical trials:* Cumulatively from clinical trial sources, there were no events reported with darvadstrocel administration. *PM data:* Cumulatively, no case reports were reported from PM sources.
Risk factors and risk groups:	Unknown
Preventability:	Unknown
Impact on the risk-benefit balance of the product:	The currently available information regarding the risk of ectopic tissue formation has not impacted the positive benefit-risk balance for Alofisel. Further data will continue to be collected in the post-marketing setting to evaluate the potential impact on the benefit-risk balance.
Public health impact:	Considering the rarity of ectopic tissue formation in patients treated with Alofisel, the potential public impact is limited.

Important Potential Risk: Hypersensitivity reactions MedDRA terms: SMQ Hypersensitivity (Broad & Narrow) and SMQ Anaphylactic reactions (Broad & Narrow)	
Potential mechanisms:	Theoretically, some patients could develop hypersensitivity to bovine serum, benzylpenicillin, streptomycin, gentamicin and/or class-related compounds. Trace amounts of antibiotics could potentially be present in Alofisel. This hypersensitivity would be an immunoglobulin E (IgE)-mediated reaction. The mechanism of the reaction includes preferential production of IgE and inducing the degranulation of mast cells. Within the reaction, mast cells release inflammatory mediators from the granules, triggering a variety of symptoms, such as flushing, swelling, itching and pain. A sub-acute reaction caused by preformed IgG to benzylpenicillin as a result of previous benzylpenicillin treatment is also theoretically possible.
Evidence source(s) and strength of evidence:	Evidence from clinical development and PM data.
Characterisation of the risk:	Data on the incidence or prevalence of hypersensitivity related to impurities in the target population or the general population are not available. *Clinical trials:* Cumulatively, there was 1 suspected unexpected

Important Potential Risk: Hypersensitivity reactions MedDRA terms: SMQ Hypersensitivity (Broad & Narrow) and SMQ Anaphylactic reactions (Broad & Narrow)	
	serious adverse reaction of Anaphylactic shock reported from study Cx601-0303. Although the patient's history of medication allergies and the concomitant medications given at the end of the surgical procedure had significantly contributed to this event, the investigator could not entirely exclude the relationship between the event of anaphylactic reaction and the study medication. *PM data:* Cumulatively, 16 events (3 serious and 13 non-serious) were received from PM sources. The reported PTs were Swelling (n=2), Conjunctivitis (n=2), and a single frequency occurrence of Pruritus allergic, Henoch-Schoenlein purpura (serious event), Bronchospasm, Dyspnoea (serious event), Erythema, Dermatitis, Pruritus, Dermatitis atopic, Rash, Dermatitis bullous (serious event), Anal eczema, and Dermatitis contact. Twelve events were assessed as not related to darvadstrocel by the reporter and a causality assessment was not reported in the remaining 4 events.
Risk factors and risk groups:	Patients with known hypersensitivity to Alofisel or any of its constituents.
Preventability:	Unknown
Impact on the risk-benefit balance of the product:	Patients with known hypersensitivity to Alofisel or any of its excipients or to bovine serum should not be treated with Alofisel. The SmPC contraindicates the use of Alofisel in these patients. Additionally, the SmPC contains precautions regarding use of Alofisel in hypersensitive patients due to trace amounts of either benzylpenicillin and streptomycin or gentamicin in the finished product.
Public health impact:	Considering the rarity of hypersensitivity related to impurities, the potential public health impact is very limited.

Important Potential Risk: Transmission of infectious agents MedDRA terms: PT: Transmission of an infectious agent via product	
Potential mechanisms:	As Alofisel is a living product, it is not feasible to perform any terminal sterilisation, purification, viral removal or viral inactivation steps. Therefore, transmission of bacterial, viral, fungal or prion pathogens might potentially occur.
Evidence source(s) and strength of evidence:	Evidence from clinical development and PM data.
Characterisation of the risk:	The risk of transmitting an infectious agent is unknown. *Clinical trials:* Cumulatively, no SAEs were reported from clinical trial sources. *PM data:*

Important Potential Risk: Transmission of infectious agents MedDRA terms: PT: Transmission of an infectious agent via product	
	Cumulatively, no case reports were received from PM sources.
Risk factors and risk groups:	Unknown
Preventability:	The quality control of Alofisel at batch release encompasses testing of endogenous retroviruses and adventitious viruses (routinely for the MCS and in 1 batch of DS per MCS). Moreover, testing of non-viral contaminants (sterility, mycoplasma and bacterial endotoxins) at the MCS, DS and Alofisel DP stage is part of the routine quality control strategy at batch release. Precautions for use exist in the SmPC as Alofisel is a living stem cell therapy it cannot be sterilised, a risk of transmission of infectious agents exists, although the risk is considered to be low and controlled in the manufacturing process. Healthcare professionals administering Alofisel must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.
Impact on the risk-benefit balance of the product:	The available information regarding this risk has not impacted the overall benefit-risk balance for Alofisel. Additional data will continue to be collected in the post- marketing setting to further evaluate the impact of this risk on the overall benefit-risk balance for Alofisel.
Public health impact:	Considering the rarity of transmission of infectious agents, the potential public impact is very limited.

Important Potential Risk: Immunogenicity/allo-immunoreactions MedDRA terms: SMQ: Immune-mediated/autoimmune disorders (Broad & Narrow)	
Potential mechanisms:	Unknown
Evidence source(s) and strength of evidence:	Evidence from clinical development and PM data.
Characterisation of the risk:	The GSDB search criteria captured a wide variety of events that are not necessarily true immunogenicity/allo-immunoreactions events below: *Clinical trials:* Cumulatively, 22 serious adverse events (SAEs) were reported: Cx601-0302 (n=5), Cx601-0303 (n=5), Darvadstrocel-3002 (n=5), and Darvadstrocel-3003 (n=7). From study Cx601-0302, 3 of the 5 events were reported as a pre-treatment event or with placebo. Therefore, the remaining 19 SAEs by PT included: Crohn's disease (n=15), and a single reported frequency of Colitis, Diabetes mellitus, Multiple sclerosis, and Terminal ileitis. The causality of the events was assessed by the investigator as not related (n=16), related (n=2), and not reported (n=1). *PM data:* Cumulatively, 35 events (26 serious and 9 non-serious) were received from PM sources, of which 1 case with 1 non-serious event was invalid. The

Important Potential Risk: Immunogenicity/allo-immunoreactions MedDRA terms: SMQ: Immune-mediated/autoimmune disorders (Broad & Narrow)	
	remaining 34 events reported PTs of Crohn's disease (n=20), Arthritis (n=2), and a single frequency of Colitis, Colitis erosive, Dermatitis, Dermatitis bullous, Enteritis, Graves' disease, Henoch-Schoenlein purpura, Psoriasis, Pyoderma gangrenosum, Terminal ileitis, Vascular purpura, and Vitiligo. The reporter provided the causality assessments for the events as not related to darvadstrocel (n=30), not reported (n=2), and related (n=2).
Risk factors and risk groups:	Patients who developed DSA. However, the number of pre-sensitised Cx601-treated patients was too low to allow for meaningful evaluation of the impact of DSA on the frequency and nature of TEAEs.
Preventability:	Unknown
Impact on the risk-benefit balance of the product:	The available information regarding this risk has not impacted the overall benefit-risk balance for Alofisel. Additional data will continue to be collected in the post-marketing setting to further evaluate the impact of the risk of immunogenicity/allo- immunoreactions on the overall benefit-risk balance for Alofisel.
Public health impact:	Considering the rarity of immunogenicity/allo-immunoreactions, the potential public impact is limited.

Important Potential Risk: Development of new anal fistula and/or anal abscess or relapse of treated fistula MedDRA terms: PT: Drug ineffective	
Potential mechanisms:	Unknown
Evidence source(s) and strength of evidence:	Evidence from clinical development and PM data.
Characterisation of the risk:	*Clinical trials:* Cumulatively, no SAEs were reported from clinical trial sources. *PM data:* Cumulatively, 29 valid events of drug ineffective, 1 event was serious and 28 events were non-serious.
Risk factors and risk groups:	All patients with CD are at risk of developing anal fistula and anal abscess.
Preventability:	Unknown
Impact on the risk-benefit balance of the product:	All patients with CD are at risk of developing anal fistulas and anal abscess. Therefore, the occurrence of a small number of serious anal fistulas does not impact the positive benefit-risk that has been seen in the clinical development programme. Additional data will continue to be collected in the post- marketing setting to further evaluate the impact of the risk of new anal fistula and/or anal abscess or relapse of treated fistula on the overall benefit-risk balance for Alofisel.

Important Potential Risk: Development of new anal fistula and/or anal abscess or relapse of treated fistula MedDRA terms: PT: Drug ineffective	
Public health impact:	Patients with anal fistula and anal abscess require significant medical resources.

Important Potential Risk: Medication error MedDRA terms: SMQ Medication Errors (Broad)	
Potential mechanisms:	Not applicable
Evidence source(s) and strength of evidence:	Evidence from clinical development and PM data
Characterisation of the risk:	*Clinical trials:* Cumulatively, no SAEs were reported from clinical trial sources. *PM data:* Cumulatively, 11 non-serious AEs of medication error were reported from PM sources. The reported PTs were Underdose (n=5), Product use issue (n=2), Accidental underdose (n=1), Drug ineffective for unapproved indication (n=1), Medication error (n=1), and Poor-quality product administered (n=1).
Risk factors and risk groups:	Risk factors for medication errors could be related to the incorrect administration of the product, to the manipulation of the product, and to the storage of the product. There are no data available about risk groups or risk factors for medication errors with Alofisel.
Preventability:	The product is provided on an individual basis for the administration exclusively by surgeons. Clear instructions on recommended dosing, handling and preparation of the product, and administration procedure will be provided in the product labelling and in educational materials for HCPs.
Impact on the risk-benefit balance of the product:	Incorrect handling, administration or storage of cells could affect the efficacy of the cells to provide fistula healing, therefore impacting the patient's quality of life and need for alternative treatment.
Public health impact:	Taking the specific indication of Alofisel in the target population into account, there is no public health impact.

Missing information: Long-term safety	
Evidence source:	*Clinical trials:* There is one long-term follow-up study (Darvadstrocel-3003) ongoing at the time of DLP. Cumulatively, 41 SAEs were reported with PTs: Anal abscess (n=6), Crohn's disease (n=5), Calculus urinary (n=3), COVID-19 (n=3), Proctalgia (n=3), Intestinal obstruction (n=2), Anal fistula (n=2), and the remaining events were reported with a single frequency: Abdominal abscess, Anorectal disorder, Basal cell carcinoma, Chronic myeloid leukaemia, Depression, Faecaloma, Fistula, Fistula discharge, Gastrointestinal obstruction, Gastrointestinal stoma

Missing information: Long-term safety	
	complication, Multiple sclerosis, Nephrolithiasis, Perineal abscess, Small intestinal obstruction, Terminal ileitis, Tonsillitis, and Urinary tract infection. The investigator's causality was assessed as not related for all except 1 that was assessed as related to study therapy. Long-term follow-up to Week 104 was conducted in the Cx601-0302 study and completed by 37 consenting patients (23 patients in darvadstrocel group and 14 patients in the placebo group) without any additional safety findings. There were 4 SAEs reported, none were considered related to the treatment administered. No new safety findings emerged at the time of DLP from the long-term use of darvadstrocel. *PM data:* Cumulatively, no safety data related to long-term use was available from PM sources. **Population in need of further characterisation:** No information is available regarding the long-term safety of Alofisel. However, there is no evidence to suggest a different safety profile with long-term use. Ongoing studies aim to provide additional information about safety of Alofisel with long-term use.

Missing information: Experience during pregnancy and lactation	
Evidence source:	*Clinical trials:* In order to assess the safety of pregnancy exposure, the Company does not exclude pregnant female subjects in the long-term extension study, Darvadstrocel-3003. Cumulatively, there have been 20 pregnancy cases reported with darvadstrocel administration from clinical trials. From study Cx601-0302, there was 1 pregnancy that resulted in a healthy baby. From study Cx601-0303, a total of 10 pregnancy cases have been received up to DLP with 5 cases reported healthy babies, 2 pregnancies underwent elective abortions, 2 pregnancies were ongoing at the time of DLP, and 1 case had an unknown pregnancy outcome. From the Darvadstrocel-3003 study, a total of 7 pregnancy cases have been received up to DLP with 6 pregnancies resulted in full term healthy babies, and 1 case reported an ectopic pregnancy and resulted in an elective abortion. From study Darvadstrocel-3002, 2 pregnancy cases were reported with one serious event by PT of Premature Labour where the baby was delivered via C-section and had jaundice and hereditary spherocytosis, which the subject has a history from her previous pregnancy prior to receiving darvadstrocel, and these conditions are explained by genetic abnormalities. The remaining case had a healthy baby with no adverse event.

Missing information: Experience during pregnancy and lactation	
	PM data: Cumulatively, 18 pregnancy cases were reported from PM sources. Seventeen pregnancies were reported in the PM study Alofisel-5003 and 1 pregnancy was reported spontaneously. In 7 of the 18 pregnancies, the outcome was delivery of a healthy baby. Four pregnancies were ongoing at the time of DLP, 4 pregnancies resulted in spontaneous abortion, 2 pregnancies resulted in an elective abortion, and 1 pregnancy outcome was unknown. Cumulatively, no cases of lactation were reported. **Population in need of further characterisation:** Pregnant and lactating women were excluded from the clinical development programme. However, there is no reasonable expectation that Alofisel could negatively affect pregnant women or lactation or the unborn or breastfed baby. Nevertheless, Alofisel is not recommended for use during pregnancy and lactation.

Missing information: Experience in the elderly	
Evidence source:	*Clinical trials:* Cumulatively, 6 elderly patients aged ≥65 years (2 from Cx601-0303 study and 4 from Cx601-0302 study) reported 8 SAEs by PT in clinical trials: Anal abscess, Diabetes mellitus, Hepatocellular carcinoma, Hypertension, Pelvi-ureteric obstruction, Peritonsillar abscess, Post procedural haemorrhage, and renal colic. All events were assessed as not related by the investigator. *PM data:* Cumulatively, 6 cases (4 serious and 2 non-serious) were reported in patients aged ≥ 65 years in PM sources with PTs of COVID-19 (n=2), and a single frequency for Anorectal swelling, Dermatitis bullous, Hyperleukocytosis, and Hyperthermia. The reporter's causality was assessed as not related (n=5) and related (n=1). **Population in need of further characterisation:** Data on the use of Alofisel in the elderly population are limited. However, given the cell- based nature of Alofisel and its local administration route, there is no reasonable expectation that the benefit/risk balance would be different in elderly patients compared to non-elderly patients. The safety of Alofisel in elderly patients will continue to be evaluated in the PM setting.

Missing information: Repeat use (Any case report when a patient received more than one dose of darvadstrocel)	
Evidence source:	*Clinical trials:*

Missing information: Repeat use (Any case report when a patient received more than one dose of darvadstrocel)	
	One serious case report from study Cx601-0101 comprised of 1 SAE with the PT Pyrexia. The patient received more than one active dose (first dose of 20 million cells and second dose of 40 million cells) per protocol of study drug. The patient's temperature went up to 39.7 degrees Celsius after the second dose. The outcome was reported as recovered after treatment with Augmentin. The event was considered as related to the study medication by the investigator. Takeda has initiated a phase 4 Post-Authorisation Safety Study (PASS) (Alofisel-4001) to investigate the long-term safety and efficacy of a repeat administration with darvadstrocel in subjects with CD and complex perianal fistula. At the time of DLP, 4 SAEs were received from this study with the reported PTs of Cerebrovascular accident (n=1), Intestinal obstruction (n=1), Leiomyoma (n=1), and Proctalgia (n=1). The investigator's causality was assessed as not related (n=3) and related (n=1). *PM data:* Cumulatively, 5 cases reported 8 events with repeat use. Of the 8 events, 2 were serious and 6 were non-serious. The reported events by PT included Abdominal abscess, Diarrhoea, Haematochezia, Pregnancy [with] No adverse event, Post procedural inflammation, Scar pain, and White matter lesion. The reporter's causality was not related (n=7) and related (n=1). **Population in need of further characterisation:** There is currently limited experience with the efficacy or safety of repeat administration of Alofisel.

PRAC assessor comment
Along with an update of the pharmacovigilance plan, the MAH also updated the table "Details of important identified risks, important potential risks, and missing information". All changes are accepted.

Part III Pharmacovigilance Plan (including post- authorization safety studies)

III.2 Additional pharmacovigilance activities

ADMIRE-CD II (Cx601-0303) Long-Term Extension Study (Darvadstrocel-3003) Summary
Study short name and title: **Long-term extension study:** A Follow-up of a Phase 3 Study to Evaluate the Long-term Safety and Efficacy of Darvadstrocel in the Treatment of Complex Perianal Fistula in Subjects with Crohn's Disease.
Rationale and Study Objectives: Darvadstrocel-3003 is the long-term extension (LTE) study for follow-up of the phase 3 ADMIRE-CD II (Cx601-0303) study to evaluate the long-term safety and efficacy of darvadstrocel in the treatment of complex perianal fistula in Crohn's disease. To be eligible for this LTE study, subjects will have completed the final assessment at the week 52 of the ADMIRE-CD II (Cx601-0303) study. The LTE study will evaluate the long-term safety of darvadstrocel including adverse events (AEs), SAEs and specific adverse events of special interest (AESIs): immunogenicity/allo-immune reactions, tumorgenicity, and ectopic tissue formation. The study will also evaluate the long-term effect of darvadstrocel treatment on fistula remission, fistula relapse major fistula-related events (hospitalisations and surgeries), and health-related quality of life measurements.
Study Design This is an extension study in which patients will continue in the treatment arm that they were allocated in ADMIRE II (Cx601-0303) study. Study visits will take place annually for up to 2 years from enrolment into the LTE of ADMIRE-CD II (Cx601-0303) study or 3 years post treatment in ADMIRE-CD II (Cx601-0303) study. At these visits, clinical assessment of the fistula will be considered for clinical remission. Additional telephone call visits will be conducted every 3 months for safety assessments. In addition, unscheduled visits may be performed for safety follow-up, and for subjects experiencing any clinically significant symptoms of perianal disease, a MRI will be performed.
Study population: Approximately 150 subjects, male or female who have participated in and completed the ADMIRE-CD II (Cx601-0303) study for treatment of complex perianal fistula in Crohn's disease.
Milestones: Interim analysis CSR: 27-February-2024 Final report: Q3/Q4 2024

Retreatment PASS (Alofisel-4001) summary
Study short name and title: Post-Authorisation Safety Study (PASS) of the Long-Term Safety and Efficacy of Repeat Administration of Darvadstrocel in Patients with Crohn's Disease and Complex Perianal Fistula.
Rationale and study objectives: This is a phase 4, multinational, single arm clinical study of adult CD subjects (aged 18 years or older) with complex perianal fistulas who have previously been administered darvadstrocel and repeat administration is planned by their physician. The overall objective of the study is to assess the long-term safety and efficacy of repeat administration of darvadstrocel in patients with CD and complex perianal fistula over a period of 3

Retreatment PASS (Alofisel-4001) summary
years after the re-administration with ongoing immunological assessment (donor-specific antibody [DSA]), central reading MRI assessment and fistula clinical assessment. Safety assessment will include AEs, SAEs, Special Situation Reports (SSRs) and AESIs.
Study design: This is a phase 4, multinational, single arm clinical study of patients with CD and complex perianal fistulas who will receive repeat administration of darvadstrocel. Patients will be followed during 156 weeks for assessment of safety and efficacy. A MRI will be performed prior to the repeat treatment and at the 24-week visit and at week 156 visit. Subjects will be assessed prior to retreatment at a baseline and a preparatory visit, and at weeks 6 (±2), 24 (±4), 52 (±4), and 104 (±4) and 156 post-repeat administrations. Blood samples for DSA levels and exploratory immunogenicity testing will be collected at retreatment baseline and at weeks 6, 24, and 156. Blood samples for these tests will be analysed in batches as the study progresses and available results will be provided with the interim reports.
Study population: Fifty adult CD subjects aged 18 years or older inclusive, with complex perianal fistulas who have been administered darvadstrocel, and for whom a repeat administration of darvadstrocel for the original fistula tract or for a new fistula tract is planned by their physician.
Milestones: Final report: Q1 2027

European Multi-Database Linkage Study (Alofisel-5005) summary
Study short name and title: An observational European multi-database linkage study to quantify malignancy rates in Crohn's disease patients with complex perianal fistula treated with darvadstrocel.
Rationale and study objectives: To better understand the safety issue of tumorigenicity, the EMA recommended to employ a retrospective approach, based on existing routinely collected data from multiple databases where information on exposure to darvadstrocel can be linked with information on malignancy outcomes and mortality. Therefore, we will conduct an observational, population-based retrospective cohort linkage study based on European healthcare databases. **Primary study objective:** o To estimate the incidence rate and cumulative incidence of malignancies among Crohn's disease patients with complex perianal fistulas (CPAF) who received treatment with darvadstrocel or an alternative standard of care (SoC). **Secondary study objectives:** o To estimate all-cause mortality and cancer-specific mortality rate among CD patients with CPAF who received darvadstrocel or an alternative SoC for CPAF o To describe clinical characteristics, clinical management, comorbidities and drug therapy in CD patients with CPAF who received darvadstrocel.
Study design: This is a non-interventional, observational, population-based retrospective cohort study based on European healthcare databases.
Study population: The study population includes eligible patients diagnosed with Crohn's disease and CPAF that have received treatment with darvadstrocel or an alternative SoC for CPAF as recorded in national or regional health care databases from 01 April 2018 to 31 December 2025.
Milestones: Final study report submitted to EMA: Q4 2027

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Table Part III.3.1 On-going and planned additional pharmacovigilance activities					
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Requesting/ Concerned Health Authority**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities, which are conditions of the marketing authorisation.					
None					
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances					
None					
Category 3 - Required additional pharmacovigilance activities					
Darvadstrocel-3003 ADMIRE-CD II (Cx601 - 0303) - Long-Term Extension Study Ongoing	To evaluate the long-term safety and efficacy of darvadstrocel including AESIs	Tumorigenicity, Ectopic tissue formation, Immunogenicity/ allo-immunoreactions	EMA	Interim report Final report	Q1 2024 (27-February-2024) Q3/Q4 2024
Alofisel-4001 Retreatment PASS Ongoing	The overall objective of the study is to assess the efficacy and safety of repeat administration of darvadstrocel in patients with CD and complex perianal	Assessment the safety of the repeated treatment and the AESIs: Tumorigenicity, ectopic tissue formation, Hypersensitivity, Immunogenicity and allo-immune reactions, Transmissio	EMA	Final Study Report	Q1 2027

Table Part III.3.1 On-going and planned additional pharmacovigilance activities					
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Requesting/ Concerned Health Authority**	**Milestones**	**Due dates**
	fistula.	n of infectious agents, and Medication errors.			
Alofisel-5005 European multi-database linkage study Ongoing	An observational European multi-database linkage study to quantify malignancy rates in CD patients with complex perianal fistula treated with darvadstrocel.	Malignancies	EMA	Final Study Report	Q4 2027
PRAC Assessment comment *All changes to the pharmacovigilance plan are correct and accepted.*					

Annex 2: Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex 2: Planned and ongoing studies

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Requesting /Concerned Health Authority**	**Milestones**	**Due dates**
Darvadstrocel-3003 Cx601-0303 (ADMIRE-CD II Study) - long-term extension	To evaluate the long-term safety and efficacy of darvadstrocel including adverse events of special interest (immunogenicity,	Long-term safety up to 156 weeks	EMA	Interim CSR approval date Final Study Report	27-February-2024 Q3/Q4 2024

Study Status	Summary of objectives	Safety concerns addressed	Requesting /Concerned Health Authority	Milestones	Due dates
Study (Category 3)	tumorigenicity and ectopic tissue formation). The study will also evaluate the long-term effect of darvadstrocel treatment on fistula remission, major fistula-related events (hospitalisations and surgeries).				
Alofisel-4001 Retreatment PASS (Category 3)	The overall objective of the study is to assess the long-term safety and efficacy of repeat administration of darvadstrocel in patients with Crohn's disease and complex perianal fistula.	Assessment of safety for the repeated treatment of darvadstrocel and AESIs: Tumorigenicity, ectopic tissue formation, Hypersensitivity Immunogenicity and allo-immune reactions, and medication errors.	EMA	Final Study Report	Q1 2027
Alofisel-5005 European multi-database linkage study (Category 3)	An observational European multi-database linkage study to quantify malignancy rates in CD patients with complex perianal fistula treated with darvadstrocel.	Malignancies	EMA	Final Study Report	Q4 2027

Table 2 Annex 2: Completed studies

Study	Summary of objectives	Safety concerns addressed	Final Study Report Date of Final Study Report submission
Cx601-0302 A phase III, randomised, double blind, parallel group, placebo controlled, multicentre study. Category: Pivotal study	To assess efficacy and safety of expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of perianal fistulising CD over a period of 24 weeks and an extended follow-up period up to 104 weeks.	General safety.	For final study report, refer to eCTD Module 5.1. Completion date: November-2017 Final CSR submission date: 14-November-2017.

Study	Summary of objectives	Safety concerns addressed	Final Study Report Date of Final Study Report submission
Cx601-0101 Multi-centre phase I/IIa study.	To assess the safety and efficacy of allogeneic expanded adipose-derived stem cells (eASCs) (Cx601), for treatment of complex perianal fistulas in pCD.	General safety.	For final study report, refer to eCTD Module 5.2 Completion date: 09-December-2014 Final CSR submission date: 02-March-2016.
Cx601-0303 ADMIRE-CD II Study: Phase III Study	To evaluate the efficacy and safety of Alofisel compared to placebo for the treatment of complex perianal fistula(s) in patients with CD at Week 24 with a follow-up period up to 52 weeks.	Long-term safety up to 52 weeks.	For final study report, refer to eCTD Module 5.3.5.1. Completion date: 09-February-2024. Final CSR submission date: May-2024.

PRAC Assessment comment

Update of Annex 2 is correct.

Annex 3: Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

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Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

Part C: Previously agreed protocols for <u>on-going studies</u> and final protocols not reviewed by the regulatory authority

- ADMIRE-CD II (Cx601-0303) long-term extension study Refer to eCTD Module 5.3.5.1
- Retreatment PASS (Alofisel-4001)

  Refer to eCTD Module 5.3.5.1
- European multi-database linkage study (Alofisel-5005)

  Refer to eCTD Module 5.3.5.2

PRAC Assessment comment

Update of Annex 3 is correct.

10.1. Overall conclusion on the RMP

☒The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

11. Changes to the Product Information

As a result of this group of variations, sections 4.8 and 5.1 of the SmPC are updated based on data from study ADMIRE-CD II, listed as an obligation in the Annex II. The Annex II is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes to the PI, including to section 4.2 of the SmPC and to the Package Leaflet.