Statistical Analysis Plan

NCT Number: NCT04075825

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

Study Number: Darvadstrocel-3003

Document Version and Date: Version 2.0, 26 May 2023

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

STATISTICAL ANALYSIS PLAN

Study Number: Darvadstrocel-3003

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

Phase: PHASE 3

Version: 2.0

Date: 26-May-2023

Prepared by:

[redacted], Statistics & Quantitative Sciences

Data Sciences Institute, Research & Development

Based on:

Protocol Version: Amendment 2

Protocol Date: 17 November 2022

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	28-Oct-2021	Not Applicable
Version 2	26-MAY-2023	To implement the changes to the protocol amendment 2, mainly to clarify the timing of the baseline assessments, include an interim analysis and define the situations in which a subject will be considered a treatment failure

Approval Signatures

Electronic signature can be found on the last page of this document.

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

Approvals:

[redacted], PhD
[redacted], Statistics and Quantitative Sciences

Date

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CD	Crohn's disease
CM	Concomitant medication
CRF	case report form
DSA	donor specific antibody
[redacted]	[redacted]
IA	Interim Analysis
IBD	inflammatory bowel disease
ICF	informed consent form
IMP	investigational medicinal product
LTE	long-term extension
mAB	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
MRI	magnetic resonance imaging
PDAI	Perianal Disease Activity Index
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
WHODrug	World Health Organization Drug Dictionary

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objective

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

1.1.3 Exploratory Objective

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoints

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

1.2.2 Secondary Endpoints

- *Proportion of subjects who achieve clinical remission at Week 104 and Week 156 after investigational medicinal product (IMP) administration.*
  - *Clinical remission is defined as closure of all treated external fistula openings that were draining at baseline of ADMIRE-CD II despite gentle finger compression.*
- *Proportion of subjects who achieve clinical response at Week 104 and Week 156 after IMP administration.*
  - *Clinical response is defined as closure of at least 50% of all treated external fistula openings that were draining at baseline of ADMIRE-CD II despite gentle finger compression.*

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

1.2.3 Exploratory Endpoints

[redacted]

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

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

For those subjects who have more than a 4-week gap between the Week 52 visit of the ADMIRE-CD II study and signing of the informed consent form (ICF) for the LTE study, a re-baseline visit will be scheduled; the re-baseline visit will include the same procedures included at this study baseline visit with the addition of interval inflammatory bowel disease (IBD) history and medical

interventions since the Week 52 visit. MRI assessment will not be performed at the re-baseline visit. The re-baseline visit cannot be performed any later than 3 months after the Week 52 visit. An MRI will be performed in all subjects at the Week 156 visit.

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

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

Enrollment into the LTE study will not prevent subjects with ongoing fistulizing disease or luminal CD from receiving any additional treatment (including any medical or surgical treatment) prescribed by his/her physician for the treatment of CD and/or perianal disease. Subjects who receive surgical and/or biologic treatment for the perianal fistulizing disease will be considered treatment failures, but patients should continue in the study.

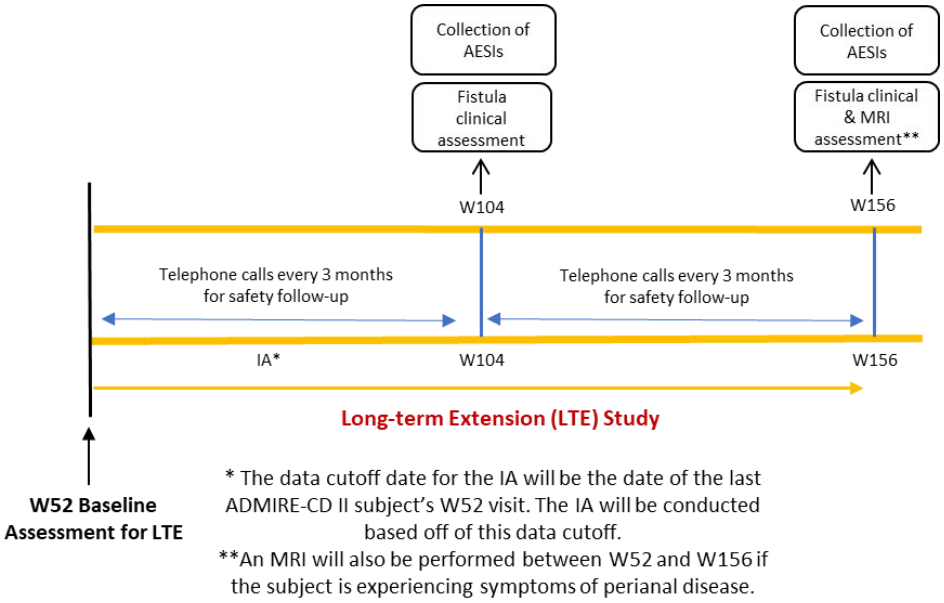
Treatment failure is documented for a subject if they require rescue medication(s) or procedure(s) for perianal fistulizing disease, defined as switch to or addition of any new monoclonal antibody or small molecule not ongoing at LTE study baseline, increase in dose or frequency of any prior ongoing monoclonal antibody or small molecule in the LTE study, subjects starting any investigational drug(s) for CD or any other local investigational treatment(s) in the perianal region while participating in the LTE study or any new surgical procedure required in the perianal region for the fistula(s) or draining of collections or established abscess(es) or any ostomy required due to fistula(s). Those subjects who are prescribed darvadstrocel will be withdrawn from the LTE study and complete an early termination visit because the study will assess the long-term follow-up of IMP administration in the ADMIRE-CD II study.

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

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

The planned visit schema is presented below (Figure 2.a). Please refer to the protocol for detailed information pertaining to the schedule of assessments and procedures at each visit.

Figure 2.a Study Schematic



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

Information pertaining to withdrawal of patients is detailed in the protocol, including information pertaining to discontinuation of individual patients, and to discontinuation of the entire study.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not Applicable

3.2 Statistical Decision Rules

Not Applicable

3.3 Multiplicity Adjustment

Not applicable since there is no inferential statistics done in this study.

4.0 SAMPLE-SIZE DETERMINATION

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

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

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

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

5.2 Full Analysis Set

Not applicable.

5.3 Per-Protocol Analysis Set

Not applicable.

5.4 Pharmacokinetic Analysis Set

Not applicable.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Two sets of baseline values will be considered in this LTE study for both efficacy and safety analysis, unless otherwise specified.

- ADMIRE-CD II Baseline value refers to the Baseline from the ADMIRE-CD II study.
- LTE Baseline value refers to the baseline (Week 52 of ADMIRE-CD II) or re-baseline values collected at the entry of LTE study.

All confidence intervals (CI) will be reported as 95% CI unless otherwise stated.

Confidence intervals will be presented using the same number of decimal places as the point estimate. Wherever possible data will be decimal aligned.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be presented.

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses. Details are provided in Section 9.2.3.

In this document when the tables are to be presented by treatment group, the treatment groups will be those as assigned according to the ADMIRE-CD II study.

6.1.1 Handling of Treatment Misallocations

This is a safety study and subject will be analyzed according to the actual treatment they received in the ADMIRE-CD II study and regardless of randomization assignment.

6.1.2 Analysis Approach for Continuous Variables

All continuous variables in this trial will use the analysis method below unless stated otherwise in the section specific to an endpoint.

Continuous data will be summarized using descriptive statistics, including the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. The minimum and maximum values will be displayed to the same number of decimal places as the raw data. In general, the maximum number of decimal places reported shall be four for any summary statistic.

6.1.3 Analysis Approach for Binary Variables

All binary variables in this trial will use the analysis method below unless stated otherwise in the section specific to an endpoint.

Categorical data will be summarized as the number and proportion of subjects in each category. Percentages will be reported to 1 decimal place. Missing values will be tabulated but will not be included in the calculation of percentages. The denominator for the proportion will be based on the number of subjects in the analysis set.

6.1.4 Analysis Approach for Time-to-Event Variables

Not applicable.

6.2 Disposition of Subjects

All patients signing the LTE ICF will be enrolled in the LTE study and hence no screen failure should be expected. The number of patients receiving study treatment or placebo in ADMIRE-CD II and consented in the LTE study, who completed or prematurely withdrew from the study, and the reasons for any premature withdrawal, will be presented by treatment group, and overall. Summaries of disposition will be performed on the Safety analysis set.

Time (in weeks) on the study as defined as

> (Maximum date of last clinical fistula assessment, MRI visit (or last visit if missing) minus the date of informed consent signature of the LTE+1)7

will be presented by treatment group. Major protocol deviations will be listed and summarized.

Enrollment will be summarized by treatment groups, region, country and site.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Re-baseline visit will be conducted if there is a gap >4 weeks between ADMIRE-CD II Week 52 visit and signing of ICF for the LTE study. The re-baseline visit must take place within 3 months of the ADMIRE-CD II Week 52 visit. In these subjects, the LTE baseline demographic and other baseline characteristic will be obtained from the re-baseline visit instead of from the baseline visit which occur on Week 52 of the ADMIRE-CD II. Height will be obtained from the screening visit of the ADMIRE-CD II study. The number of subjects with a re-baseline visit will be summarized by treatment group.

Baseline demographic including baseline age, race, gender, ethnicity, height, weight, body mass index and smoking status will be summarized by treatment group. The summary will be provided for ADMIRE-CD II baseline and LTE baseline, respectively.

6.3.2 Medical History

Medical History from ADMIRE-CD II study will become Medical History for this LTE study. For re-baselined subjects, new events or ongoing AEs/SAEs from ADMIRE-CD II that change severity after completion of the week 52 ADMIRE CD II visit will be recorded as medical history for this LTE study if they occur before the ICF for LTE being signed. Interval inflammatory bowel disease (IBD) history collected in this LTE study will be summarized.

The coding dictionary to be used for medical history is MedDRA.

Prior and ongoing medical history of ADMIRE-CD II will be summarized by system organ class and preferred term by treatment group.

Listings will also be provided for medical history.

6.3.3 Baseline Characteristics

ADMIRE-CD II baseline fistula clinical assessment will also be summarized by treatment group.

6.4 Concomitant Medications

Concomitant medications are all medications CD-related and not CD-related:

- ongoing at Visit 6 (week 52) of ADMIRE-CD II study
- medication started after Visit 6 (week 52) of ADMIRE-CD II study
- taken during the course of the LTE study

Medications will be coded using the WHO DRUG. Concomitant medication use will be summarized descriptively using frequency and percentage of patients by treatment group, drug

class and preferred drug name. Concomitant medications will also be summarized by indication (as per the eCRF).

Refer to the Section 9.2.4 for handling of missing dates.

Prior treatment for CD and fistulas at ADMIRE-CD II baseline will be summarized as counts and percentages by treatment group. The subset of prior treatment for CD and fistulas ongoing at screening of ADMIRE-CD II will be summarized separately.

Concomitant procedures will be summarized by treatment group, system organ class, and preferred term, also by indication as well as by modality.

6.5 Efficacy Analysis

Efficacy analyses will be performed using the Safety Analysis set.

All efficacy endpoints will be summarized by visit and treatment group starting from ADMIRE-CD II, as applicable. The proportions along with their 95% 2-sided CIs will be provided by visit (whenever applicable) and treatment group for: clinical remission, clinical response, combined remission, relapse, new anal abscess in treated fistula.

Continuous endpoints will be summarized descriptively by visit and treatment group for: change from ADMIRE-CD II baseline in PDAI subscore (discharge and pain) [redacted] ADMIRE-CD II baseline will be used as the baseline for efficacy analysis. The LTE baseline will be considered as a visit and presented in the summaries as described above.

6.5.1 Primary Endpoints Analysis

Safety is the primary endpoint in this study.

6.5.2 Secondary Endpoints Analysis

The secondary endpoints analysis will be descriptive in nature.

The following definition will be used to derive the secondary endpoints:

Endpoint	Definition
Combined Remission	– Combined remission of complex perianal fistula(s), defined as the clinical assessment of closure of all treated external openings that were draining at baseline of ADMIRE-CD II (ie, screening visit), despite gentle finger compression AND – Absence of collection(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by centrally read blinded MRI assessment.

Endpoint	Definition
Clinical Remission	Closure of all treated external fistula openings that were draining at baseline of ADMIRE-CD II despite gentle finger compression.
Clinical Response	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	In patients who were in combined remission at Week 52 of the ADMIRE-CD II study, and who have either: – Reopening of any of the treated fistula(s) external openings with active drainage as clinically assessed OR – The development of a perianal fluid collection >2 cm of the treated perianal fistulas confirmed by centrally read magnetic resonance imaging (MRI) assessment.
New anal abscess in treated fistula	New anal abscess confirmed by centrally read MRI assessment at week 156
PDAI SubScore	The PDAI is a scoring system to evaluate the severity of perianal CD. From the 5-item instrument, discharge and pain will be used. Each category is graded on a 5-point Likert scale ranging from no symptoms (score of 1) to severe symptoms (score of 5); a higher score indicates more severe disease.

Refer to the Section 9.2.5 for handling of missing data.

The proportion of subjects who achieve combined remission will be presented for Week 156.

The proportion of subjects who achieve clinical remission will be presented for Week 104 and Week 156.

The proportion of subjects who achieve clinical response will be presented for Week 104 and Week 156.

The proportion of subjects with a relapse will be presented for Week 156.

The proportion of subjects with new anal abscess in treated fistula will be presented for Week 156.

The change from ADMIRE-CD II baseline in scores of discharge and pain items of Perianal Disease Activity Index (PDAI) score will be presented for LTE baseline, Week 104 and Week 156.

6.5.3 Exploratory Endpoints Analysis

[redacted]

6.5.4 Subgroup Analyses

No subgroup analyses are planned in this study.

6.5.5 Rescue medication and procedure

Subjects who receive surgical and/or biologic treatment for the perianal fistulizing disease will be considered non-responders for the analysis of binary endpoints from the next day of "rescue medication" or "rescue procedure" and onwards.

The following situation qualify as "rescue medication" or "rescue procedure"

- Switch to or addition of any new mAb or small molecules, not ongoing at baseline of LTE
- Increase in dose or frequency of any prior ongoing mAb or small molecules in the LTE study.
- Subjects starting any investigational drugs for CD or any other local investigational treatments in the perianal region while participating in the study.
- Any new surgical procedure required in the perianal region for the treated fistula(s) or draining of collections or established abscess(es) or any ostomy required due to treated fistula.

Listings of rescue medications and rescue procedures taken by subjects during the study will be provided.

6.6 Safety Analysis

For safety analyses, patients will be grouped according to the actual treatment received, and the Safety analysis set will be used for all analyses. Patients will be evaluated for safety from the date the ICF is being signed for the LTE study through the Week 156 visit. Summaries will be provided by treatment group.

Safety data (including physical examination and vital signs) will be summarized using descriptive statistics.

6.6.1 Adverse Events

Adverse events will be collected throughout the study and summarized descriptively with counts and percentages. AEs are coded using MedDRA dictionary. The number of patients experiencing each AE category will be summarized by body system and preferred term.

Since this LTE study is the extension of the ADMIRE-CD II study where the study drug was administered, TEAE will be all AEs occurring on or after the time the ICF is being signed for the LTE (AE onset date ⩾ LTE-ICF date). Prior events (i.e. those AEs occurring prior to ICF date) will not be reported in this LTE study.

Refer to the Section 9.2.4 for handling of missing dates.

AE summaries will be produced and split by treatment group, outcome, whether concomitant medication was given, relationship to study drug and intensity of AE, as well as split by system organ class (SOC) and preferred term (PT).

The following summaries of AEs will be provided:

- Treatment Emergent Adverse Events (TEAEs)
- TEAEs related to study treatment of ADMIRE-CD II
- Treatment Emergent Serious Adverse Events (TESAEs)
- TESAEs related to study treatment of ADMIRE-CD II
- TEAEs and TESAEs according to their intensity/severity
- TEAEs leading to study withdrawal
- TESAEs leading to study withdrawal
- Fatal SAEs

These summaries will be counts and percentages through Week 156. Missing severity, relationship or outcome will be classed as unknown.

Related events are defined as events with relationship to study medication of probably related, possibly related, or unknown; unrelated events are defined as events with relationship to study medication of unlikely or not related.

Summary of TEAEs by SOC and PT up to Week 52 of ADMIRE-CD II for subjects in LTE study will also be provided.

All other information collected (e.g., action taken) will be listed as appropriate.

6.6.2 Adverse Events of Special Interest

The following Special interest AE/abnormality criteria (AESIs) (identified based on medical review) are included in this study:

- Immunogenicity/alloimmune reactions
- Ectopic tissue formation
- Tumorigenicity

The following summaries will be generated for the AESI:

- Treatment-emergent Adverse Events of Special Interest by SOC and PT - number and percentage of subjects, number of events.

Listing of AESI will also be presented.

6.6.3 Clinical Laboratory Evaluations

Not applicable since no laboratory test results will be collected in this study.

6.6.4 Vital Signs

Vital signs measurements (sitting blood pressure [mmHg], pulse rate [beats/min], and body temperature [ºC]) will be also measured at all study visits.

The observed value and the change from ADMIRE-CD II baseline in vital signs measurements will be summarized using descriptive statistics by visit and treatment group.

ADMIRE-CD II baseline will be used as the baseline for the vital sign analysis. The LTE baseline will be considered as a visit and presented in the summaries as described above.

6.6.5 12-Lead ECGs

Not applicable since no lead ECG test results will be collected in this study.

6.6.6 Extent of Exposure and Compliance

There is no IMP administration in this study.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Not applicable.

6.7.2 Pharmacodynamic Analysis

Not applicable.

6.7.3 Biomarker Analysis

The following analysis will be performed for the biomarker data.

- Frequency of the HLA+ as well as the pre-sensitized (DSA+) and naïve subjects at ADMIRE-CD II baseline will be provided.
- Frequency and percentage of immunogenicity events (DSA+) for both treatment arms will be summarized by visits. Subgroup analysis will include frequency of immunogenicity events for naïve and pre-sensitized groups.

- Combined remission will be summarized by subgroups of naïve vs pre-sensitized at ADMIRE-CD II baseline and for DSA+ and DSA- population within each subgroup.
- TEAE through week 156 will be summarized for each treatment arm by subgroups of naïve vs pre-sensitized and for DSA+ and DSA- population within each subgroup.

6.8 [redacted]

6.8.1 [redacted]

[redacted]

6.8.2 [redacted]

[redacted]

6.9 Interim Analyses

Interim Analysis (IA) will be done after ADMIRE-CD II unblinding to support the long-term benefit-risk profile of darvadstrocel. The data cutoff date for the IA will be the date of the last ADMIRE-CD II subject's Week 52 visit. The IA will include safety analyses and selected efficacy analyses (such as clinical remission and clinical response, etc.) based on available data. All available safety and efficacy data by the time of interim data cut will be included with the following exceptions:

- Biomarker analysis
- Efficacy endpoints involving MRI test results

6.10 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

[redacted]

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

1. Two sets of baseline values are defined: ADMIRE-CD II Baseline value refers to the Baseline from the ADMIRE-CD II study; LTE Baseline value refers to the baseline (Week 52 of ADMIRE-CD II) or re-baseline values collected at the entry of LTE study.

9.0 APPENDIX

9.1 Changes from the Previous Version of the SAP

Changes made from the previous version of the statistical analysis plan (SAP) that have a material impact to the planned statistical analysis methods are described below. In addition, there were textual changes purely to improve the flow, organization and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

SAP Section	Change	Rationale for Change
1.2.2	Changed baseline to "Baseline of ADMIRE -CD II." Editorial changes	To clarify the timing of the baseline assessments that will be used for the study's efficacy analysis and secondary endpoints analyses. To clarify the study's definition of "relapse"
1.2.3	Changed baseline to "Baseline of ADMIRE -CD II." Editorial changes	[redacted] To clarify baseline for exploratory endpoints
2.0 Study Design	Language addition	To define the situations in which a subject will be considered a treatment failure. To clarify that the double-blind design will be maintained up to Week 52 to allow for evaluation of longer term efficacy and safety
Figure 2.a	Language addition	Added IA to Study Schematic
6.1.2	Editorial changes	To clarify method of handling decimal places for summary statistics
6.2	Editorial changes	To clarify definition/calculation of time on the study
6.3.2	Editorial changes	To clarify on how to report medical history data for LTE study, added information on reporting IBD data collected in the LTE study
6.4	Editorial changes	Remove "Prior," team agree not reporting prior medication for the LTE study
6.6.1	Editorial changes	Textual changes purely to improve the flow

SAP Section	Change	Rationale for Change
6.5.2	Editorial changes	Textual changes purely to improve the flow Removed the sentence "No imputation of missing values will be performed; all tables will be presented using observed;" added refer section for handling of missing data. To clarify the timing of the baseline assessments that will be used for the study's efficacy analysis and secondary endpoints analyses. To clarify that centrally read MRI assessment at week 156 will be used to confirm new anal abscess.
6.5.5	Language addition	Added information on rescue medications and procedures which will be used to define the situations in which a subject will be considered a treatment failure.
6.6.1	Editorial changes	Textual changes purely to improve the flow
6.6.4	Editorial changes	To clarify the baseline
6.7.3	Editorial changes	To clarify the baseline. To clarify on definition of pre-sensitized
6.8.1	Editorial changes	To make to top categories grouping consistent to the definition in ADMIRE CD II
6.8.2	Editorial changes	To clarify baseline and textual changes to improve the flow
6.9	Editorial changes and Language addition	Addition of IA to support the long-term benefit-risk profile of darvadstrocel at the time of completion of Study Cx601-0303 ADMIRE-CD II
9.1	Editorial changes	To improve the flow
9.2.5	Language addition	Added section on conventions for missing data
9.3	Language addition	Added APPENDIX for AESI

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Reporting conventions were discussed in Section 6.1.

9.2.2 Definition of Baseline

Baseline at entry to LTE study is defined as the date of ICF signature. The relevant assessments from the Week 52 Visit of ADMIRE-CD II study may be used as the LTE baseline assessments.

For those subjects who have more than a 4-week gap and less than 3 months gap between the Week 52 visit of the ADMIRE-CD II study and signing of the informed consent form (ICF) for the LTE study, a re-baseline visit will be scheduled and the relevant assessments from the re-baseline visit will be used as the LTE baseline assessments.

ADMIRE-CD II baseline refers to the baseline as collected in the ADMIRE-CD II study.

9.2.3 Definition of Visit Windows

Study Day 1 is defined as the date on which a subject signed the informed consent form. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

For measurements not considered as LTE baseline, 'study days' will be used to assign the measurement to the visit:

- Week 104 (target day: Day 365): 1< study day $\leqslant$ 547.
- Week 156 (target day: Day 729): 548 $\leqslant$ study day $\leqslant$ when the last patient completes the week 156 visit.

Of note, visit designation as Week 104 and Week 156 corresponds to the weeks from the study drug administration occurring in ADMIRE-CD II but the study days are calculated from the ICF signature date from the LTE study. If a subject has more than 1 non-missing measurement in the same visit window, the measurement closest to the target day will be used. If 2 non-missing measurements in the same window are of equal distance to the target day, the measurement that occurs later will be used.

9.2.4 Conventions for Missing Dates

The conventions for missing dates (adverse event [AE] and concomitant medication [CM]) are as follows:

For AE/CM start date:

– If completely missing, then start date is imputed with stop date. (i.e. if stop date $\geqslant$ ICF date then the AE will be considered treatment emergent and CM will be considered concomitant, if stop date < ICF date it will be considered prior). If AE/CM stop date is also missing, impute the ICF date.

- If year and month are present and day is missing then day is imputed as the 1st of the month, except where the ICF date month is the same as the AE/CM start date month, then AE/CM start date is imputed as the ICF date.
- If year is present and day and month missing, or year and day are present, and month is missing, impute as 1st January, except where the ICF date year equals AE/CM start date year, then AE/CM start date is imputed as the ICF date.

For AE/CM stop date:

- If "ongoing" is checked, no imputation is necessary, and CM is considered concomitant.
- If completely missing, then impute maximum of ICF date or CM start date. If CM start date is also missing, impute the ICF date.
- If year and month are present and day is missing, it can be imputed as the last day of the month.
- If year is present and day and month missing
- o If YYYY ≤ year of the ICF date, then 31st of December will be imputed
- o If YYYY > year of the ICF date, then 1st of January will be imputed

For AEs, if the start and end dates are both missing, the AE will be considered treatment emergent. For CM, if the start and end dates are both missing, the CM will be considered concomitant.

If a subject dies during the study and the AE/CM stop date is missing, then the death date will be used for AE/CM stop date. After the imputation, all the imputed stop dates are compared with the start dates to ensure the stop date does not occur before the start date. If the imputed stop date occurs prior to the start date, then the imputed stop date will be the same as the start date.

Listings should not present imputed date, listing should present partial dates or "." if data entirely missing.

9.2.5 Conventions for Missing Data

Unless otherwise stated, the missing data for efficacy endpoints will be managed as follows:

- Missing data for dichotomous (ie, proportion-based) primary and secondary endpoints in Darvadstrocel-3003:
  - For subjects who have completed or withdrawn from Darvadstrocel-3003 by the time of interim data cut or at final analysis, the missing data for determination of status of dichotomous efficacy endpoints will be imputed using non-responder imputation method.
  - [Interim analysis only] For ongoing subjects, missing data for determination of status of dichotomous efficacy endpoints at the visits that have been reached by the time of interim data cut will be imputed using non-responder method. Data for future visits that have not been reached by the time of interim data cut will not be imputed.

9.3 AESI

The following AEs are considered AESI.

- Tumorigenicity
  - SOC 'Neoplasms benign, malignant and unspecified (including cysts and polyps).'
  - SMQ 'Malignancies' (Broad and Narrow).
- Ectopic tissue formation
  - HLGT 'Benign neoplasms gastrointestinal.'
- Immunogenicity/allo-immunoreactions
  - SMQ ('Immune-mediated/autoimmune disorders' (Broad and Narrow).

9.4 Analysis Software

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

Signature Page for Darvadstrocel-3003_LTE_Statistical Analysis Plan_v2_CleanVers
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