Statistical Analysis Plan

NCT Number: NCT04701411

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

Study Number: Darvadstrocel-3004

Document Version and Date: Version2, 18 JUL 2024

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

STATISTICAL ANALYSIS PLAN

Study Number: Darvadstrocel-3004

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

Phase: PHASE 3

Version: Version 2

Date: 18-JUL-2024

Prepared by:

[redacted]

[redacted], Statistics, Statistical & Quantitative Sciences

Data Sciences Institute, Research & Development

Based on:

Protocol Version: Protocol Amendment #3

Protocol Date: 22-MAY-2024

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	04-FEB-2021	Not Applicable
Version 2	18-JUL-2024	To implement protocol amendment 2 and 3, and to add interim analysis per protocol amendment 3.

Approval Signatures

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

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

Approvals:

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

Date

1.1 Approval Signatures

Approval Signatures:

Electronic signatures can be found on the last page of this document

2.0 TABLE OF CONTENTS

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3.0 ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
anti-TNF	anti-tumor necrosis factor
AST	aspartate aminotransferase
BMI	body mass index
CTR	Clinical Trials Regulations
eCRF	electronic case report form
EDC	electronic data capture
CD	Crohn's disease
CI	confidence interval
COVID-19	coronavirus disease 2019
eASC	expanded adipose-derived mesenchymal stem cells
ECG	electrocardiogram
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
FAS	full analysis set
IA	interim analysis
ITT	intent-to-treat
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
[redacted]	[redacted]
PCDAI	Pediatric Crohn's Disease Activity Index
PDAI	Perianal Disease Activity Index
[redacted]	[redacted]
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment emergent adverse events
TESAE	treatment emergent serious adverse events
VAS	visual analogue scale
WHODrug	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

4.0 OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective

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

4.1.2 Secondary Objective(s)

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

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

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

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

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

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

4.1.3 Exploratory Objective(s)

To evaluate the impact of darvadstrocel on perianal disease activities

4.2 Endpoints

4.2.1 Primary Endpoint(s)

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

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

AND

b) Absence of collections(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by central magnetic resonance imaging (MRI) assessment.

4.2.2 Secondary Endpoint(s)

Efficacy at Week 24

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

Efficacy at Week 52

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

4.2.3 Exploratory Endpoint(s)

1. *Change from baseline in subscale scores for discharge and pain domains from the Perianal Disease Activity Index (PDAI) scores by visit.*
2. *Change from baseline in Pediatric Crohn's Disease Activity Index (PCDAI) scores by visit.*
3. *Change from baseline in perianal pain visual analogue scale (VAS) by visit.*

4.2.4 Safety Endpoints

1. *AEs.*

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

5.0 STUDY DESIGN

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

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

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

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

On the treatment administration day (Day 0, Visit 0), eligible subjects will visit the study site and receive fistula curettage and fistula clinical assessment (FSA) under anesthesia of all fistula tracts, with special emphasis in the internal opening areas, using a metallic curette followed by suturing closed the internal openings. After conditioning of the fistula tracts, perilesional

injection(s) of darvadstrocel will be administered. A surgical procedure manual will be provided to detail the procedure to administer darvadstrocel. Thereafter, study visits will take place as shown in Figure 5.a and Appendix A of the protocol. At each visit, a clinical assessment of the fistula(s) will be performed.

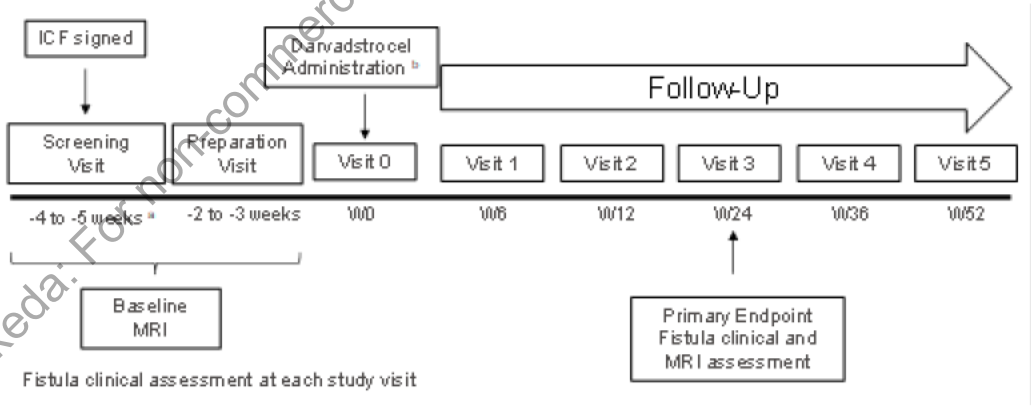
Sites will employ all efforts to see subjects in the clinic for assessments. In unavoidable circumstances such as the coronavirus disease 2019 (COVID-19) pandemic, exceptions may be granted for alternative methods for conducting subject visits with approval by the medical monitor and/or sponsor. Such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

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

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

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

Figure 5.a Study Schematic



ICF: informed consent form; MRI: magnetic resonance imaging; W: week.

[a] Screening visit to take place within a minimum of 4 and a maximum of 5 weeks before the preparation visit.

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

This is a single-arm study with no stratification or randomization.

6.0 STATISTICAL HYPOTHESES AND DECISION RULES

The statistical objective of the trial is estimation of treatment effect rather than formal hypothesis testing.

6.1 Statistical Hypotheses

Not Applicable

6.2 Statistical Decision Rules

Not Applicable

6.3 Multiplicity Adjustment

Not applicable.

7.0 [redacted]

[redacted]

8.0 ANALYSIS SETS

The following analysis sets will be defined:

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

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

9.0 STATISTICAL ANALYSIS

9.1 General Considerations

Baseline values are defined as the observed values before the dosing of study medication.

All confidence intervals (CIs) will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated.

Confidence intervals will be presented using the same number of decimal places as the point estimate. The maximum number of decimal places reported shall be four for any summary statistic. 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 for all subjects. Missing values will be tabulated but will not be included in the calculation of percentages. 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 12.2.3.

9.1.1 Handling of Treatment Misallocations

This is an open-label study and hence no treatment misallocation is expected.

9.1.2 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 maximum number of decimal places as the raw data.

9.1.3 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. The denominator for the proportion will be based on the number of subjects in the analysis set.

9.1.4 Analysis Approach for Time-to-Event Variables

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

9.2 Disposition of Subjects

A summary of screen failures including reasons for screen failure will be presented by region and country for all screened patients. The number of patients receiving study treatment, who completed or prematurely withdrew/discontinued from the study, and the reasons for any premature withdrawal/discontinuation, will be presented overall and split by country/region.

Summaries will be performed on the ITT analysis set.

Time on the study will be presented for all subjects.

Before the database lock, protocol deviations will be evaluated and classified as major or minor protocol deviations.

Major protocol deviations will be listed and summarized for the ITT analysis set, including protocol deviations leading to exclusion from the per-protocol population. Major protocol deviations leading to the exclusion [redacted] will be summarized at Week 24.

Enrolment will be summarized overall and by region, country, and site.

9.3 Demographic and Other Baseline Characteristics

9.3.1 Demographics

Baseline demographic and clinical characteristics including baseline age, race, gender, ethnicity, baseline height, baseline weight, baseline BMI, alcohol use, and smoking status will be summarized. These will be presented for the ITT, safety[redacted]analysis sets.

Data of birth, if not provided at enrolment, will be set as 1 January of the year of birth, which is collected in CRF.

9.3.2 Medical History and Concurrent Medical Conditions

All baseline conditions should be recorded as part of medical history. If a condition is present at the time of signature of the informed consent form, it will only be considered an AE if it worsens after this time-point. The coding dictionary to be used for medical history is MedDRA.

Prior and ongoing medical history will be summarized by system organ class, and preferred term for all subjects. Prior medical history includes all medical conditions with a stop date prior to Visit 0. A concurrent medical condition is a condition which occurs on or after the date of Treatment administration (Visit 0), including those started before but which are ongoing on the day of Visit 0.

Listings will provide summaries of medical history for all subjects.

The distribution of the topography of internal and external openings (tracts) at the preparation visit will be summarized for all subjects.

9.3.3 Baseline Characteristics

Fistula clinical assessment and colonoscopy information will be summarized for the ITT analysis set.

Crohn's Disease history will be summarized overall and by region, which will include time since CD diagnosis, previous surgery related to CD, number of CD-related surgeries, the location of the surgery related to CD, time from CD surgery to screening and type of surgery. These measures will be assessed on the ITT analysis set.

If the day of the date of diagnosis or the start date for complex perianal fistula(s) is missing, they will be imputed as follows: it is assumed to be 1st of the month; if the month of the date of CD diagnosis is missing, it will be replaced by January. If the date is completely missing, it will not be imputed.

9.4 Medication History and Concomitant Medications

The medication history and concomitant medications are defined as follows:

- Medication history refers to the medication that the study subjects stopped taking prior to treatment administration visit.
- Concomitant medications are defined as medications taken on or after the date of Treatment administration (Visit 0), including those started before but which are ongoing the day of Visit 0.

Medications will be coded using the WHODRUG dictionary's last version available at the time of data cleaning. Prior, concomitant, rescue and prohibited medication use will be summarized descriptively using frequency and percentage of patients for all subjects, therapeutic class and preferred drug name for the ITT and safety analysis sets. Concomitant medications will also be summarized by indication for the ITT and safety analysis sets.

Prior treatment for CD and fistulas will be summarized as counts and percentages for all subjects, as well as for all subjects and whether they are induction or maintenance therapy. The subset of prior treatment for CD and fistulas ongoing at screening will be summarized separately.

Concomitant procedures will be summarized by system organ class, and preferred term for the ITT analysis sets. These procedures will also be presented by indication as well as by modality, for the ITT analysis sets.

9.5 Efficacy Analysis

The analyses of the primary endpoint will be performed on ITT [redacted] with the ITT as the primary analysis set.

The analyses of the secondary endpoints, and the exploratory endpoints will be performed on ITT analysis set.

All efficacy endpoints except the primary endpoint and relapse at week 52 will be summarized by visit, as applicable. The proportions along with their 95% 2-sided CIs will be provided by visit for clinical remission and clinical response, as well as combined remission at week 24 only, and relapse at week 52.

Continuous endpoints will be summarized descriptively by visit: change from baseline in PDAI total score and subscores, PCDAI total score and subscores, and VAS.

All efficacy endpoints will be presented in listing.

9.5.1 Primary Endpoint(s) Analysis

9.5.1.1 Derivation of Endpoint(s)

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

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

AND

b) Absence of collections(s) >2 cm (in at least 2 dimensions) of the treated perianal fistula(s) confirmed by central magnetic resonance imaging (MRI) assessment.

9.5.1.2 Main Analytical Approach

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

[redacted]

[redacted].

9.5.1.3 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

9.5.2 Secondary Endpoint Analysis

9.5.2.1 Derivation of Endpoints

The secondary endpoints are defined in section 4.2.2.

9.5.2.2 Main Analytical Approach

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

- Clinical remission at Weeks 24 and 52.
- Clinical response at Weeks 24 and 52.
- Relapse by Week 52 in subjects who achieve combined remission at Week 24. The denominator in the calculation of the percentages is the number of subjects with combined remission at Week 24.

[redacted]

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

Subjects without documented time-to-event of interest by the end of study (Week 52), will be censored at the date of last assessment. Also, subjects who discontinue without clinical remission before week 52 will be censored at the date of last visit. Similarly, subjects who discontinue without clinical response before week 52 will be censored at the date of last visit.

9.5.3 Exploratory Endpoints Analysis

9.5.3.1 Severity of the perianal Crohn's disease with the Perianal Disease Activity Index (PDAI)

Severity of the perianal Crohn's disease assessed with the Perianal Disease Activity Index (PDAI) will be assessed at Screening, Visit 0 (Day 0, before treatment administration), Visit 1 (Week 6), Visit 3 (Week 24), Visit 5 (Week 52) or Early Termination Visit.

The PDAI is a scoring system to evaluate the severity of perianal Crohn's disease (Irvine, 1999). It includes five items: (a) discharge; (b) pain; (c) restriction of sexual activity; (d) type of perianal disease; and (e) degree of induration. Each category is graded on a 5-point Likert scale ranging from no symptoms (score of 0) to severe symptoms (score of 4); a higher score indicates a more severe disease.

Table 9.a Perianal Disease Activity Index (PDAI) Questionnaire

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

Source: Irvine E.J, 1999.

[redacted]

9.5.3.2 Pediatric Crohn's Disease Activity Index (PCDAI)

The PCDAI was specifically designed for use in children based upon a one-week (7 day) history recall of symptoms (Hyams, 1991). The PCDAI includes a child-specific item: the height velocity variable as well as 3 laboratory parameters: hematocrit (adjusted for age and sex), ESR, and albumin level.

Table 9.b Pediatric Crohn's Disease Activity Index (PCDAI) Questionnaire

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

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

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

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

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

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

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

The limitation of activity should be based on the most significant limitation during the past week, even if it is only for 1 day. However, if the activity limitation is due to another illness (eg, upper respiratory infection), the illness period should be excluded from the patient's PCDAI score.

To calculate the PCDAI total score for a study visit, sum of the 11 subscores at that particular study visit. If any of the 11 subscores is missing, the PCDAI total score cannot be calculated and the PCDAI total score for that study visit will be set to missing.

The PCDAI score can range from 0-100, with higher scores signifying more active disease. A score of <10 is consistent with inactive disease, 11 to 30 indicates mild disease, and >30 is moderate-to-severe disease.

[redacted]

9.5.4 [redacted]

[redacted]

9.6 Safety Analysis

Safety analysis set will be used for all analyses. Patients will be evaluated for safety through the Week 24 visit, and through the Week 52 visit. Summaries will be provided for all subjects. For cumulative data (i.e., data not presented by study visit), separate displays will be provided through Week 24, and through Week 52. Safety data (including physical examination, vital signs and laboratory tests) will be summarized using descriptive statistics. Missing safety data will generally not be imputed. However, safety assessment values of the form of "<x" (i.e., below the lower limit of quantification) or ">x" (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

9.6.1 Adverse Events

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

A treatment-emergent AE is an AE which occurs after exposure to study treatment (AE onset date $\geqslant$ dose date). Events which occur before administration of the study treatment are Non-Treatment Emergent AEs.

AE summaries will be produced and split for all subjects, outcome, whether concomitant medication was given, relationship to study drug and intensity of AE, as well as split by system organ class, and preferred term.

The following summaries of AEs will be provided:

- Overall Summary including TEAEs, treatment-related TEAEs, serious TEAEs, treatment-related serious TEAEs, TEAEs leading to study withdrawal, Serious TEAEs leading to study withdrawal, TEAEs related to study procedure, serious TEAEs related study procedure, TEAEs related to study Treatment, serious TEAEs related study Treatment, fatal SAEs, Treatment-emergent adverse events of special interest.
- TEAEs by SOC and PT
- Treatment related TEAEs by SOC and PT,
- Study procedure related TEAEs by SOC and PT.
- Serious TEAEs by SOC and PT
- Treatment related Serious TEAEs by SOC and PT,
- Study procedure related Serious TEAEs by SOC and PT
- TEAEs by severity, SOC and PT
- Serious TEAEs by severity, SOC and PT
- TEAEs or TESAEs leading to study withdrawal by SOC and PT
- Serious TEAEs by relationship, SOC and PT
- Fatal TESAEs by SOC and PT

These summaries will be counts and percentages up to Week 24 and up to Week 52. The AE categories above will also be summarized by system organ class, preferred term and severity. Missing severity, relationship or outcome will be classed as unknown.

Non-treatment emergent events (starting prior to exposure to study treatment) will be included in the patient listings but not included in the above summaries.

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

9.6.2 Adverse Events of Special Interest

Special interest AE/abnormality criteria (AESIs) include:

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

The following summaries will be generated for the AESI on CRF:

- Treatment-emergent Adverse Events of Special Interest by Category, SOC and PT.

Listing of AESI will also be presented.

9.6.3 Clinical Laboratory Evaluations

The laboratory test will be performed at Screening, Visit 0 (Day 0), Visit 1 (Week 6), Visit 3 (Week 24), Visit 5 (Week 52) or Early Termination Visit, and will include the following parameters:

Hematology: Hemoglobin, Hematocrit, Red blood cell, MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), White blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils and basophiles), Platelet count and ESR

Serum biochemistry: CRP, urea, creatinine, , AST, ALT, albumin, total bilirubin (direct bilirubin if total is above the ULN), potassium, sodium, chloride.

Pregnancy test will be performed in women of childbearing potential (WOCBP). Serum pregnancy tests will be mandatorily performed at Screening visit in any WOCBP.

Urine pregnancy test for or WOCBP will be performed at Preparation Visit, Visit 0 (Day 0) before treatment administration and Visit (Week 6), Visit 2 (Week 12), Visit 3 (Week 24), Visit 4 (Week 36), Visit 5 (Week 52) or Early Termination Visit.

Severity is described in Section 10.1.6 of the protocol.

Changes in laboratory parameters (chemistry, hematology), as well as abnormal results of other tests, that the investigator considers to be clinically relevant should be recorded as adverse events or serious adverse events, provided the definitions given in Protocol Sections 10.1.1 (“Definition of AEs”) and 10.1.3 (“Definition of SAEs”) respectively are met. Clinically significant changes in laboratory parameters or other tests that are detected after administration of study medication or are present at baseline and worsen after study start will be considered AEs or SAEs. In contrast, clinically significant changes in laboratory parameters or other tests that are associated to the disease under study will not be rated as AEs or SAEs, unless the investigator judges them to be more serious than expected based on the patient condition.

The observed value and the change from baseline in hematology and serum biochemistry laboratory data will be summarized descriptively by visit.

9.6.4 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 - visit and will be assessed as either clinically or non-clinically significant findings defined by the investigator.

The observed value and the change from baseline in vital signs measurements will be summarized descriptively by visit.

9.6.5 12-Lead ECGs

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

9.6.6 Extent of Exposure and Compliance

9.7 This study contains a single dose administration of study treatment at Day 0. The frequency and proportion for subjects treated will be summarized. Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

9.7.1 Pharmacokinetic Analysis

Not applicable.

9.7.2 Pharmacodynamic Analysis

Not applicable.

9.7.3 Biomarker Analysis

Not applicable

9.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

For all variables collected daily prior to a visit; the data will be averaged over the period of collection prior to the visit prior to performing the statistical analysis.

If the total score is derived by the investigator, this will be used in the analysis rather than being re-derived.

9.8.1 PRO Analysis

The following variables will be assessed at Day 0, Weeks 6, 24 and 52:

- Visual Analogue Scale (VAS) from 0 to 10 for perianal pain while standing, sitting, and defecating along last 2 weeks prior to the visit.

The above variables and their change form baseline will be summarized using descriptive statistics by visit.

VAS score will be collected for each of three pain scales (Perianal pain while standing, perianal pain while sitting, perianal pain while defecating) each day for two weeks prior to the visit; the average scores and average change from baseline will be presented. If a subject has less than two weeks' worth of data, the average will be taken over the available data. If a subject has more than two weeks' worth of data, the average will be taken for the two weeks prior to the visit. Baseline value for VAS score is defined as the average of the observed values over 14 days closest to the dosing of study medication.

9.8.2 Health Care Utilization Analysis

Not applicable.

9.9 Interim Analyses

An interim analysis (IA) will be conducted to evaluate the safety and the efficacy of darvadstrocel. All available safety and efficacy data will be included.

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

No data monitoring committee (DMC) is planned for this study.

10.0 REFERENCES

1. Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1999;28(4):S23-7.
2. Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr 1991;12(4):439-47.

11.0 CHANGES TO PROTOCOL PLANNED ANALYSES

No change from the protocol.

12.0 APPENDIX

12.1 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.

Table 12.a Revision History

Version	SAP Section	Change	Rationale for Change
2.0	3.0	Editorial changes	add Abbreviations per PA2 and PA3
	4.2.3	Editorial changes	To clarify exploratory endpoint analysis
	4.2.4	Language editing	Remove words per PA2
	5.0	Language editing	Remove/add words per PA3

Table 12.a Revision History

Version	SAP Section	Change	Rationale for Change
	7.0	Language editing	Language editing per PA3
	9.1	Editorial changes	Active link added
	9.1.4	Editorial changes	To clarify time to event endpoint analysis
	9.3.1	Language editing	To clarify analysis endpoints
	9.3.2	Editorial changes	Remove words
	9.4	Language editing	Remove/add words per PA3
	9.5	Language editing	To clarify Efficacy endpoint analysis
	9.5.1.2	Editorial changes	Active link added
	9.5.2.1	Editorial changes	Active link added
	9.5.2.2	Editorial changes	Editorial changes
	9.5.3	Editorial changes	Updated per PA3
	9.5.4	Editorial changes	To clarify 95% CI calculation
	9.6.1	Editorial changes	Editorial changes
	9.6.2	Language editing	Remove words per PA3
	9.6.3	Editorial changes	Updated per PA3
	9.6.4	Editorial changes	Editorial changes
	9.6.6	Language editing	Wording changes
	9.8	Editorial changes	Updated per PA3
	9.8.1	Editorial changes	Clarify definition of VAS score baseline
	9.9	Editorial changes and Language addition	Addition of IA to evaluate the safety and efficacy of darvadstrocel in enrolled subjects.
	11.0	Editorial changes	Updated per PA3
	12.2.3	Editorial changes	Updated per PA3

12.2 Data Handling Conventions

Reporting conventions were discussed in Section 6.1.

12.2.1 General Data Reporting Conventions

12.2.2 Definition of Baseline

Study Day 1 is defined as the date on which a subject is administered their dose of the investigational product. 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.

12.2.3 Definition of Visit Windows

Actual visit (and telephone calls) will be used to assign week based on "relative days", except for the Early Termination Visit. 'Relative days' (assessment/visit date – treatment start date +1) will be used to assign the measurement to the correct week:

For MRI:

- Week 24: 1< relative day ⩽ maximum observed relative days for MRI.

For clinical assessments, vital sign:

- Week 6: 1< relative day ⩽ 63;
- Week 12: 64 ⩽ relative day ⩽ 126;
- Week 24: 127 ⩽ relative day ⩽ 210;
- Week 36: 211 ⩽ relative day ⩽ 308;
- Week 52: 309 ⩽ relative day ⩽ maximum observed relative days.

For VAS, PCDAI and PDAI:

- Week 6: 1< relative day ⩽ 105;
- Week 24: 106 ⩽ relative day ⩽ 266;
- Week 52: 267 ⩽ relative day ⩽ maximum observed relative days.

If a subject has more than one non-missing measurement in the same visit window, the measurement closest to the target day will be used. If two non-missing measurements in the same window are of equal distance to the target day, the measurement that occurs later will be used.

12.2.4 Conventions for Missing Dates

The conventions for missing dates (adverse event [AE], concomitant medication [CM], medical history [MH]) are as follows:

For **AE/CM/MH** start date:

- If completely missing, then start date is imputed with stop date. (i.e. if stop date ⩾ IP date then the AE will be considered on-treatment/CM and MH will be considered concomitant, if stop date < IP date it will be considered prior). If AE/CM/MH stop date is also missing, impute the maximum of IP date or informed consent signature date.
- If year and month are present and day is missing then day is imputed as the 1st of the month, except where the treatment start date month is the same as the AE/CM/MH start date month, then AE/CM/MH start date is imputed as treatment start 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 treatment start date year equals

AE/CM/MH start date year, then AE/CM/MH start date is imputed as treatment start date if not missing.

For **AE/CM/MH** stop date:

- If completely missing, then impute maximum of IP start date or AE/CM/MH start date. If AE/CM/MH start date is also missing, impute the maximum of IP date or informed consent signature date.
- If year and month are present and day is missing, it can be imputed as the 1st day of the month, except where the AE/CM/MH start date month is the same as the AE/CM/MH end date month, then last date of the month will be imputed.
- If year is present and day and month missing, then AE/CM/MH end date imputed as 1st January, except where the AE/CM/MH start date year is the same as the AE/CM/MH end date year, then 31st December will be imputed.

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

The conventions for missing dates rule only applicable to dates designed to be collected on eCRF.

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

12.3 Analysis Software

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

Signature Page for Darva-3004_Statistical Analysis Plan_V2
Title:

Approval	[redacted] Statistics 18-Jul-2024 15:29:55 GMT+0000

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