NCT03169894

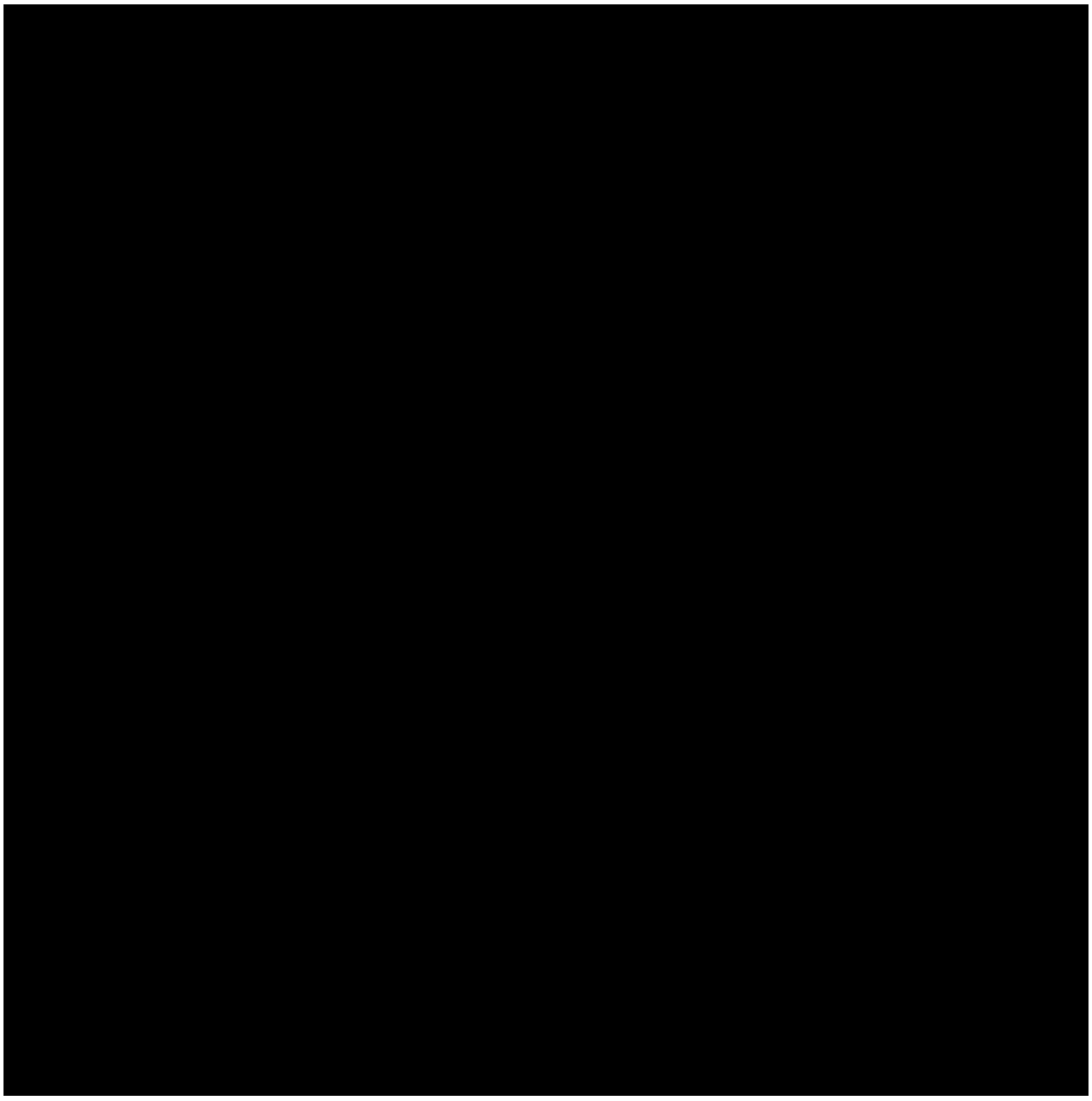
STATISTICAL ANALYSIS PLAN

Phase Ib Escalating Dose, Open-Label, Signal-Finding Study to Evaluate the Safety, Tolerability, and Short-Term Efficacy of the Anti-Light Monoclonal Antibody MDGN-002 in Adults with Moderate to Severe Active Crohn's Disease (CD) or Ulcerative Colitis (UC) who have Failed Prior Treatment with an Anti-TNFα Agent

PROTOCOL NO. MDGN-002-CD-101

Protocol Version 11.0 (23JUL2021)

SPONSORED BY
Avalo Therapeutics, Inc.
(formerly known as Cerecor, Inc.,
Aevi Genomic Medicine, LLC,
Aevi Genomic Medicine, Inc., and
Medgenics, Inc.)
1500 Liberty Ridge Drive, Suite 321
Wayne, PA 19087



REVISION HISTORY

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	05OCT2021	Not Applicable	Original version

ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
ADA	Anti-drug Antibodies
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CM	Concomitant Medication
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ET	Early Termination
FAS	Full Analysis Set
GI	Gastrointestinal
IBD-Q	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PT	Preferred Term
SAP	Statistical Analysis Plan
SES-CD	Simple Endoscopy Score for Crohn's Disease
SOC	System Organ Class
SQ	Subcutaneous
TEAE	Treatment-emergent Adverse Event
TNFα	Tumor Necrosis Factor Alpha
UC	Ulcerative Colitis
WHO	World Health Organization

TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Avalo Therapeutics, Inc. protocol number MDGN-002-CD-101, version 11.0, dated 23Jul2021: "Phase Ib Escalating Dose, Open-Label, Signal-Finding Study to Evaluate the Safety, Tolerability, and Short-Term Efficacy of the Anti-Light Monoclonal Antibody MDGN-002 in Adults with Moderate to Severe Active Crohn's Disease (CD) or Ulcerative Colitis (UC) who have Failed Prior Treatment with an Anti-TNFα Agent".

This SAP will be signed off, at a minimum, before the final database lock and contains detailed information to aid in the performance of the statistical analysis and reporting of the study data for use in the final clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Council for Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, the most recent ICH E3 Guideline and the Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, safety, and efficacy assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. If additional analyses are performed after database lock to supplement the planned analyses described in this SAP, they will be clearly identified as post-hoc in the CSR.

In addition to the study protocol, the case report form (CRF) was reviewed in preparation of this SAP.

The reader of this SAP is encouraged to also read the study protocol for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

Although methods applicable to pharmacokinetic (PK) data may be mentioned in this document, further PK analysis will be described in a separate document as needed.

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of MDGN-002 administered by subcutaneous (SQ) injection to adults with moderate to severe, active CD or UC who have failed prior treatment with an anti-TNFα agent.

1.1.2 Secondary Objectives

- Estimate plasma concentrations of MDGN-002 administered by SQ injection to adults with moderate to severe, active CD or UC.

- Evaluate response to treatment with MDGN-002 administered by SQ injection to adults with moderate to severe, active CD or UC.

2. STUDY DESIGN AND PROCEDURES

This is a Phase 1b, open-label, dose-escalation, signal-finding, multi-center study to evaluate the safety, tolerability, pharmacokinetics, and short-term efficacy of MDGN-002 in adults with moderate to severe, active CD or UC who have previously failed anti-TNFα treatment. The study is a pilot study using a dose-escalation design to characterize the safety and tolerability of 2 different doses of MDGN-002 (1.0 mg/kg and 3.0 mg/kg) in the CD population, and 3.0 mg/kg in the UC population. All subjects will receive a total of 4 doses of MDGN-002 by SQ injection at 14-day intervals. The study will consist of a screening period, an open-label treatment period and a safety follow-up visit.

In this document, MDGN-002 will be referred to as "study drug" regardless of dosage, and "cohort" will refer to 1.0 mg/kg (Cohort 1) or 3.0 mg/kg (Cohort 2) as described above.

The following study visits will be performed:

- Visit 1 (Screening). This period may be up to 14 weeks, inclusive of a washout period for subjects who have received a biologic treatment within 12 weeks of Visit 1. The amount of time required is determined based on the subject's last dose of the medication and may be up to 12 weeks.
- Visit 2 (Pre-/Post-Dose Day 0);
- Visit 3 (Day 7);
- Visit 4 (Pre-/Post-Dose Day 14);
- Visit 5 (Day 21);
- Visit 6 (Pre-/Post-Dose Day 28);
- Visit 7 (Day 35);
- Visit 8 (Pre-/Post-Dose Day 42);
- Visit 9 (Day 49);
- Visit 10 (Day 56/Early Termination (ET));
- Visit 11 (Day 84 or 28 days after ET).

3. DETERMINATION OF SAMPLE SIZE

This is the first use of MDGN-002 in the intended population of patients with CD or UC who have failed prior treatment with an anti-TNFα agent. The sample size of the study was based on feasibility.

4. STUDY ASSESSMENTS

4.1 CROHN'S DISEASE ACTIVITY INDEX (CROHN'S DISEASE PATIENTS)

The Crohn's Disease Activity Index (CDAI) consists of the following 8 items: abdominal pain, number of liquid stools, general well-being, extraintestinal complication, use of antidiarrheal drugs, abdominal mass, hematocrit, and body weight. Information on abdominal

pain, general well-being, and frequency of loose and watery stools will be taken from a daily diary completed by the subject.

Total CDAI scores can range from 0 to approximately 600 with higher scores indicating more active disease. Disease severity as measured by CDAI is categorized as: Remission (<150), Mildly active disease (150 - 219); Moderately active disease (220 - 450); Severe disease (> 450).

Item and total scores, as outlined below, will be derived programmatically for Visit 1 (Screening), Visits 2 (Day 0), 4 (Day 14), 6 (Day 28), 8 (Day 42), and Visit 10 (Day 56/ET).

The CDAI total score consists of 8 item scores:

1) The liquid stools score is calculated as the sum of the number of loose/watery stools values recorded for the 7 days prior to the visit;

2) The abdominal pain score is calculated as the sum of the abdominal pain values recorded for the 7 days prior to the visit. Abdominal pain severity (graded from 0 - 3 with higher values indicating greater severity) summed over the previous 7 days, where 0 = “None”, 1 = “Mild”, 2 = “Moderate”, 3 = “Severe”;

3) The general well-being score is calculated as the sum of the general well-being values recorded for the 7 days prior to the visit. General well-being is graded from 0 - 4 with higher values indicating a poorer condition of health, where 0 = “Generally well”, 1 = “Slightly under par”, 2 = “Poor”, 3 = “Very poor”, 4 = “Terrible”;

4) The extraintestinal complications score is calculated as the number of complications present (0 to 6) from the following list:
   - Arthritis/arthralgia
   - Iritis/uveitis
   - Skin/mouth lesions
   - Peri-anal disease
   - Other fistula
   - Fever >37.8 °C, >100 °F (in the last week);

5) Taking medication for symptomatic relief from diarrhea (0 = No, 1 = Yes);

6) Presence of an abdominal mass (0 = None, 2 = Questionable, 5 = Definite);

7) Hematocrit score is calculated as follows, adding to or subtracting from total score according to sign:
   - 47 minus hematocrit value for males
   - 42 minus hematocrit value for females;

8) Weight percentage difference from standard weight, is calculated by 100 x (1 – (current weight / standard weight)) where the standard weight is defined as height in m^2 x 22.1 for males and height in m^2 x 20.8 for females. Values > 0 and indicate the subject is below standard weight; values < 0 indicate that the subject is over standard weight.

The CDAI total score is calculated as the weighted sum to the above 8 scores as follows:

CDAI = **2** x (Item 1) + **5** x (Item 2) + **7** x (Item 3) + **20** x (Item 4) +

30 x (Item 5) + **10** x (Item 6) + **6** x (Item 7) + **1** x (Item 8)

Please refer to section 5.7 for handling missing data.

4.2 MODIFIED MAYO SCORE (ULCERATIVE COLITIS PATIENTS)

The Modified Mayo Score (excluding the Physician's Global Assessment [PGA] component) includes stool frequency, rectal bleeding, and the appearance of mucosa upon endoscopy. Stool frequency is based on a scale of 0 to 3 (0 = "normal", 1 = "1 to 2 stools/day > normal", 2 = "3 to 4 stools/day > normal", 3 = "> 4 stools/day > normal"). Rectal bleeding will be based on a scale of 0 to 3 (0 = "none", 1 = "streaks of blood", 2 = "obvious blood", 3 = "blood alone passed"). Appearance of mucosa upon endoscopy will be based on a scale of 0 to 3 (0 = "normal", 1 = "mild friability", 2 = "moderate friability", 3 = "exudation, spontaneous bleeding"). The score consists of the sum of all 3 criteria and can range from 0 to 9, with higher scores indicating more severe disease. This score will be derived programmatically for Visit 1 and Visit 10 using the Modified Mayo Endoscopic score from the central reader and self-reported data on stool frequency and rectal bleeding from 7 days prior to Visit 1 (Screening) and Visit 10 (Day 56/ET).

4.3 ENDOSCOPY WITH BIOPSY AND HISTOLOGY

All subjects who enroll in the study will undergo an endoscopy with biopsy at screening and again at Visit 10 (Day 56) or at early termination.

Endoscopy evaluation for patients with CD will use the Simple Endoscopy Score for Crohn's Disease (SES-CD). The SES-CD is assessed through endoscopic review of 5 predefined gastrointestinal (GI) segments (ileum; right colon; transverse colon; left colon; rectum). For each segment, 4 endoscopic variables are assessed (presence of ulcers, ulcerated surface, affected surface, and presence of narrowing). Each variable is scored from 0 to 3 with higher scores indicating more severe symptoms as defined below (Daperno et al 2004).

	SES-CD Score			
Variable	**0**	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers (0.1–<0.5 cm)	Large ulcers (0.5–2 cm)	Very large ulcers (> 2 cm)
Ulcerated surface	None	< 10%	10–30%	> 30%

Affected surface	Unaffected segment	< 50%	50–75%	> 75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

For each variable, the total score is calculated as the sum across all segments of the GI tract. The SES-CD total score, ranging from 0-60, is calculated as the sum of all variable total scores with a higher score indicating more severe endoscopic activity as shown (Moskovitz et al 2007).

SES-CD Score	**Severity Category**
0-2	Remission
3-6	Mild endoscopic activity
7-15	Moderate endoscopic activity
>15	Severe endoscopic activity

Endoscopic evaluation for patients with UC will use the Modified Mayo Endoscopic Score. Appearance of mucosa (friability) upon endoscopy will be based on a scale of 0 to 3 (0 = “normal”, 1 = “mild friability”, 2 = “moderate friability”, 3 = “exudation, spontaneous bleeding”).

4.4 PATIENT-REPORTED ASSESSMENT OF ABDOMINAL PAIN AND STOOL FREQUENCY (CROHN’S DISEASE PATIENTS)

All CD subjects who enroll in the study will be required to report their daily assessment of abdominal pain, general well-being and stool frequency including loose and/or watery stools via an electronic diary. Derived 7-day interval average scores, explained in Section 5.8 for Time Windowing, will be provided that correspond to all visits from Visit 1 (Screening) to Visit 10 (Day 56/ET).

Abdominal pain will be assessed on a scale of 0 to 3 with higher values indicating greater pain severity: 0 = “None”, 1 = “Mild”, 2 = “Moderate”, 3 = “Severe”.

The stool frequency including number of loose and/or watery stools per day, equivalent to a score of a 6 or 7 on the Bristol Stool Scale, will be recorded.

General well-being will be assessed on a scale of 0 to 4 with higher values indicating a poorer condition of health: 0 = “Generally well”, 1 = “Slightly under par”, 2 = “Poor”, 3 = “Very poor”, 4 = “Terrible”.

4.5 PATIENT-REPORTED ASSESSMENT OF STOOL FREQUENCY AND RECTAL BLEEDING (ULCERATIVE COLITIS PATIENTS)

All UC subjects who enroll in the study will be required to report their daily assessment of stool frequency and rectal bleeding via an electronic diary. Derived 7-day interval average scores, explained in Section 5.8 for Time Windowing, will be provided that correspond to all visits from 1 (Screening) to 10 (Day 56/ET).

Stool frequency will be based on a scale of 0 to 3 (0 = "normal", 1 = "1 to 2 stools/day > normal", 2 = "3 to 4 stools/day > normal", 3 = "> 4 stools/day > normal"). Normal is defined as the patient's bowel movement pattern during a period of remission where remission means that their symptoms of UC resolve, they feel well, and their UC is not interfering with daily activities. If the subject has not achieved remission, then normal is their bowel movement pattern when healthy prior to being diagnosed with Ulcerative Colitis.

Rectal bleeding is to be reflective of the most severe bleeding of the day and will be based on a scale of 0 to 3 (0 = "none", 1 = "streaks of blood", 2 = "obvious blood", 3 = "blood alone passed"). If the subject had no stools in a day, then "None" would be selected.

4.6 QUALITY OF LIFE ASSESSMENT – INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE

The IBD-Q is a 32-item questionnaire validated to measure quality of life in CD and UC subjects. The IBD-Q will be completed by all subjects at screening (Visit 1), before dosing (Visit 2), and at the end of the open-label treatment period or early termination (Visit 10/ET). The IBD-Q assesses the dimensions of bowel function, emotional status, systemic symptoms, and social function (Guyatt G, 1989).

Each of the 32 items is scored on a 1 to 7 scale, where higher scores represent a more positive response. The mapping of questionnaire items to each domain is given in the table below.

Domain Name	Questionnaire items
Bowel symptoms	1, 5, 9, 13, 17, 20, 22, 24, 26, 29
Systemic symptoms	2, 6, 10, 14, 18
Emotional status	3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32
Social functioning	4, 8, 12, 16, 28

Each domain score is calculated as the sum of the items in that domain. The IBD-Q total score is calculated as the sum of all 32 items in the questionnaire, ranging from 32 to 224.

5. GENERAL ANALYSIS AND REPORTING CONSIDERATIONS

Descriptive statistics will be used to summarize all safety, pharmacokinetic, efficacy, and quality of life variables.

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum, and maximum unless otherwise noted. The mean and median will be rounded to one decimal place greater that in the raw data; the standard deviation will be rounded to two decimal places greater than in the raw data; the minimum and maximum will be reported to the same number of decimal places as present in the raw data. These will be referred to as "continuous summaries" in this document.

Categorical variables will be summarized using frequency counts and percentages. When count data are presented, the percentage for zero counts will be suppressed to draw attention to the non-zero counts. Unless otherwise noted the denominator for all percentages within the analysis set of interest will be the number of subjects by disease and cohort as shown below:

Crohn's Disease			Ulcerative Colitis
Cohort 1 1 mg/kg (N = xx)	Cohort 2 3 mg/kg (N = xx)	Total (N = xx)	Cohort 2 3 mg/kg (N = xx)

Frequency counts will be presented as whole numbers and percentages will be rounded to one decimal place. These will be referred to as "categorical summaries" in this document.

5.1 BASELINE AND CHANGE FROM BASELINE MEASUREMENTS

The baseline measurement will be defined as the last non-missing assessment on the day of or prior to first study dose administration (includes all data up to the first dose administration).

Change from baseline will be calculated as:

- (value at analysis visit – baseline value)

A positive change signifies an increase in the measurement while a negative change signifies a decrease.

5.2 STUDY DAY CALCULATION

Study Day defined:

- for dates on or after date of first dose administration: (analysis date – date of first dose administration) + 1.
- for dates prior to date of first dose administration: (analysis date – date of first dose administration).

5.3 NUMBER OF DAYS EXPOSED TO STUDY DRUG

Based upon the pharmacokinetics of the drug (t1/2 of 18.0 to 27.0 days), each dose will count as 14 days of exposure to investigational product. Therefore, days of exposure to study drug will be calculated as:

- (last dose date – first dose date + 14).

5.4 LAST DOSE DATE

The last dose date is defined for subjects who either completed, or ET'd from, the study (i.e., have an ET visit), as the last dose administration date.

5.5 ADJUSTMENTS FOR COVARIATES

Not applicable due to the use of descriptive statistics only.

5.6 STUDY HYPOTHESES

No specific hypotheses are being tested in this pilot study. All data will be summarized using descriptive statistics only.

5.7 HANDLING OF MISSING DATA

All efforts will be made to minimize missing data.

CD patient diary data (total stools, loose/watery stools, abdominal pain, and general well-being) used in calculating the CDAI total score will handle missing data as follows: in cases where at least 4 days of data are non-missing for a given 7-day interval leading up to the visit date, the average of the non-missing values for all days in the 7-day interval will be imputed for missing diary days. If less than 4 days of data are non-missing, then the 7-day interval will be set to missing (Henao M.P., et al, 2015). To maintain consistency, the same approach of needing at least 4 days of non-missing data for imputation will also be used for UC patient diary data (stool frequency, rectal bleeding).

Missing laboratory data will not be imputed, unless otherwise stated.

All medications with partial or missing dates recorded on the concomitant medication electronic case report form (eCRF) page will be considered concomitant unless a partial stop date clearly indicates it was stopped before the first dose of study treatment. Start and stop dates will be imputed when partial dates are present as needed to determine concomitant medications.

Table 2: Table of Imputation Rules for Missing AE and Medication Date Times

Missing Date Portion	*Prior to Treatment*	*Same as Treatment Start Date*	*After Treatment Start Date*
Day	*Month and Year < Month and Year of first treatment:* Start Day = 1 Stop Day = last day of the month reported	*Month and Year = Month and Year of first treatment:* Start Day = Day of first treatment Stop Day = last day of the month	*Month and Year > Month and Year of first treatment:* Start Day = 1 Stop Day= last day of the month
Day and Month Define Day as above, then:	*Year < Year of first treatment:* Start Month = January Stop Month = Dec	*Year = Year of first treatment:* Start Month = Month of first treatment Stop Month = Dec	*Year > Year of first treatment:* Start Month = January Stop Month = Dec
Day, Month, and Year	To be conservative, completely missing start dates will be set to the date of first treatment, completely missing end dates will be set to the date of last contact.		
Time	Missing start times will be imputed as 00:01 (or the start time of the first dose administration if AE occurred on the date of first dose administration) Missing stop times will be imputed as 23:59		

After following these imputation rules, if the start date/time is imputed as a date after the end date/time, the start date/time will be set to the end date/time to provide a positive duration for the event or medication. No imputation will be done for subjects who did not receive the study drug.

Missing assessments for study medication relationship or severity for AEs starting on or after first dose administration will be analysed as related or Grade 3 respectively.

No other imputation is planned for safety data.

5.8 ASSESSMENT TIME WINDOWING

Most safety and efficacy assessment summaries will be based on the nominal protocol-specified assessment times. Thus, if the protocol specified Visit 3 (Day 7) visit occurs on study Day 8, it will still be summarized as a Visit 3 (Day 7), acknowledging that all visits after Visit 2 (Day 0) have a time window of ±3 days.

The only exception is for daily diary data. The CD diary collects abdominal pain score, frequency of loose/watery stools, frequency of total stools, and general well-being, while the UC diary collects stool frequency and rectal bleeding. These will have 7-day interval

averages calculated, corresponding to the 7 days leading up to weekly visit dates. For screening data, the 7-day intervals will be relative to the date of first dose.

Unscheduled visits prior to first dose might be considered as the baseline value while post-baseline unscheduled visits will be listed only. Unscheduled visits are possible for biologic washout, clinical laboratory assessment, ECG, physical exam, pregnancy test, and vital signs.

5.9 POOLING OF INVESTIGATOR SITES

Not applicable.

5.10 ADJUSTMENTS FOR MULTIPLICITY

Not applicable due to the use of descriptive statistics only.

5.11 EXAMINATION OF SUBGROUPS

Not applicable.

6. SUBJECT SUMMARIES

6.1 ANALYSIS DATASETS

6.1.1 Full Analysis Set

The Full Analysis Set (FAS) will include subjects who receive at least one dose of study drug and have a baseline and at least one post-baseline value for any efficacy variable. As a result, dosed subjects will be included in the summarization of data in the FAS population for any efficacy variable for which they have data.

6.1.2 Safety Analysis Set

The Safety Analysis Set will include all subjects who are enrolled and receive at least one dose of study drug.

6.1.3 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all subjects who receive at least one dose of study drug and for whom plasma concentration data are available, minimally at baseline and one post-baseline visit.

6.2 PATIENT DISPOSITION

The number and percentage of subjects in each of the following groups will be presented in a by-subject listing and summarized by disease and cohort:

- Subjects screened
- Subjects screen failed
- Subjects enrolled

- Subjects included in each analysis set
- Subjects who have completed treatment (defined as receiving four doses)
- Subjects who have completed study (defined as completing the follow-up visit)
- Subjects who have discontinued from the study including the reasons for discontinuation

Enrolled subjects are those who are not a screen failure.

6.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

6.3.1 Demographic and Baseline Characteristics

Demographic variables will include age, sex, race, and ethnicity. Baseline characteristics include height (cm), weight (kg), body mass index (BMI; kg/m2), and time since diagnosis (</=10 years vs >10 years). Demographics and baseline characteristics will be presented in a by-subject listing and summarized by disease and cohort using the safety analysis set.

6.3.2 Baseline Disease Status/Disease History

Crohn's Disease and Ulcerative Colitis history will be presented in by-subject listings using the safety analysis set.

6.3.3 Medical History

Medical history conditions will be collected at screening. The number of subjects with any medical history will be presented in a by-subject listing using the safety analysis set.

6.3.4 Prior and Concomitant Medications

Prior medications are those received prior to the start of the study drug administration. Any medication that stops on or after the start of the first study drug administration or with missing stop dates is considered a concomitant medication. A medication can be both prior and concomitant (e.g., a medication that started before first dose and is ongoing at the end of the study).

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical (WHO/ATC) classification index version 2020-03-01, ATC Level 3. The number and percentage of subjects who take prior and concomitant medications will be summarized by drug class and preferred term, disease and cohort for the safety analysis set.

All medications captured in CRFs will also be presented in a by-subject listing.

6.4 PROTOCOL DEVIATIONS

Protocol deviations will be collected in a tracker and presented in a by-subject listing including description, category/type, and importance (Important or Not Important) as determined by Avalo prior to database lock. Important deviations will be summarized by disease and cohort by category/type for the safety analysis set.

7. MEASUREMENTS OF TREATMENT EXPOSURE AND COMPLIANCE

Because study medication is administered at the study center by trained study personnel, compliance with respect to study medication will not be calculated. The total number of doses/injections and number of days exposed to study drug (defined in Section 5.3) will be summarized by disease and cohort for the safety analysis set. A listing of study drug administration and exposure data will be provided.

8. EFFICACY EVALUATION

8.1 EFFICACY ENDPOINT(S)

8.1.1 Primary Efficacy Endpoints

CD subjects only:

- Change from baseline in SES-CD total score at Visit 10 (Day 56/ET)

UC subjects only:

- Change from baseline in Modified Endoscopic Score at Visit 10 (Day 56/ET)

8.1.2 Secondary Efficacy Endpoint(s)

CD subjects only:

- Change from baseline in CDAI item and total scores at Visits 4 (Day 14), 6 (Day 28), and 8 (Day 42)
- Change from baseline in number of total stools for 7-day interval averages from Visit 3 (Day 7) to Visit 10 (Day 56/ET)
- Change from baseline in number of loose/watery stools for 7-day interval averages from Visit 3 (Day 7) to Visit 10 (Day 56/ET)
- Change from baseline in abdominal pain score for 7-day interval averages from Visit 3 (Day 7) to Visit 10 (Day 56/ET)
- Change from baseline in general well-being for 7-day interval averages from Visit 3 (Day 7) to Visit 10 (Day 56/ET)

UC subjects only:

- Change from baseline in stool frequency for 7-day interval averages from Visit 3 (Day 7) to Visit 10 (Day 56/ET)
- Change from baseline in rectal bleeding for 7-day interval averages from Visit 3 (Day 7) to Visit 10 (Day 56/ET)

- Change from baseline in Modified Mayo Score at Visit 10 (Day 56/ET)

Both CD and UC subjects:

- Change from baseline in IBD-Q total score at Visit 10 (Day 56/ET)

8.2 EFFICACY ANALYSIS

The efficacy analyses will be conducted using the full analysis set as defined in Section 6.1, unless otherwise stated.

The efficacy endpoints mentioned in section 8.1 are described in detail in section 4.

No statistical tests will be generated. Only descriptive statistics will be presented.

8.2.1 Primary Efficacy Analyses

SES-CD (CD subjects only)

The SES-CD total score and the variable scores will be summarized by cohort and visit using continuous and categorical disease severity summaries; the change from baseline for each post-baseline visit will also be summarized.

SES-CD total score and the variable scores will be presented in a listing.

Modified Endoscopic Score (UC subjects only)

Mean Modified Endoscopic Score will be summarized for baseline and Visit 10 (Day 56/ET) using continuous summaries; the change from baseline will also be summarized.

Modified Endoscopic Score will be presented in a listing.

8.2.2 Supportive and Sensitivity Analyses of the Primary Endpoint

Not applicable.

8.2.3 Secondary Efficacy Analyses

CD subjects only:

CDAI

The CDAI item and total scores will be summarized by cohort and visit using continuous summaries; the change from baseline for each post-baseline visit will also be summarized.

Disease severity as defined by the CDAI total score will be summarized by cohort and visit using categorical summaries: Remission (<150); Mild (150 - 219); Moderate (220 - 450); Severe (> 450).

The CDAI total score and each of the 8 item scores will be presented in a listing. Listings will also be provided for daily diary data, as well as non-diary item data and CDAI related questions.

Abdominal Pain, Frequency of Loose Stools, and Total Stools

Mean abdominal pain score, frequency of loose stools, total stools, and general well-being will be summarized for baseline and post-baseline visits by cohort and 7-day interval averages (corresponding to weekly visit dates) using continuous summaries; the change from baseline for each post-baseline visit will also be summarized.

Since these endpoints are collected in the CD subject diary, they will be presented together in one listing.

UC subjects only:

Stool Frequency and Rectal Bleeding

Mean stool frequency and rectal bleeding will be summarized for baseline and post-baseline visits by 7-day interval averages (corresponding to weekly visit dates) using continuous summaries; the change from baseline for each post-baseline visit will also be summarized.

Since these endpoints are collected in the UC subject diary, they will be presented together in one listing.

Modified Mayo Score

The Modified Mayo Score will be summarized by visit using continuous summaries; the change from baseline for each post-baseline visit will also be summarized.

The Modified Mayo Score and each of the 3 criteria will be presented in a listing.

Both CD and UC subjects:

IBD-Q

The IBD-Q total score and the domain scores (Bowel; Systemic; Emotional; and Social) will be summarized by disease, cohort, and visit using continuous summaries; the change from baseline to Visit 10/ET will also be summarized.

IBD-Q data will be presented in a listing.

9. SAFETY EVALUATIONS

9.1 OVERVIEW OF SAFETY ANALYSIS METHODS

The safety analyses will be conducted using the safety analysis set as defined in Section 6.1, unless otherwise stated.

9.2 ADVERSE EVENTS

Any untoward medical event that occurs after signing the informed consent form (ICF) is considered to be an adverse event (AE). Adverse events recorded between the time of signature of informed consent until the first dose administration will be considered baseline signs and/or symptoms.

A treatment-emergent adverse event (TEAE) is an adverse event with onset on or after the first dose administration date or an adverse event present before the first dose administration date that worsens (i.e., increases in severity) on or after the first dose administration date. TEAEs will be summarized from the first dose administration date through:

- the Safety Follow-Up/Visit 11 for subjects who completed the study **or**
- 28 days after the last dose administration date for subjects who discontinued prematurely from the study.

Verbatim terms used by investigators to identify AEs in the CRFs will be coded to the appropriate preferred term (PT) and system organ class (SOC) using a standardized coding dictionary (MedDRA Version 23.0 April 2020). All coding will be reviewed prior to database lock. All recorded AEs will be listed, but only TEAEs will be summarized.

Adverse events will be classified according to severity (CTCAE Grades 1-5) and relationship to study drug (not related, possibly related, or probably related). For summary tables, a "related" adverse event is one judged to be possibly related or probably related to study drug.

The following adverse event categories will be summarized by disease and cohort:

- Overall TEAEs
- TEAEs related to study drug
- TEAEs leading to discontinuation
- Serious AEs
- Severe TEAEs (Grade 3 or higher)

The number of subjects with AEs will be further summarized by SOC and PT (TEAEs, as well as related TEAEs), by PT only, and by SOC, PT and severity. Sorting will be in descending order of frequency.

If a patient has multiple occurrences of a TEAE within the same SOC and PT, only the most related or most severe will be included in the summaries.

Separate listings for all AEs, serious AEs, and AEs leading to discontinuation will be generated.

9.3 CLINICAL LABORATORY EVALUATIONS

Clinical laboratory tests (hematology, serum chemistry, fecal chemistry, and LIGHT [serum and tissue]) will be summarized from baseline through Visit 10/ET by visit. For each individual lab test value, the observed value and change from baseline will be summarized by disease and cohort.

All results, along with urinalysis and other laboratory tests, will be listed.

Other laboratory tests include cytokines (e.g. IL-1 beta, IL-6, IL-8, and TNF-alpha, and other exploratory cytokines), flow cytometry analysis of peripheral blood leukocytes, and RNA sequencing.

9.4 VITAL SIGNS

Vital signs results including systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), and body temperature (C) will be listed for individual subjects. These will be collected at Visits 1 (Screening), 2 (Day 0), 4 (Day 14), 6 (Day 28), 8 (Day 42), 10/ET (Day 56).

Summary statistics, including change from baseline, will be determined for each measure, and will be summarized by disease, cohort and by visit and time point (pre-/post-dose).

9.5 PHYSICAL EXAMINATION

A complete physical examination including all major body systems will be performed at Visits 1 (Screening), 2 (Day 0), 6 (Day 28), and 10/ET (Day 56). In addition, a brief physical exam will be performed at Visits 4 (Day 14) and 8 (Day 42).

Physical examination results will be listed for individual subjects.

9.6 ECG EXAMINATION

ECG examination will be assessed at Visits 1 (Screening), 6 (Day 28), and 10/ET (Day 56).

Observed values and changes from baseline for ECG parameters, including abnormal results and significance, will be displayed by disease, cohort, and time point. All ECG data will be listed, including shifts from normal at baseline to abnormal post-baseline.

9.7 PREGNANCY TEST

Pregnancy tests (for female subjects of childbearing potential) will be performed at Visits 1 (Screening), 2 (Day 0), 6 (Day 28), and 10/ET (Day 56).

Urine test results will be presented on the urinalysis listing while serum test results will be presented on the serum chemistry listing. Each test result will be defined to be “negative” or “positive”.

10. PK ANALYSIS

PK concentration data will be presented in a by-subject listing and summarized by disease, cohort and visit using continuous summaries for the PK analysis set. Continuous summaries will include arithmetic as well as geometric statistics: n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, geometric standard deviation, and geometric coefficient of variation.

Plasma concentrations that are reported as lower limit of quantification (LLOQ) will be set to 0 (zero) for reporting and summary statistics, except for geometric mean and error, for which only nonzero data is included.

11. ADA ANALYSIS

Anti-drug Antibodies (ADA) data will be collected at Visits 2 (Day 0), 4 (Day 14), 6 (Day 28), 10 (Day 56/ET), and 11 (Day 84 or 28 days after ET). Screening result, confirmation result, and titration result using the safety analysis set will be presented in a by-subject listing.

12. INTERIM ANALYSIS

No interim analyses will be performed.

13. DATA MONITORING COMMITTEE

An external, independent Data Monitoring Committee (DMC) comprising physicians, scientists and a biostatistician will review the study data at separate meetings after enrollment in the first and second cohorts, respectively.

The DMC’s role is to protect the interests of the subjects in the study and those still to be entered in the study by reviewing information such as safety, tolerability, pharmacokinetic and efficacy data.

Additional details will be outlined in the DMC charter.

14. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Not applicable.

15. TABLE OF CONTENTS FOR APPENDICES

15.1 TABLES

Table Number	*Analysis Set*	*Title*
14.1.1	All Subjects	Patient Disposition
14.1.2	Safety	Important Protocol Deviations
14.1.3	Safety	Demographics and Baseline Characteristics
14.1.4	Safety	Prior Medications by ATC Class and Preferred Term
14.1.5	Safety	Concomitant Medications by ATC Class and Preferred Term
14.1.6	PK	Pharmacokinetic Concentration
14.2.1	FAS	Simple Endoscopy Score for Crohn's Disease (SES-CD)
14.2.2	FAS	Modified Mayo Score for Ulcerative Colitis
14.2.3	FAS	Ulcerative Colitis Subject Diary
14.2.4	FAS	Crohn's Disease Activity Index (CDAI) Item and Total Scores
14.2.5	FAS	Crohn's Disease Subject Diary
14.2.6	FAS	Inflammatory Bowel Disease Questionnaire (IBD-Q)
14.3.1	Safety	Study Drug Exposure
14.3.2.1	Safety	Overall Summary of Treatment Emergent Adverse Events
14.3.2.2	Safety	Treatment Emergent Adverse Events by System Organ Class and Preferred Term
14.3.2.3	Safety	Study Drug Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term
14.3.2.4	Safety	Treatment Emergent Adverse Events by Preferred Term
14.3.2.5	Safety	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity
14.3.3.1	Safety	Hematology Parameters
14.3.3.2	Safety	Chemistry Parameters
14.3.3.3	Safety	Fecal Chemistry Parameters
14.3.4.1	Safety	Soluble LIGHT Levels
14.3.4.2	Safety	Tissue LIGHT Levels
14.3.5	Safety	Vital Signs
14.3.6	Safety	Electrocardiogram (ECG)

15.2 LISTINGS

Listing Number	*Analysis Set*	*Title*

16.2.1.1	All Subjects	Subject Disposition
16.2.2.1	All Subjects	Subjects Not Meeting Inclusion / Meeting Exclusion Criteria
16.2.2.2	All Subjects	Protocol Deviations
16.2.3	All Subjects	Study Populations
16.2.4.1	Safety	Demographics and Baseline Characteristics
16.2.4.2.1	Safety	Medical History
16.2.4.2.2	Safety	Crohn's Disease History
16.2.4.2.3	Safety	Ulcerative Colitis History
16.2.4.3	Safety	Prior and Concomitant Medications
16.2.5.1	Safety	Drug Administration and Accountability
16.2.5.2	PK	Pharmacokinetic Sample Collection and Concentration
16.2.5.3	Safety	Anti-drug Antibodies (ADA)
16.2.6.1.1	FAS	Quantitative Endoscopy (SES-CD) and Biopsy – Part 1
16.2.6.1.2	FAS	Quantitative Endoscopy (SES-CD) and Biopsy – Part 2
16.2.6.2.1	FAS	Modified Mayo Score for Ulcerative Colitis
16.2.6.2.2	FAS	Ulcerative Colitis Subject Diary
16.2.6.3.1	FAS	Crohn's Disease Activity Index (CDAI) Scores
16.2.6.3.2	FAS	Crohn's Disease Subject Diary
16.2.6.3.3	FAS	Crohn's Disease Activity Index (CDAI) Non-Diary Item Data and Related Questions
16.2.6.4	FAS	Inflammatory Bowel Disease Questionnaire (IBD-Q)
16.2.7.1	Safety	Adverse Events
16.2.7.2	Safety	Serious Adverse Events
16.2.7.3	Safety	Adverse Events Leading to Discontinuation
16.2.8.1	Safety	Hematology Laboratory Results
16.2.8.2	Safety	Serum Chemistry Laboratory Results
16.2.8.3	Safety	Fecal Chemistry Laboratory Results
16.2.8.4	Safety	Urinalysis Laboratory Results
16.2.8.5	Safety	LIGHT and Confirmatory Disease Biopsy Results
16.2.8.6	Safety	Other Laboratory Results
16.2.9.1	Safety	Vital Sign Measurements
16.2.9.2	Safety	Physical Examination
16.2.9.3	Safety	12-Lead Electrocardiogram (ECG)

16. REFERENCES

Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterol.* 1976;70:439-44.

Daperno M, D'Haens G, Van Assche G et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastroinest Endosc*. 2004 Oct; 60(4):505-12.

Guyatt G, Mitchell A, Irvine EJ et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterol*. 1989;96:804-10.

Henao, M.P., Bewtra M., Osterman M.T., et al [2015]. Measurement of Inflammatory Bowel Disease Symptoms: Reliability of an Abbreviated Approach to Data Collection. *Inflamm Bowel Dis. 21*(*10*): 2262–2271. [PubMed: 26193348]

Moskovitz, David N., et al. Defining and validating cut-offs for the simple endoscopic score for Crohn's disease. *Gastroenterol.* 2007;132.4:A173-A173.

Sostegni R, Daperno M, Scaglione N, Lavagna A et al. Review: Crohn's disease: monitoring disease activity. *Aliment Pharmacolo Ther*. 2003: 17 (Suppl. 2) 11-17