DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

GED-0301-CD-002

PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF MONGERSEN (GED-0301) FOR THE TREATMENT OF SUBJECTS WITH ACTIVE CROHN'S DISEASE

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STATISTICAL ANALYSIS PLAN

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF MONGERSEN (GED-0301) FOR THE TREATMENT OF SUBJECTS WITH ACTIVE CROHN'S DISEASE

STUDY DRUG: GED-0301

PROTOCOL NUMBER: GED-0301-CD-002

DATE FINAL: **20 Mar 2018**

Prepared by:

on behalf of

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SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	GED-0301-CD-002 Statistical Analysis Plan
SAP VERSION, DATE	Version 1.0, 20 Mar 2018
SAP AUTHOR	Printed Name and Title / Signature and Date
PROTOCOL TITLE	A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF MONGERSEN (GED-0301) FOR THE TREATMENT OF SUBJECTS WITH ACTIVE CROHN'S DISEASE
INVESTIGATIONAL PRODUCT	GED-0301
PROTOCOL NUMBER	GED-0301-CD-002
PROTOCOL VERSION, DATE	Amendment 3, 15 Aug 2017
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.
Celgene Lead Statistician	
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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation	Meaning
AE	Adverse event
ALT	Alternating
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
ATC	Anatomical Therapeutic Chemical
ATC2	Anatomical Therapeutic Chemical: Therapeutic (Level 2)
AZA	Azathioprine
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
DAO	Data as observed
ECG	Electrocardiograms
eCRF	Electronic case report form
ET	Early Termination

Abbreviation	Meaning
IP	Investigational product
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LDH	Lactic dehydrogenase
LOCF	Last observation carried forward
LS	Least-squares
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing not at random
6-MP	6-mercaptopurine
MTX	Methotrexate
NRI	Nonresponder imputation
PP	Per-protocol
PT	Preferred term

Abbreviation	Meaning
Q1	25th percentile
Q3	75th percentile
QD	Once Daily
RBC	Red blood cell
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SES-CD	Simple Endoscopic Score for Crohn's Disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	System organ class
TEAE	Treatment-emergent adverse event
TNF- α	Tumor necrosis factor-alpha
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol GED-0301-CD-002 "A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Investigate the Efficacy and Safety of Mongersen (GED-0301) for the Treatment of Subjects with Active Crohn's Disease" as amended on 15 Aug 2017. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

The study was terminated early by Celgene following an October 2017 recommendation of the Data Monitoring Committee. As such, changes are made to some protocol-specified analyses; these changes are described in relevant sections and summarized in Section 16.

In this SAP, GED-0301 160 mg once daily (QD) and GED-0301 40 mg QD are referred to as GED 160 and GED 40, respectively. Subjects will be randomized to receive 1 of 3 GED-0301 treatment regimens or placebo during the study. For the first 12 weeks of the study, each GED-0301 treatment regimen will consist of GED 160. These 12 weeks will be followed by either 1) placebo QD for 4 weeks followed by alternating (ALT) GED 160 for 4 weeks and placebo QD for 4 weeks until the end of the study; 2) placebo QD for 4 weeks followed by alternating GED 40 for 4 weeks and placebo QD for 4 weeks until the end of the study; or 3) continuous GED 40 until the end of the study. These 3 GED-0301 treatment regimens will be referred to as GED 160/GED 160 4 WK ALT, GED 160/GED 40 4 WK ALT, and GED 160/GED 40, respectively. Investigational product (IP) refers to placebo, GED 160, or GED 40.

3. STUDY OBJECTIVES

Table 2: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the efficacy of GED-0301 compared with placebo on clinical activity at Week 12 in subjects with active Crohn's disease (CD).
Secondary Objectives
The secondary objectives are: • To evaluate the efficacy of GED-0301 compared with placebo on endoscopic outcomes in subjects with active CD; • To evaluate the long-term efficacy of GED-0301 compared with placebo on clinical activity in subjects with active CD; • To evaluate the efficacy of GED-0301 compared with placebo on corticosteroid-free clinical remission in subjects with active CD; • To evaluate the safety and tolerability of GED-0301 in subjects with active CD.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of 3 treatment regimens of oral GED-0301 versus placebo in subjects with active CD (defined by a CDAI score ≥ 220 and ≤ 450 and a total SES-CD ≥ 6 at screening, or the ileum segmental SES-CD ≥ 4 at screening). Approximately 1064 subjects will be randomized in a 1:1:1:1 ratio (266 subjects per GED-0301 arm [total 798]; 266 subjects in the placebo arm) to receive 1 of 3 double-blind, oral GED-0301 treatment regimens, or identically appearing placebo once daily (QD) for 52 weeks. The total number of subjects with a total SES-CD score ≥ 6 is targeted to comprise approximately 80% of the study population.

Treatment assignment at baseline (Week 0/Visit 2) will be stratified via an Interactive Web Response System (IWRS) based on concomitant use of corticosteroids (yes/no); concomitant use of immunosuppressants (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) (yes/no), and previous exposure to biologics (ie, infliximab, adalimumab, certolizumab or vedolizumab) (yes/no). The total number of subjects with previous exposure to biologics is targeted to comprise approximately 35% of the study population.

Subjects will receive double-blind, oral GED-0301 or identically appearing placebo QD as follows:

- GED-0301 160 mg QD for 12 weeks; followed by placebo QD for 4 weeks; followed by alternating GED-0301 160 mg QD for 4 weeks and placebo QD for 4 weeks, until the the Week 52 Visit;
- GED-0301 160 mg QD for 12 weeks; followed by placebo QD for 4 weeks; followed by alternating GED-0301 40 mg QD for 4 weeks and placebo QD for 4 weeks, until the Week 52 Visit;
- GED-0301 160 mg QD for 12 weeks; followed by continuous GED-0301 40 mg QD, until the Week 52 Visit;
- Placebo QD until the Week 52 Visit.

Subjects who complete the GED-0301-CD-002 study at the Week 52 Visit may enter the Long-term Active-treatment Study (GED-0301-CD-004). Subjects who meet the criteria for early escape beginning at the Week 12 Visit and thereafter until the Week 52 Visit, may (a) continue in the study at the discretion of the Investigator based on the totality of clinical data, (b) enter the Long-term Active-treatment Study (GED-0301-CD-004), or (c) discontinue the study.

The criteria for early escape are defined as

Subjects may discontinue the study at any time. Subjects who discontinue from the study at Week 12 (either because they meet the early escape criteria or for any other reason), will complete the Week 12 Visit. Subjects who prematurely discontinue from the study at any other

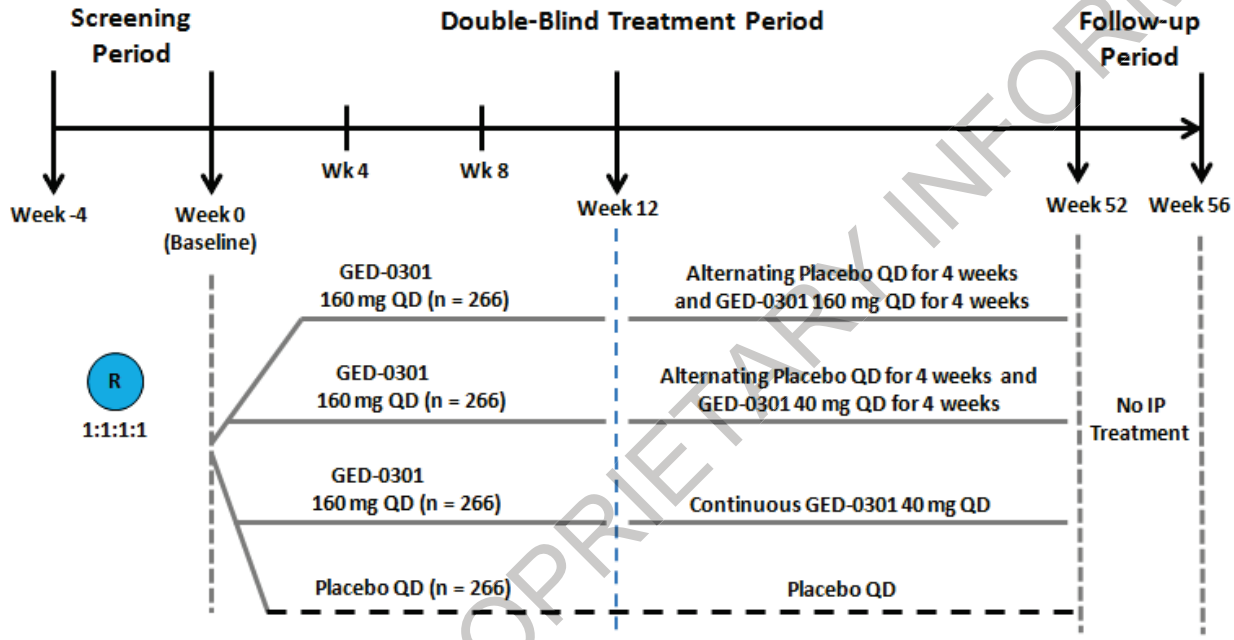
time prior to the Week 52 Visit, including subjects who early escape into the Long-term Active-treatment Study, will complete the Early Termination (ET) Visit. The ET Visit should be scheduled as soon as possible after the last dose of IP.

Subjects who complete the Week 52 Visit, as well as subjects who prematurely discontinue from the study, will have a 4-week Follow-up Visit. If the ET Visit occurs 28 days or more after the last dose of IP, then the Follow-up Visit is not required.

Subjects entering the Long-term Extension Study will not have the Follow-up Visit.

A schematic of the study design is in Figure 1.

Figure 1 Overall Study Design



4.2. Study Endpoints

Table 3: Protocol-specified Endpoints

Endpoint	Name	Description	Timeframe
Primary	Efficacy (Clinical remission)	The proportion of subjects achieving clinical remission, defined as a CDAI score < 150, at Week 12	Week 12
Secondary	Efficacy	The proportion of subjects achieving clinical remission, defined as a CDAI score < 150, at Week 52	Week 52

Table 3: Protocol-specified Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Efficacy	The proportion of subjects with endoscopic response-50 (ER-50), defined as a reduction of at least 50% in the SES-CD compared with baseline, at Week 52	Week 52
	Efficacy	The proportion of subjects who have a clinical response, defined as a decrease from baseline in CDAI ≥ 100 points, at Week 12	Week 12
	Efficacy	The proportion of subjects who achieve corticosteroid-free clinical remission (CDAI <150) at Week 52 among subjects receiving oral corticosteroids for CD at baseline	Week 52
	Efficacy	The proportion of subjects achieving sustained clinical remission, defined as a CDAI score < 150 at both Week 12 and Week 52	Week 12 and Week 52
	Efficacy	The proportion of subjects with endoscopic response-25 (ER-25), defined as a reduction of at least 25% from baseline in SES-CD, at Week 12	Week 12
	Efficacy	The proportion of subjects with endoscopic remission, defined as SES-CD ≤ 2, at Week 52	Week 52
	Safety	Type, frequency, severity, seriousness, and relationship of AEs to IP	Through Week 52
	Safety	Number of subjects who discontinue IP due to any AE	Through Week 52
	Safety	Clinically significant changes in vital signs, ECGs, and/or laboratory findings	Through Week 52

Table 3: Protocol-specified Endpoints (Continued)

Endpoint	Name	Description	Timeframe

Table 3: Protocol-specified Endpoints (Continued)

Endpoint	Name	Description	Timeframe

AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; ECG = electrocardiogram; ; IP = investigational product; SES-CD = Simple Endoscopic Score for Crohn's disease

4.3. Stratification, Randomization, and Blinding

Approximately 1064 eligible subjects will be randomized via an IWRS in a 1:1:1:1 ratio to receive 1 of 3 double-blind, oral GED-0301 treatment regimens, or identically appearing placebo QD for 52 weeks, as follows:

- GED-0301 160 mg QD for 12 weeks; followed by placebo QD for 4 weeks; followed by alternating GED-0301 160 mg QD for 4 weeks and placebo QD for 4 weeks, until the Week 52 Visit
- GED-0301 160 mg QD for 12 weeks; followed by placebo QD for 4 weeks; followed by alternating GED-0301 40 mg QD for 4 weeks and placebo QD for 4 weeks, until the Week 52 Visit
- GED-0301 160 mg QD for 12 weeks; followed by continuous GED-0301 40 mg QD, until the Week 52 Visit
- Placebo QD until the Week 52 Visit.

Treatment assignment at baseline (Week 0/Visit 2) will be stratified via an IWRS based on concomitant use of corticosteroids (yes/no); concomitant use of immunosuppressants (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) (yes/no), and previous exposure to biologics (ie, infliximab, adalimumab, certolizumab or vedolizumab) (yes/no). The total number of subjects with previous exposure to biologics is targeted to comprise approximately 35% of the study population.

4.4. Sample Size Determination and Power Considerations

With a total of approximately 1064 subjects and a randomization ratio of 1:1:1:1, this study will randomize approximately 266 subjects into each of the three GED-0301 treatment groups and the placebo group. For the efficacy analyses of the first 12 weeks of the study, the three GED-0301 treatment groups will be pooled, due to the same treatment of GED-0301 160 mg QD received during the first 12 weeks, and the treatment comparisons will be made between GED-0301 160 mg QD (approximately 798 subjects) and placebo. For the efficacy analyses beyond Week 12, the treatment comparisons will be made between each of the three GED-0301 treatment groups and placebo. The study sample size is driven by the comparison of each of the three GED-0301 treatment groups with placebo with respect to the proportion of subjects with ER-50 at Week 52. The sample size and power calculations (not accounting for multiplicity adjustment) at a 2-sided significance level of 0.05 are given in Table 5.

Table 5: Sample Size and Power Calculations

Endpoint	Assumptions	Sample Size per Group	Power[a]
Clinical remission (CDAI score < 150) at Week 12	Placebo = 22% GED-0301 160 mg QD = 36%	Placebo = 266 GED-0301 160 mg QD = 798	99%
Clinical remission (CDAI score < 150) at Week 52	Placebo = 22% GED-0301 160 mg QD = 36%	Placebo = 266 Any GED-0301 group = 266	95%
ER-50 at Week 52	Placebo = 10% Any GED-0301 group = 20%	Placebo = 266 Any GED-0301 group = 266	90%

CDAI = Crohn's Disease Activity Index; ER-50 = endoscopic response defined as a reduction of at least 50% in the SES-CD; QD = once daily; SES-CD = Simple Endoscopic Score for Crohn's Disease.

[a] All power calculations do not account for multiplicity adjustment and are based on a 2-group chi-square test at a 2-sided significance level of 0.05, using East™ 6.3.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

The following reporting conventions apply generally to tables, listings, and figures:

- Stratified analyses will use the randomization stratification factors (concomitant use of corticosteroids, concomitant use of immunosuppressants, and previous exposure to biologics), unless otherwise specified.

- Efficacy analyses will be presented by GED-0301 treatment regimen and placebo (the efficacy analyses of the first 12 weeks will additionally include a total group combining all 3 GED-0301 treatment regimens), and safety analyses will be presented by GED-0301 treatment regimen, placebo, and a total group combining all 3 GED-0301 treatment regimens.

- Confidence intervals (CIs) will be presented as 2-sided 95% CIs.
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, standard deviation (SD), median, minimum, 25th percentile (Q1), 75th percentile (Q3), and maximum for continuous variables.

- Change from baseline is calculated as the post-baseline value minus the baseline value.

- All laboratory data will be reported using standard international units.

5.2. Time Points

5.2.2. Screening and Baseline Definitions

Unless otherwise specified, the baseline value is defined as the last assessment on or before the date of the first dose of IP in the study.

5.3. Analysis Populations

5.3.1. Intent-to-treat Population

The intent-to-treat (ITT) population will be the primary population for the efficacy analysis. The ITT population is defined to include all subjects who are randomized and receive at least 1 dose of IP.

Due to the early termination of the study, for binary efficacy endpoints, the denominator at the time point under consideration will include subjects who have either completed that time point or discontinued at any time due to reasons other than "study terminated by sponsor", instead of all subjects included in the ITT population (Section 11.2.2.1).

Subjects will be included in the treatment group to which they were randomized for the efficacy analysis using the ITT population.

5.3.3. Safety Population

The analysis of safety data in this study will be based on the safety population, which will consist of all subjects who are randomized and receive at least 1 dose of IP.

At least 1 post-baseline assessment is required for inclusion in the analysis of each specific laboratory, vital sign, weight, or ECG parameter. To assess the change from baseline, a baseline assessment is also required.

Subjects will be included in the treatment group corresponding to the IP they actually received for the analysis using the safety population.

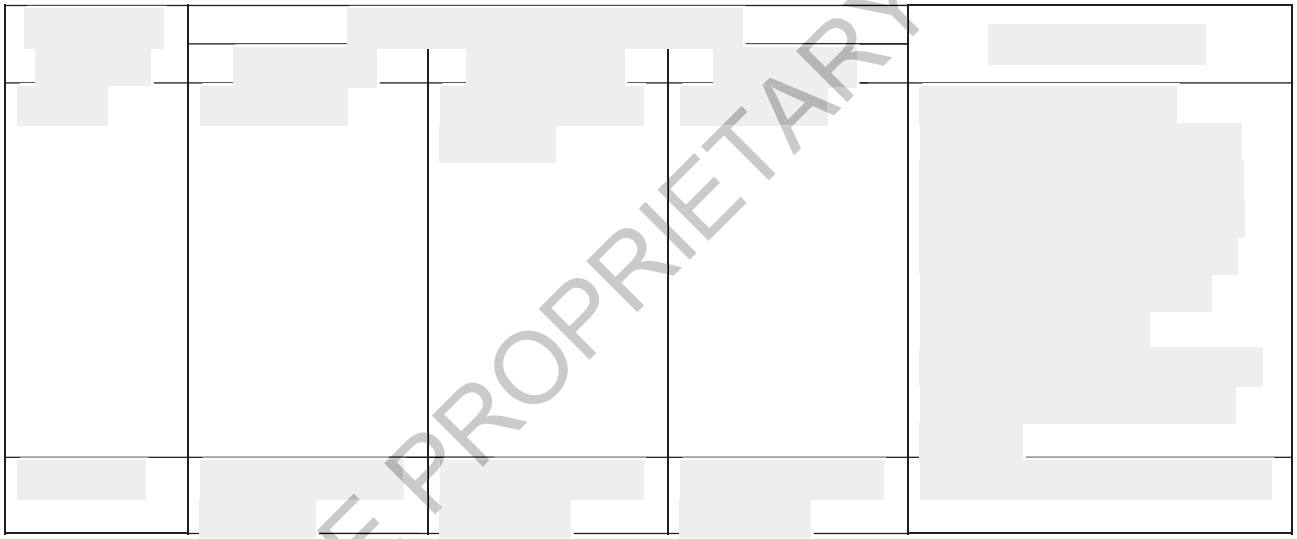
6. SUBJECT DISPOSITION

The number of subjects screened, the numbers and percentages of subjects randomized and not randomized, and the numbers and percentages of the eligibility criteria failed will be summarized based on all subjects screened.

The number and percentage of subjects included in the analysis populations will be summarized based on all subjects randomized.

Subject disposition (entered, completed, discontinued, along with the primary reason for discontinuation) will be summarized for

- Double-blind Treatment Period (based on all subjects randomized): Weeks 0-12, Weeks 12-52, and Weeks 0-52
- Follow-up Period (based on all subjects who enter the Follow-up Period): Weeks 0-12, Weeks 12-52, and Weeks 0-52



A listing of discontinued subjects with reason for discontinuation will be provided.

The number and percentage of subjects by region, country, and site will be provided based on all subjects randomized.

7. PROTOCOL DEVIATIONS/VIOLATIONS

Protocol violations and deviations will be summarized for the screening period, Weeks 0-12 and the entire study using the ITT population, and for Weeks 12-52 for subjects who complete Week 12/Visit 5.

A listing of all protocol violations and deviations in the study will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized descriptively based on the ITT population. The comparability of the treatment groups for each relevant characteristic will be assessed descriptively in table format; no statistical hypothesis tests will be performed on these characteristics. Subject data listings will be provided.

8.1. Demographics and Baseline Characteristics

The following characteristics will be summarized as continuous variables:

- Age (years)
- Baseline body weight (kg)
- Baseline body mass index (BMI = weight (kg)/[height(m)]^2; kg/m^2)

The following characteristics will be summarized as categorical variables:

- Age (< 65, ≥ 65 years; < 40, 40 – < 65, 65 – < 75, ≥ 75 years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Collected or Reported, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown, Not Reported)
- Region (North America, Western Europe, Eastern Europe, Asia Pacific)
- Baseline body weight (< 55, 55 – < 70, 70 – < 85, 85 – < 100, ≥ 100 kg)
- Baseline BMI (< 18.5, 18.5 – < 25, 25 – < 30, 30 – < 35, 35 – < 40, and ≥ 40 kg/m^2)
- Alcoholic beverages (yes [< 1 drink per week, 1 – 14 drinks per week, > 14 drinks per week], no)
- Tobacco history (never smoked, past smoker, current smoker, passive smoker, smokeless tobacco user)

Age will be calculated as (date of informed consent – date of birth + 1) / 365.25 when the full date of birth is collected; otherwise, the age recorded will be used.

8.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized as continuous variables:

- Baseline CDAI score
- Baseline SES-CD score (central read)

- Baseline CDAI score (≤ 300, > 300; < 220, 220 – < 270, 270 – < 330, 330 – < 390, 390 – ≤ 450, > 450)
- Baseline SES-CD (central read; < 6, 6 – 12, > 12)

8.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized based on the ITT population by system organ class (SOC) and preferred term (PT), with SOCs sorted in alphabetical order and PTs within each SOC in descending order of frequency, and by PT only in descending order of frequency.

8.4. Prior Medications/Procedures

Prior medications are defined as medications with a start date before the date of the first dose of IP in the study (whether or not the end date is before the date of the first dose of IP). Prior medications that continue on or after the date of the first dose of IP will be also reported as concomitant medications. The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHODD) will be used to group medications into relevant categories. Prior medications will be summarized based on the ITT population by ATC2 level and standardized medication name, with ATC2 levels and standardized medication names within each ATC2 level sorted in descending order of frequency.

Prior procedures are similarly defined. Prior procedures will be coded according to the MedDRA, and summarized based on the ITT population by SOC and PT, with SOCs sorted in alphabetical order and PTs within each SOC in descending order of frequency.

9. EXTENT OF EXPOSURE TO INVESTIGATIONAL PRODUCT

9.1. Treatment Duration

Treatment duration will be summarized for Weeks 0-12 and Weeks 0-52 using the safety population, and for Weeks 12-52 for subjects who receive at least 1 dose of IP after Week 12/Visit 5

Treatment duration will be summarized as a continuous variable, and as a categorical variable with the following exposure intervals:

- Weeks 0-12: ≤ 4, > 4 – 8, > 8 weeks
- Weeks 12-52: ≤ 8, > 8 – 16, > 16 – 24, > 24 – 32, > 32 weeks (intervals denote the number of weeks relative to the date of the first dose of IP in Weeks 12-52 as defined above)
- Weeks 0-52: ≤ 4, > 4 – 8, > 8 – 12, > 12 – 20, > 20 – 28, > 28 – 36, > 36 – 44, > 44 weeks

A subject data listing of study drug records will be provided.

9.2. Treatment Compliance

As part of the routine recording of the amount of IP taken by each subject, the numbers of tablets dispensed and returned will be recorded at each visit (except the screening and follow-up visits). These records will be used to calculate treatment compliance. Treatment compliance will be summarized for Weeks 0-12 and Weeks 0-52 using the ITT population, and for Weeks 12-52 for subjects who receive at least 1 dose of IP after Week 12/Visit 5

Treatment compliance rate will be summarized as a continuous variable, and as a categorical variable with the following categories: < 75%, 75% – 120%, and > 120%.

A subject data listing of drug accountability records will be provided.

9.3. Overdose

A subject data listing of overdose records will be provided.

10. CONCOMITANT MEDICATIONS AND PROCEDURES

Concomitant medications and procedures will be summarized for Weeks 0-52 using the safety population.

10.1. Concomitant Medications

The ATC coding scheme of the WHODD will be used to group medications into relevant categories. Concomitant medications will be summarized by ATC2 level and standardized medication name, with ATC2 levels and standardized medication names within each ATC2 level sorted in descending order of frequency.

10.2. Concomitant Procedures

Concomitant procedures are defined similarly to concomitant medications. Concomitant procedures will be coded according to the MedDRA, and summarized by SOC and PT, with SOCs sorted in alphabetical order and PTs within each SOC in descending order of frequency.

11. EFFICACY ANALYSIS

All efficacy analysis tables will be presented by GED-0301 treatment regimen, placebo, and a total group combining all 3 GED-0301 treatment regimens. The 3 GED-0301 treatment regimens will be labeled as GED 160/GED 160 4 WK ALT, GED 160/GED 40 4 WK ALT, and GED 160/GED 40, and the total group combining all 3 GED-0301 treatment regimens will be labeled as GED Total. Formal treatment comparisons will be made between GED Total (ie, GED 160) and placebo for the efficacy analyses of the first 12 weeks, and between each of the 3 GED-0301 treatment regimens and placebo for the efficacy analyses beyond Week 12.

11.1. Multiplicity

The protocol specifies that a gatekeeping closed testing procedure will be used to control the family-wise Type I error rate at the 2-sided significance level of 0.05 for the primary and secondary efficacy endpoints. Due to the early termination of the study, however, no multiplicity adjustment will be performed.

11.2. Missing Data Handling

11.2.2. Binary Efficacy Endpoints

11.2.2.1. Primary Approach for Analysis

For binary efficacy endpoints, the primary approach to handling missing data will be nonresponder imputation (NRI), where subjects who are included in the denominator at the time point under consideration but have insufficient data for response determination at that time point will be considered nonresponders for that time point.

To eliminate the downward bias to the estimate of a binary endpoint due to the inclusion of subjects (as nonresponders due to NRI) who have not had a chance to reach the time point under consideration but have discontinued due to “study terminated by sponsor”, the denominator at

the time point under consideration will include subjects who have either completed that time point or discontinued at any time due to reasons other than "study terminated by sponsor", instead of all subjects in the ITT population.

11.3. Analysis of Primary Endpoint

11.3.1. Primary Analysis of Primary Endpoint

The primary analysis of the primary endpoint, the proportion of subjects achieving clinical remission at Week 12, will be based on the ITT population. Missing data will be handled by the NRI method.

The within-group proportion, standard error (SE), and 2-sided 95% CI for the within-group proportion will be provided for placebo, GED-0301 treatment regimens, and GED 160 (combining all 3 GED-0301 treatment regimens). The treatment comparison will be made between GED 160 and placebo. The unstratified treatment difference in proportions, stratified treatment difference in proportions using the weighted average of the treatment differences across the strata with the Cochran-Mantel-Haenszel (CMH) weights, stratified 2-sided 95% CI for the treatment difference in proportions, and the 2-sided p-value from the CMH test stratified by the randomization stratification factors, will be provided for the comparison of GED 160 and placebo.

11.4. Analyses of Secondary Efficacy Endpoints

11.4.1. Primary Analyses of Secondary Efficacy Endpoints

The primary analysis of each secondary efficacy endpoint will be performed similarly to the primary analysis of the primary endpoint. The treatment comparisons will be made between GED 160 (combining all 3 GED-0301 treatment regimens) and placebo for the endpoints at Weeks 4 and 12 and between each of the 3 GED-0301 treatment regimens and placebo for the endpoints at Week 52.

The analysis of the proportion of subjects who achieve corticosteroid-free clinical remission at Week 52 among subjects receiving oral corticosteroids at baseline will be based on the subjects included in the ITT population who receive oral corticosteroids for CD at baseline.

11.7. Assessing Study Center Effect and Treatment-by-center Interaction

This study is a multicenter study and has hundreds of study sites planned. The limited number of subjects expected at many sites does not allow for a meaningful assessment of study center effect.

12. SAFETY ANALYSIS

Safety will be evaluated via descriptive statistics and point estimates. No inferential testing for statistical significance will be performed.

The safety analyses will be based on the safety population. All safety analysis tables will be presented by GED-0301 treatment regimen, placebo, and a total group combining all 3 GED-0301 treatment regimens. The 3 GED-0301 treatment regimens will be labeled as GED 160/GED 160 4 WK ALT, GED 160/GED 40 4 WK ALT, and GED 160/GED 40, and the total group combining all 3 GED-0301 treatment regimens will be labeled as GED Total.

12.2. Adverse Events

Adverse events will be coded according to the MedDRA. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs sorted in alphabetical order and PTs within each SOC in descending order of subject incidence of the total group combining all 3 GED-0301 treatment regimens.

For the analyses of AEs, the following point estimates are provided, unless otherwise specified:

- Subject incidence: Subject incidence (ie, percentage [%] used in a frequency summary) is defined as the number of subjects with the specific event divided by the number of subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period will be counted only once in the numerator.
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All AE summaries will be provided for Weeks 0-52. Where so indicated, select AE summaries will also be provided for Weeks 0-12 and/or Weeks 12-52.

A subject data listing of all AEs (including treatment-emergent AEs [TEAEs] and non-TEAEs) will be provided.

12.2.1. Overall Summary of TEAEs

An overall summary of the following TEAE categories will be provided for Weeks 0-12, Weeks 12-52, and Weeks 0-52:

- Any TEAE
- Any drug-related TEAE
- Any severe TEAE
- Any serious TEAE

- Any serious drug-related TEAE
- Any TEAE leading to drug interruption
- Any TEAE leading to drug withdrawal
- Any TEAE leading to death

12.2.2. All TEAEs

All TEAEs will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence of the total group combining all 3 GED-0301 treatment regimens) for Weeks 0-12, Weeks 12-52, and Weeks 0-52.

12.2.3. Drug-related TEAEs

Drug-related TEAEs will be summarized for Weeks 0-12, Weeks 12-52, and Weeks 0-52.

12.2.4. TEAEs by Maximum Severity

All TEAEs will be summarized by maximum severity (mild, moderate, and severe) for Weeks 0-52. If a subject reports multiple occurrences of a specific event within a specific analysis period, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used.

12.2.5. Serious TEAEs

Serious TEAEs will be summarized for Weeks 0-12, Weeks 12-52, and Weeks 0-52.

A subject data listing of all serious AEs (both TEAEs and non-TEAEs) will be provided.

12.2.6. TEAEs Leading to Drug Withdrawal

TEAEs leading to drug withdrawal will be summarized for Weeks 0-12, Weeks 12-52, and Weeks 0-52.

A subject data listing of AEs leading to drug withdrawal will be provided.

12.2.7. Deaths

A subject data listing of all deaths will be provided.

12.3. Clinical Laboratory Evaluations

The following protocol-specified parameters from the central laboratory will be summarized:

- Hematology panel will include: complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count (with differential), and platelet count.
- Serum chemistry panel will include: total protein, albumin, calcium, phosphorous, glucose, total cholesterol, triglycerides, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT),

alanine aminotransferase/serum glutamic pyruvic transaminase (SGPT), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, lactic dehydrogenase (LDH), magnesium.

- Complement activation (Bb, C3a and C5a).
- Coagulation assessment will include: prothrombin time and activated partial thromboplastin time (APTT).
- Urinalysis will include specific gravity and pH,.

Summary statistics of observed values and changes from baseline will be provided by time point (time points include the scheduled visits for labs, the follow-up visit, the end of Weeks 0-12, the end of Weeks 12-52, and the end of Weeks 0-52).

Frequency summaries (shift tables) of shifts from baseline to post-baseline time points (time points include the scheduled visits for labs, the end of Weeks 0-12, the end of Weeks 12-52, the end of Weeks 0-52, and the worst value of Weeks 0-52) by category of low/normal/high/both low and high (the last category for the shift to the worst value only) will be provided for hematology and serum chemistry.

A summary of laboratory marked abnormalities as defined in Section 18.4 will be provided for Weeks 0-52.

A separate summary of laboratory marked abnormalities will also be presented by normal baseline and abnormal baseline.

A subject data listing of all laboratory data (including urinalysis) will be provided.

12.4. Vital Signs and Body Weight

For vital signs and body weight, summary statistics of observed values and changes from baseline (also percent change from baseline for body weight) will be provided by time point (time points include the scheduled visits for vital signs/body weight, the follow-up visit, the end of Weeks 0-12, the end of Weeks 12-52, and the end of Weeks 0-52).

A subject data listing of all vital signs and body weight will be provided.

12.5. Electrocardiogram

A frequency summary (shift table) of the shift from baseline to the end of Weeks 0-52 in investigator clinical interpretation of ECG (normal; abnormal, not clinically significant; and abnormal, clinically significant) will be provided.

15. INTERIM ANALYSIS

There will be no interim analysis for this study.

16. CHANGES TO THE STATISTICAL CONSIDERATIONS SECTION OF THE PROTOCOL

Due to the early termination of the study, the following changes to the Statistical Considerations section of the protocol have been made in this SAP.

- For binary efficacy endpoints, the denominator at the time point under consideration will include subjects who have either completed that time point or discontinued at any time due to reasons other than "study terminated by sponsor", instead of all subjects included in the ITT population (Sections 5.3.1 and 11.2.2.1).

- The protocol specifies that a gatekeeping closed testing procedure will be used to control the family-wise Type I error rate at the 2-sided significance level of 0.05 for the primary and secondary efficacy endpoints. This SAP specifies no multiplicity adjustment will be performed (Section 11.1).