DISCLOSURE

REDACTED PROTOCOL AMENDMENT 3

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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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

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PROTOCOL SUMMARY

Study 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.

Indication

Mongersen (GED-0301) is being studied for the treatment of subjects with active Crohn's disease (CD) and ulcerative colitis (UC). Although the etiology of CD has not been completely elucidated, there has been significant advancement in the understanding of the disease pathogenesis. There is evidence that the chronic intestinal inflammation is caused by an excessive immune response to mucosal antigens that is not appropriately controlled by the normal counter-regulatory mechanisms. One of the counter-regulatory mechanisms involves transforming growth factor-beta 1 (TGF-β1). TGF-β1 is a multifunctional factor that has been shown to be involved in regulating growth, differentiation, and function of immune and nonimmune cells (Monteleone, 2001). TGF-β1 has been shown to play an important role in the control of immune homeostasis and acts as a potent negative regulator of mucosal inflammation. TGF-β1 knockout mice developed a severe multiple-organ inflammatory disease, in which the lymphocytic infiltration of the affected organs was associated with increased production of tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ). Studies have shown that abrogation of TGF-β1 signaling in T cells alone is sufficient to disrupt T and B cell homeostasis and induce T cell-mediated inflammatory lesions in various organs, including the intestine. It has been widely demonstrated that neutralization of TGF-β1 results in the induction and/or amplification of pathogenic responses responsible for the development of experimental colitis resembling either CD or UC (Monteleone, 2012).

TGF-β1 signaling is regulated by Smads, a family of proteins that serve as substrates for TGF-β1 type I and type II receptors. The TGF-β type I receptor recognizes Smad2 and Smad3 which, upon phosphorylation of Smad3, en route to the nucleus, associate with Smad4, forming complexes that participate in transcriptional control of target genes. In addition to the activating Smads, inhibiting Smad also exists. Smad7 interacts with activated receptors and prevents phosphorylation of Smad2 and Smad3. The advance in the understanding of the involvement of the TGF-β signaling pathway in the pathogenesis of CD and the identification of the role of Smad7 in IBD has provided the rationale for the development of a new drug that, through the inhibition of Smad7 expression, could restore TGF-β1 signaling, thus inhibiting the production of pro-inflammatory molecules such as TNF-α and IFN-γ.

GED-0301 is an investigational medicinal product in clinical development for the treatment of CD and UC. GED-0301 is an antisense oligodeoxynucleotide that is complementary to the sequence of the messenger ribonucleic acid (mRNA) transcript of Smad7. Orally administered GED-0301 is formulated as a gastro-resistant delayed release pH-dependent tablet designed to deliver the active substance in the distal gastrointestinal (GI) tract with negligible systemic exposure.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational product (IP).

Objectives

Primary Objective

- To evaluate the efficacy of GED-0301 compared with placebo on clinical activity at Week 12 in subjects with active CD

Secondary Objectives

- 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

Endpoints

Primary Endpoint

- The proportion of subjects achieving clinical remission, defined as a CDAI score < 150, at Week 12

Secondary Endpoints

- The proportion of subjects achieving clinical remission, defined as a CDAI score < 150, at Week 52
- 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
- The proportion of subjects who have a clinical response, defined as a decrease from baseline in CDAI ≥ 100 points, at Week 12
- The proportion of subjects who achieve corticosteroid-free clinical remission (CDAI <150) at Week 52 among subjects receiving oral corticosteroids for CD at baseline
- The proportion of subjects achieving sustained clinical remission, defined as a CDAI score < 150, at both Week 12 and Week 52
- The proportion of subjects with endoscopic response-25 (ER-25), defined as a reduction of at least 25% in the SES-CD compared with baseline, at Week 12
- The proportion of subjects with endoscopic remission, defined as SES-CD ≤ 2, at Week 52
- Type, frequency, severity, seriousness, and relationship of AEs to IP

- Number of subjects who discontinue investigational product (IP) due to any AE
- Clinically significant changes in vital signs, electrocardiograms (ECGs) and/or laboratory findings

Study Design

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] and 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 (Table 4):

- 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 [redacted] (Table 7).

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 (Section 6.3). 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.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs) and applicable regulatory requirements.

Study Population

The study population will consist of female and male subjects 18 years of age and older at the time of signing the Informed Consent Form (ICF).

The key inclusion criteria for this study are as follows:

- Diagnosis of CD with a duration of at least 3 months prior to the Screening Visit
- Presence of ileitis, ileocolitis or colitis, as determined by ileocolonoscopy at screening.
- Active disease, defined as a CDAI score ≥ 220 and ≤ 450 at screening
- Must have a 7-day average stool frequency ≥ 3.5 or abdominal pain ≥ 1.5 at screening.
- Must have a total SES-CD ≥ 6 at screening, or the ileum segmental SES-CD ≥ 4 at screening
- Must have failed or experienced intolerance to at least one of the following: budesonide; systemic corticosteroids; immunosuppressants (ie, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]); or biologics for the treatment of CD (ie, infliximab, adalimumab, certolizumab or vedolizumab, see Appendix H for details)

The key exclusion criteria for this study are as follows:

- Diagnosis of ulcerative colitis (UC), indeterminate colitis, ischemic colitis, microscopic colitis, radiation colitis or diverticular disease-associated colitis
- Local manifestations of CD such as abscesses, short bowel syndrome, or other disease complications for which surgery might be indicated or could confound the evaluation of efficacy
- Strictures with prestenotic dilatation, requiring procedural intervention, or with obstructive symptoms. In addition, colonic strictures that are not passable with an adult colonoscope, or strictures in the ileum or ileocecal valve that are fibrotic in nature, will be excluded.
- Any intestinal resection within 6 months or any intra-abdominal surgery within 3 months prior to the Screening Visit
- Prior treatment with mycophenolic acid, tacrolimus, sirolimus, cyclosporine, thalidomide or apheresis (eg, Adacolumn®) within 8 weeks prior to the Screening Visit

- Use of intravenous (IV) corticosteroids within 2 weeks prior to the Screening Visit
- Use of topical GI treatments such as 5-aminosalicylic acid (5-ASA) or corticosteroid enemas or suppositories within 2 weeks prior to the Screening Visit
- Use of bile acid sequestrants, (eg, cholestyramine) within 3 weeks prior to the Screening Visit
- Prior treatment with biologics for the treatment of CD (approved or investigational), other than infliximab, adalimumab, certolizumab or vedolizumab
- Prior treatment with more than 3 biologics for the treatment of CD (ie, infliximab, adalimumab, certolizumab or vedolizumab). Treatment with a biologic within 8 weeks prior to the Screening Visit, or 5 elimination half lives, whichever is longer. (See Table 8 for elimination half-life timeframes of biologics.)

Permitted concomitant medications during the study include:

- Oral aminosalicylates (sulfasalazine [SSZ] or 5-aminosalicylic acid [ASA] compounds), provided that treatment has been given at a stable dose for at least 2 weeks prior to the Screening Visit. The dose of oral aminosalicylates must remain stable through the duration of the study or early termination from the study. If oral aminosalicylates have been recently discontinued, treatment must have been stopped at least 2 weeks prior to the Screening Visit.
- Oral corticosteroids, provided that the dose (prednisone ≤ 20 mg/day or equivalent, budesonide ≤ 9 mg/day) has been stable for 3 weeks prior to the Screening Visit. If oral corticosteroids were recently discontinued, discontinuation must have been completed at least 3 weeks prior to the Screening Visit. Corticosteroid doses should remain stable until the subject is eligible to start corticosteroid tapering, beginning at the Week 12 Visit (see Section 6.7 for details).
- Immunosuppressants, such as AZA, 6-MP, or MTX, provided that treatment was initiated ≥ 12 weeks prior to the Screening Visit, must be at a stable dose for ≥ 8 weeks prior to the Screening Visit and remain stable for the duration of the study. If immunosuppressants have been recently discontinued, treatment must have been stopped at least 8 weeks prior to the Screening Visit.
- Antibiotics used for the treatment of CD (eg, ciprofloxacin, metronidazole), provided that the dose has been stable for at least 2 weeks prior to the Screening Visit. If antibiotics have been recently discontinued, discontinuation must have been completed at least 2 weeks prior to the Screening Visit.
- Acetaminophen and low-dose aspirin for cardiovascular prophylaxis are allowed.

Note: The dose of concomitant CD medications noted above may not be increased above the baseline dose during the study. No new CD therapy can be prescribed once the subject has been screened in the study.

Length of Study

Subjects will participate for a maximum of 60 weeks in this study: up to 4 weeks in the Screening Period; 52 weeks in the Double-blind Treatment Period; and 4 weeks in the Follow-up Period.

The End of Study is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

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 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.

Additional information pertaining to treatment is described in Section 7.

Overview of Key Efficacy Assessments

- Crohn's Disease Activity Index (Section 6.6.2)
- Simple Endoscopic Score for Crohn's Disease (Section 6.6.6)

Overview of Key Safety Assessments

- Type, frequency, severity, seriousness, and relationship of AEs to IP
- Number of subjects who discontinue IP due to any AE
- Clinically significant changes in ECGs, vital signs, and/or laboratory findings

Statistical Methods

The intent-to-treat (ITT) population will be the primary population for the efficacy analysis. The ITT population will consist of all subjects who are randomized and receive at least 1 dose of IP. Subjects will be included in the treatment group to which they were randomized for the efficacy analysis using the ITT population.

For the efficacy analyses of the first 12 weeks of the study, the 3 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 and placebo. For the efficacy analyses beyond Week 12, the treatment comparisons will be made between each of the 3 GED-0301 treatment groups and placebo.

Binary endpoints will be analyzed by the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. Subjects who have insufficient data for response determination for the time point under consideration will be considered nonresponders for that time point.

Formal statistical tests are planned for the primary and secondary efficacy endpoints. In order to control the family-wise Type I error rate at the 0.05 level, formal statistical tests will be carried out using a gatekeeping closed testing procedure.

The safety analysis will be based on the safety population, which will consist of all subjects who are randomized and receive at least 1 dose of IP. Subjects will be included in the treatment group corresponding to the IP they actually received for the analysis using the safety population.

Treatment-emergent adverse events (TEAEs) will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to IP. TEAEs leading to death or to discontinuation from treatment and serious TEAEs will also be tabulated. In the by-subject analysis, a subject having the same event more than once will be counted only once and by greatest severity.

Laboratory, vital signs, weight, and ECG data will be summarized descriptively by time point. In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal ranges at baseline versus postbaseline will be provided for laboratory tests.

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 3 GED-0301 treatment groups and the placebo group. 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 study has > 90% power (at a 2-sided significance level of 0.05 and not accounting for multiplicity adjustment; same for the power statements below) to demonstrate the superiority of GED-0301 160 mg QD (approximately 798 subjects) over placebo with respect to clinical remission at Week 12, assuming response rates of 36% and 22% for the GED-0301 160 mg QD and placebo groups, respectively. The study has > 90% power to demonstrate the superiority of a GED-0301 treatment regimen over placebo with respect to clinical remission at Week 52, assuming response rates of 36% and 22% for the GED-0301 and placebo groups, respectively. The study has 90% power to demonstrate the superiority of a GED-0301 treatment regimen over placebo with respect to ER-50 at Week 52, assuming response rates of 20% and 10% for the GED-0301 and placebo groups, respectively.

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1. INTRODUCTION

1.1. Disease Background

Crohn's disease (CD) is a chronic, disabling, relapsing, systemic inflammatory disease that mainly affects the ileum and the colon, although it may involve any segment of the gastrointestinal (GI) tract. Crohn's disease may also present with extraintestinal manifestations and associated immune disorders (Baumgart, 2012). It is one of the most common forms of inflammatory bowel disease (IBD). The precise cause of CD is unknown, but it is considered to be an autoimmune disease due to a combination of genetic, environmental and immunologic factors (MacDonald, 2005). The peak age of disease onset is between 15 and 25 years of age.

In North America, the incidence of the disease is estimated to be between 3.1 and 14.6 cases per 100,000 person-years, with 10,000 to 47,000 new cases of CD diagnosed annually (Loftus, 2004). The overall incidence of CD in Europe is about 5.6 per 100,000 inhabitants (7.0 per 100,000 person-years in northern centers versus 3.9 in southern centers) (Loftus, 2004).

Patients with CD may present with symptoms that include abdominal pain, diarrhea, and weight loss, and the course of the disease can be associated with systemic symptoms such as malaise, anorexia, or fever. Crohn's Disease has a chronic relapsing course, with approximately half of the patients having been in remission at any given time (Loftus, 2002). Common complications are intestinal strictures and fistulas, with an increased frequency over time, occurring in more than half of the patients at 20 years after diagnosis, and often requiring surgery (Baumgart, 2012). Extraintestinal manifestations have been reported in 6% to 47% of the patients with CD, including manifestations which are associated with intestinal activity (eg, peripheral arthritis, erythema nodosum, aphthous ulcers); or not (eg, pyoderma gangrenosum, uveitis, spondylarthropathy, primary sclerosing cholangitis); non CD-specific autoimmune diseases which represent a major susceptibility to autoimmunity only (eg, hemolytic anemia, vitiligo, diabetes mellitus, psoriasis) as well as CD-related complications due to metabolic or anatomical abnormalities (eg, thromboembolic events, osteopathy, nephrolithiasis) (Vavricka, 2011; Bernstein, 2005). Additionally, patients with CD are at increased risk of developing small bowel and colorectal cancer (Baumgart, 2012).

Treatment of patients with CD represents a difficult challenge. The natural history of CD is characterized by a remitting and relapsing course that progresses to complications and surgery in the majority of patients. A stepwise approach according to disease location and severity at presentation has been advocated, with the primary aim of inducing and maintaining clinical remission, improving quality of life (QoL), and minimizing short- and long-term toxicity and complications (Lichtenstein, 2009; Dignass, 2010). Treatment of CD currently involves pharmacological treatment and surgery, the latter of which is indicated for medically refractory disease, strictures, abscesses and neoplastic lesions. Pharmacological treatment may involve aminosalicylates, antibiotics, glucocorticoids, immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]), and biologic compounds, such as tumor necrosis factor-alpha (TNF-α) blockers, natalizumab, and vedolizumab. Patients with mild to moderate disease usually receive aminosalicylates, antibiotics, or budesonide; systemic steroids and immunosuppressants, which are used when the initial approach fails or in cases of moderate to severe disease, and biologics are usually reserved for refractory cases or severe disease (Lichtenstein, 2009).

Although these drugs can provide clinical benefit, they have important limitations. Aminosalicylates are minimally effective in patients with CD, antibiotics have not consistently demonstrated efficacy in controlled trials, and glucocorticoids, although effective in the short term, can cause unacceptable adverse events (AEs) and do not provide a benefit as maintenance therapy (Lichtenstein, 2009). Additionally, immunosuppressant use has been restricted to maintenance therapy and is also associated with significant potential toxicities, such as malignancies and infections. Biologics, such as TNF-α blockers, have improved the care of patients with CD by providing induction and maintenance of remission and decreasing the need for hospitalizations and surgeries, but roughly two-thirds of patients do not achieve remission after 1 year of treatment. Additionally, after failing a TNF-α blocker, the response to a second TNF-α blocker is significantly lower. The TNF-α blockers may predispose to serious safety concerns, including opportunistic infections and malignancies (Clark, 2007).

There is a clear need for new therapeutic approaches with a good safety profile in patients with CD who do not respond, lose response, or are intolerant to currently available treatments.

1.2. Compound Background

GED-0301 inhibits the expression of Smad7, a key regulatory modulator of TGF-β1, by targeting a sequence in Smad7 messenger ribonucleic acid (mRNA) (Boirivant, 2006). There is a marked overexpression of Smad7 in the inflamed intestine of patients with IBD, such as CD and UC (Monteleone, 2001). This is associated with a reduction in p-Smad3, a crucial step in TGF-β1-mediated signal transduction. By blocking TGF-β1 activity, high Smad7 levels contribute to sustained production of proinflammatory molecules (such as IFN-γ and TNF-α) in IBD-affected tissues. The identification of the role of Smad7 in IBD provided the rationale for the development of mongersen (GED-0301).

GED-0301 is an investigational medicinal product in clinical development for the treatment of CD and ulcerative colitis (UC). GED-0301 is an antisense oligodeoxynucleotide (21-mer) that is complementary to the sequence of the messenger ribonucleic acid (mRNA) transcript of Smad7. It has a phosphorothioate backbone. It may be described chemically as the fully neutralized sodium salt of a 3'→ 5' linked 2'-deoxyribophosphorothioate oligonucleotide 21-mer in which each of the 20 internucleotide linkages is an O,O-linked phosphorothioate. Orally administered GED-0301 is formulated as a gastro-resistant delayed release pH-dependent tablet designed to deliver the active substance in the distal GI tract with negligible systemic exposure.

Although the etiology of CD has not been completely elucidated, there has been significant advancement in the understanding of the disease pathogenesis. There is evidence that the chronic intestinal inflammation is caused by an excessive immune response to mucosal antigens that is not appropriately controlled by the normal counter-regulatory mechanisms. One of the counter-regulatory mechanisms involves transforming growth factor-β1 (TGF-β1). TGF-β1 is a multifunctional factor that has been shown to be involved in regulating growth, differentiation, and function of immune and nonimmune cells (Monteleone, 2001). TGF-β1 has been shown to play an important role in the control of immune homeostasis and acts as a potent negative regulator of mucosal inflammation. TGF-β1 knockout mice developed a severe multiple-organ inflammatory disease, in which the lymphocytic infiltration of the affected organs was associated with increased production of TNF-α and interferon-gamma (IFN-γ). Studies have shown that abrogation of TGF-β1 signaling in T cells alone is sufficient to disrupt T and B cell homeostasis

and induce T cell-mediated inflammatory lesions in various organs, including the intestine. It has been widely demonstrated that neutralization of TGF-β1 results in the induction and/or amplification of pathogenic responses responsible for the development of experimental colitis resembling either CD or UC (Monteleone, 2012).

TGF-β1 signaling is regulated by Smads, a family of proteins that serve as substrates for TGF-β1 type I and type II receptors. The TGF-β type I receptor recognizes Smad2 and Smad3 which, upon phosphorylation of Smad3, en route to the nucleus, associate with Smad4, forming complexes that participate in transcriptional control of target genes. In addition to the activating Smads, inhibiting Smad also exists. Smad7, on the other hand, interacts with activated receptors and prevents phosphorylation of Smad2 and Smad3. The advance in the understanding of the involvement of the TGF-β signaling pathway in the pathogenesis of CD and the identification of the role of Smad7 in IBD has provided the rationale for the development of a new drug that, through the inhibition of Smad7 expression, could restore TGF-β1 signaling, thus inhibiting the production of pro-inflammatory molecules such as TNF-α and IFN-γ.

1.2.1. Nonclinical Experience

Overall, GED-0301 exhibits an acceptable safety profile in preclinical species and the toxicology program for GED-0301 adequately supports the conduct of clinical studies.

Please refer to the Investigator's Brochure (IB) for information concerning the available preclinical, pharmacology, toxicology and drug metabolism studies of GED-0301.

1.2.2. Clinical Summary

1.2.2.1. Clinical Pharmacology

The pharmacokinetics (PK) of GED-0301 were characterized in a Phase 1 first-in-human study in subjects with active CD. The systemic bioavailability of GED-0301 following oral administration at dose levels up to 160 mg/day for 7 days to human patients is negligible.

1.2.2.2. Clinical Safety

Three clinical studies have been completed to date: , a Phase 1, dose-escalating, safety and PK study of 7 days of oral administration of GED-0301 in subjects with active CD, a Phase 2 randomized, double-blind, placebo-controlled, dose-finding study of GED-0301 in subjects with active CD and , a Phase 2 randomized, double-blind, placebo-controlled, long-term extension study to evaluate the safety and tolerability of GED-0301 40 mg for the maintenance of CD in remission.

No deaths were reported during the conduct of the studies. No safety concerns that could modify the study conduct and/or investigational product (IP) administration arose from the studies.

Please refer to the IB for information concerning the available clinical studies and adverse event (AE) profile of GED-0301.

1.3. Rationale

1.3.1. Study Rationale and Purpose

The purpose of this Phase 3 study is to demonstrate the efficacy and safety of GED-0301 in subjects with active CD to support its registration for the indication of the treatment of active CD. Active CD is defined as a CDAI score ≥ 220 and ≤ 450 at screening and a total Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥ 6 at screening, or the ileum segmental SES-CD ≥ 4 at screening. Subjects must have failed or experienced intolerance to at least one of the following: budesonide; systemic corticosteroids; immunosuppressants (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]); or biologics (ie, infliximab, adalimumab, certolizumab or vedolizumab).

1.3.2. Rationale for the Study Design

GED-0301-CD-002 is a double-blind, placebo-controlled study that will evaluate both short-term and long-term efficacy, as well as safety, of GED-0301 in subjects with active CD. Efficacy will be based on clinical activity, as measured by the Crohn's Disease Activity Index (CDAI) or average daily liquid or stool frequency and abdominal pain score, and endoscopic outcomes, as measured by the SES-CD. Crohn's Disease Activity Index, the current standard for evaluation of clinical disease activity, is a validated, reproducible and responsive measure of CD that has been widely used in clinical trials for approximately 35 years.

The SES-CD is a validated endoscopic index that is considered the most suitable endoscopic outcome measure due to its ease of use and close correlation with the Crohn's Disease Endoscopic Index of Severity (CDEIS), considered the gold standard for endoscopic evaluation.

The primary efficacy measure will be clinical remission (defined as a CDAI score < 150) during the Treatment Phase at Week 12. Key secondary efficacy measures will include: clinical remission at Week 52; endoscopic response-50 ([ER-50], defined as a reduction of at least 50% compared with baseline in SES-CD) at Week 52; clinical response (defined as a decrease from baseline in CDAI ≥ 100 points) at Week 12; steroid-free clinical remission at Week 52; sustained clinical remission at both Week 12 and Week 52; endoscopic response-25 ([ER-25], defined as a reduction of at least 25% compared with baseline in SES-CD) at Week 12; and the evaluation of endoscopic remission (defined as SES-CD ≤ 2) at Week 52.

Laboratory evaluations, AEs, vital signs, electrocardiograms (ECGs), pregnancy tests and physical examinations will be monitored during the study to evaluate safety.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

Three oral dose regimens of GED-0301 versus placebo are being evaluated for the treatment of subjects with active CD:

- 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.

The doses and dose regimens for this study were selected based on pre-clinical data and clinical data from the Phase 1 study and the Phase 2 dose-finding study in subjects with active CD.

The key considerations for the selection of the appropriate dose and dosing regimens were:

1. the very low systemic exposure in animals without signs of toxicity when given orally in doses at least 10 times higher, by body weight, than the proposed GED-0301 160 mg QD dose in humans;
2. the negligible systemic exposure of GED-0301 in humans;
3. the demonstrated efficacy of GED-0301 in Phase 1 and Phase 2 studies;
4. the similar safety profile of the various GED-0301 dose treatment groups in Study ; comparable numbers and types of TEAEs across all treatment groups, including the placebo treatment group were observed, with few SAEs or AEs leading to discontinuation of IP.

Study demonstrated GED-0301 40 mg QD and 160 mg QD to be efficacious and safe after 2 weeks of treatment in subjects with steroid dependent or refractory CD.

Therefore, these data, in addition to the similar and favorable safety profiles of GED-0301 40 mg QD and 160 mg QD, provide supportive evidence for the selection of 160 mg QD as the initial dose of GED-0301 for a 12-week treatment induction of clinical remission and endoscopic response . The 12-week duration was selected in order to optimize therapeutic benefit, since it is expected that it would take a longer duration of treatment to achieve endoscopic benefit, such as endoscopic response, than to achieve clinical signs and symptoms benefit or clinical remission, in a moderate to severe CD population. Also, there is no consensus about the appropriate timing to assess the endoscopy evaluation, ranging from 10 to 26 weeks in different clinical studies

(Dave, 2012). In addition, endoscopic assessments at time points later than 12 weeks in placebo-controlled studies have posed the problem of limited comparative data due to the low number of placebo subjects remaining beyond the 12-week time point. Hence, the 12-week time point was selected for the endoscopic endpoint in this study.

Three active dosing regimens will be evaluated following the initial 12-week treatment with GED-0301 160 mg QD, in which two different doses (160 mg QD and 40 mg QD) and different dosing schedules (continuous and alternating) will be evaluated in order to determine dose and dosing regimen that provides the best benefit to risk for subjects with active CD.

Two doses, 160 mg QD and 40 mg QD, were selected to be evaluated after the initial 160 mg QD 12-week treatment since the 160 mg QD dose is expected to provide the highest level of efficacy, and the 40 mg QD dose is the lowest efficacious dose, which has been demonstrated in subjects with active CD . This is clinically pertinent, since subjects who achieve clinical response or clinical remission after the initial 12-week treatment may require a lower dose than that initially needed for the treatment of moderate to severe CD.

Three different dosing regimens will be evaluated: one continuous dosing regimen (GED-0301 40 mg QD) and two alternating dosing regimens (GED-0301 40 mg QD for 4 weeks on/4 weeks off and GED-0301 160 mg QD for 4 weeks on/4 weeks off). Consequently, these 3 different dosing regimen strategies correspond to incremental increases of 2-fold differences between each of the 3 arms in total IP exposure during the 40-week long-term maintenance treatment. The alternating dosing regimen is supported by findings from Study , in which after 2 weeks of dosing, the majority of subjects had a prolonged clinical improvement up to Week 12, suggesting that patients may not need continuous dosing. This strategy may be more advantageous for longer term treatment in patients with CD, including the potential for a more favorable benefit to risk profile than a continuous dosing regimen.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: 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.

Table 2: Study 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 2: Study 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 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe

Table 2: Study 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

3. OVERALL STUDY DESIGN

3.1. Study Design

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 (Table 4):

- 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 (Table 7).

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-

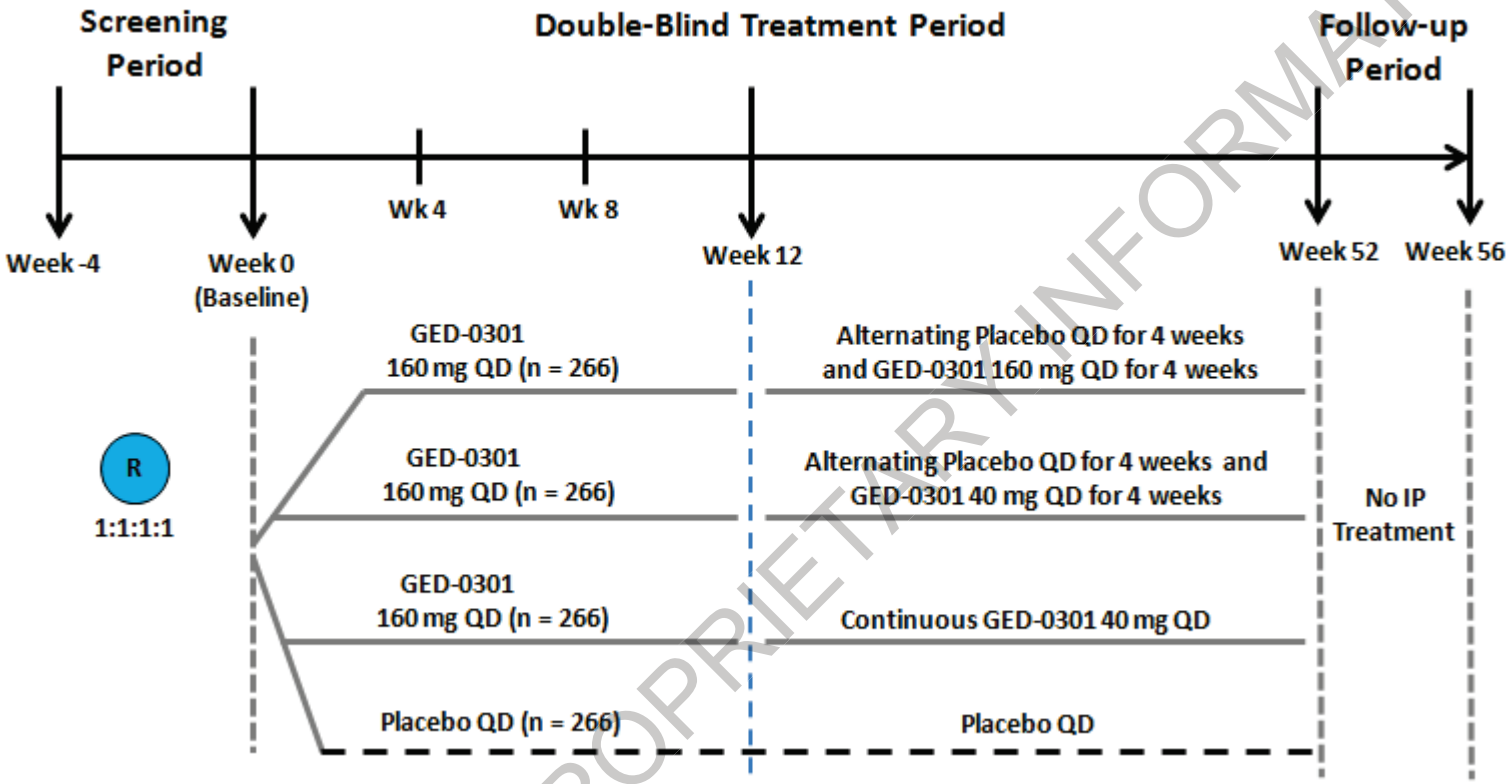
treatment Study, will complete the Early Termination Visit (Section 6.3). The ET Visit should be scheduled as soon as possible after the last dose of IP.

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.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs) and applicable regulatory requirements.

Figure 1: Overall Study Design



IP = Investigational Product; QD = once daily
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 in Table 7. 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 (GED-0301-CD-004), will complete the Early Termination (ET) Visit (Section 6.3).
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 after the last dose of investigational product (IP), then the Follow-up Visit is not required. Subjects entering the Long-term Extension Study will not have the Follow-up Visit.

3.1.1. Study Duration for Subjects

Subjects will spend up to 60 weeks in this study: up to 4 weeks in the Screening Period; 52 weeks in the Double-blind Treatment Period; and 4 weeks in the Follow-up Period.

3.1.2. Early Termination Visit

The Early Termination Visit is based on the subject's withdrawal from the study prior to the Week 52 Visit, with the exception of the Week 12 Visit (whereby the subject will complete the Week 12 Visit). This includes subjects who early escape into the Long-term Active-treatment Study after Week 12. In addition, the Investigator may discontinue the subject from the study at any time based on his/her assessment of clinical efficacy and/or safety. The decision to discontinue a subject remains the responsibility of the treating physician, and will not be delayed or refused by the sponsor. When a subject withdraws or is discontinued from the study, every effort should be made to complete as many safety and efficacy assessments as reasonably appropriate. Refer to the Table of Events (Table 3) for the assessments to be performed at the ET Visit. The ET Visit should be scheduled as soon as possible after the decision is made to permanently discontinue study treatment.

3.1.3. Lost to Follow-up

Subjects will be considered lost to follow-up when they fail to attend study visits without stating an intention to withdraw from the study. The Investigator should show due diligence by documenting in the source documents the steps taken to contact the subject through multiple telephone calls and/or emails and one registered letter. After all reasonable attempts have been made to contact the subject, the subject should be recorded as "lost to follow-up" in the electronic case report form (eCRF).

3.2. End of Study

The End of Study is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study completion for an individual subject is defined as reaching the Week 52 Visit. Subjects not meeting this definition will be considered early termination subjects. 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 (Section 6.3). 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 and do not enter into the Long-term Active-treatment 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.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 1064 subjects with active CD will be enrolled worldwide.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is a male or female ≥ 18 years at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to conducting any study-related assessments/procedures.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject must have a diagnosis of CD with a duration of at least 3 months prior to the Screening Visit.
5. Subject must have ileitis, ileocolitis or colitis, as determined by ileocolonoscopy during screening.
6. Subject must have active CD disease, defined as a CDAI score ≥ 220 and ≤ 450 at screening.
7. Subject must have a 7-day average stool frequency ≥ 3.5 or abdominal pain ≥ 1.5 at screening.
8. Subject must have a total SES-CD ≥ 6 at screening, or the ileum segmental SES-CD ≥ 4 at screening.
9. Subject must have failed or experienced intolerance to at least one of the following: budesonide; systemic corticosteroids; immunosuppressants (eg, AZA, 6-MP, or MTX); or biologics for the treatment of CD (ie, infliximab, adalimumab, certolizumab or vedolizumab). (See Appendix H for details.)
10. Subject must meet the following laboratory criteria
    a. White blood cell count ≥ 3000/mm^3 (≥ 3.0 x 10^9/L)
    b. Platelet count ≥ 100,000/mm^3 (≥ 100 x 10^9/L)
    c. Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 µmol/L)
    d. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) ≤ 2.5 x upper limit of normal (ULN)
    e. Total bilirubin ≤ 2 mg/dL (34 µmol/L), unless the subject has a confirmed diagnosis of Gilbert's Disease
    f. Hemoglobin ≥ 8 g/dL (≥ 4.97 mmol/L)

g. Activated partial thromboplastin time (APTT) ≤ 1.5 x ULN

11. Females of childbearing potential (FCBP)[1] must have a negative pregnancy test at the Screening and Baseline Visits. While on IP and for at least 28 days after taking the last dose of IP, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options described below:

    Option 1: Any one of the following highly effective methods: hormonal contraception (oral[2], injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy

    OR

    Option 2: Male or female condom PLUS 1 additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has a diagnosis of ulcerative colitis (UC), indeterminate colitis, ischemic colitis, microscopic colitis, radiation colitis or diverticular disease-associated colitis.
2. Subject has local manifestations of CD such as abscesses, short bowel syndrome, or other disease complications for which surgery might be indicated or could confound the evaluation of efficacy.
3. Subject had any intestinal resection within 6 months or any intra-abdominal surgery within 3 months prior to the Screening Visit.
4. Subject has an ileostomy or a colostomy.
5. Subject had prior treatment with mycophenolic acid, tacrolimus, sirolimus, cyclosporine, thalidomide or apheresis (eg, Adacolumn®) within 8 weeks prior to the Screening Visit.
6. Subject has received IV corticosteroids within 2 weeks prior to the Screening Visit.
7. Subject has changed or discontinued the dose of oral aminosalicylates within 2 weeks prior to the Screening Visit.
8. Subject has changed or discontinued the dose of oral corticosteroids (prednisone ≤ 20 mg/day or equivalent, budesonide ≤ 9 mg/day) within 3 weeks prior to the Screening Visit.

[1] A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

[2] A female of childbearing potential taking an oral contraceptive may need a backup or an alternative method of birth control based on Investigator judgment as the subject's Crohn's disease may potentially decrease the effectiveness of oral contraceptives.

9. Subject has initiated immunosuppressants (eg, AZA, 6-MP, or MTX) within 12 weeks prior to the Screening Visit and has changed or discontinued the dose of immunosuppressants within 8 weeks prior to the Screening Visit.
10. Subject has received topical GI treatments, such as, 5-aminosalicylic acid (5-ASA) or corticosteroid enemas or suppositories within 2 weeks prior to the Screening Visit.
11. Subject has received bile acid sequestrants (eg, cholestyramine) within 3 weeks prior to the Screening Visit.
12. Subject has changed or discontinued antibiotics used for the treatment of CD (eg, ciprofloxacin, metronidazole), within 2 weeks prior to the Screening Visit.
13. Subject had prior treatment with more than 3 biologics for the treatment of CD (ie, infliximab, adalimumab, certolizumab or vedolizumab).
14. Subject had treatment with a biologic within 8 weeks or 5 elimination half lives, whichever is longer, prior to the Screening Visit. (See Table 8 for elimination half-life timeframes of biologics.)
15. Subject has received total parenteral nutrition within 4 weeks prior to the Screening Visit.
16. Subject has evidence of enteric infection or Clostridium (C.) difficile toxin at the Screening Visit.
17. Subject has a history of any clinically significant neurological, renal, hepatic, gastrointestinal, pulmonary, metabolic, cardiovascular, psychiatric, endocrine, hematological disorder or disease, or any other medical condition that, in the Investigator's opinion, would prevent the subject from participating in the study.
18. Subject has any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she was to participate in the study or confounds the ability to interpret data from the study.
19. Subject is pregnant or breastfeeding.
20. Subject has a history of any of the following cardiac conditions within 6 months prior to the Screening Visit and at any time during the Screening Period, up through the first dose of IP: myocardial infarction, acute coronary syndrome, unstable angina, new onset atrial fibrillation, new onset atrial flutter, second- or third-degree atrioventricular block, ventricular fibrillation, ventricular tachycardia, heart failure, cardiac surgery, interventional cardiac catheterization (with or without a stent placement), interventional electrophysiology procedure, or presence of implanted defibrillator.
21. Subject has a known active current or history of clinically significant bacterial, viral, fungal, or other infections, or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to the Screening Visit and at any time during the Screening Period, up through the first dose of IP.
22. Subject has a history of congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease).

23. Subject has a history of colorectal cancer or a confirmed diagnosis of colorectal dysplasia (with the exception of adenomatous colonic polyps that have been completely resected).
24. Subject has a history of malignancy, except for:
    a. Treated (ie, cured) basal cell or squamous cell in situ skin carcinomas
    b. Treated (ie, cured) carcinoma in situ of the cervix that has been treated at least 5 years prior to the Screening Visit

    Note: History of treated (ie, cured) cancer >10 years before the Screening Visit and without recurrence can be considered based on the nature of the cancer and must be discussed with the sponsor on a case-by-case basis.
25. Subject has received any investigational drug or device within 1 month or 5 elimination half-lives, whichever is longer, prior to the Screening Visit.
26. Subject has a history of alcohol, drug, or chemical abuse within the 6 months prior to the Screening Visit.
27. Subject has a known hypersensitivity to oligonucleotides or any ingredient in the IP.
28. Subject has received prior treatment with GED-0301, or participated in a clinical study involving GED-0301.
29. Subject has strictures with prestenotic dilatation, requiring procedural intervention, or with obstructive symptoms. In addition, subjects with colonic strictures that are not passable with an adult colonoscope, or strictures in the ileum or ileocecal valve that are fibrotic in nature, will be excluded.
30. Subject had prior treatment with biologics for the treatment of CD (approved or investigational), other than infliximab, adalimumab, certolizumab or vedolizumab.

5. TABLE OF EVENTS

Table 3: Table of Events

	Screening Period	Double-blind Treatment Period															Follow-up Period
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**ET[a]**	**16[b]**
Week	**-4**	**0**	**4**	**8**	**12[c]**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52[d]**	**NA**	**Follow-up**
(Visit Window)	**28 days**		**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**NA**	**4 weeks after the last dose of IP (± 3 days)**
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion Criteria	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior / Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior / Concomitant Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[e]	X	X	-	-	X	-	-	-	-	-	-	-	-	-	X	X	X
Contraception Education[f]	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vital Signs / Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Complete Physical Exam	X	-	-	-	X	-	-	-	-	-	-	-	-	-	X	X	-
Limited Physical Exam	-	X	-	-	-	-	-	X	-	-	X	-	-	-	-	-	X
12-lead ECG	X	-	-	-	X	-	-	-	-	-	-	-	-	-	X	X	-

Table 3: Table of Events (Continued)

	Screening Period	Double-blind Treatment Period														Follow-up Period
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**ET[a]**	**16[b]**
Week	**-4**	**0**	**4**	**8**	**12[c]**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52[d]**	**NA**	**Follow-up**
(Visit Window)	**28 days**		**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**NA**	**4 weeks after the last dose of IP (± 3 days)**
Stool Assessment	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical Lab (Hematology)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Lab (Coagulation)[g]	X	X	-	-	X	-	X	-	X	-	X	-	X	-	X	X	X
Clinical Lab (Chemistry)[g]	X	X	-	-	X	-	X	-	X	-	X	-	X	-	X	X	X
Clinical Lab (Urinalysis)[g]	X	X	-	-	X	-	X	-	X	-	X	-	X	-	X	X	X
Efficacy Assessments																	
Subject Diary[h] *Instruct use of electronic device/assess compliance*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDAI[i]	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ileocolonoscopy[j]	X	-	-	-	X	-	-	-	-	-	-	-	-	-	X	X	-

Table 3: Table of Events (Continued)

	Screening Period	Double-blind Treatment Period															Follow-up Period
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**ET[a]**	**16[b]**
Week	**-4**	**0**	**4**	**8**	**12[c]**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52[d]**	**NA**	**Follow-up**
(Visit Window)	**28 days**		**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**(± 3 days)**	**NA**	**4 weeks after the last dose of IP (± 3 days)**
Dosing																	
Dispense IP	-	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-
Return and Count IP	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

CDAI = Crohn's Disease Activity Index; ECG = Electrocardiogram; ET = Early Termination Visit; ; FCBP = females of childbearing potential;
; IP = investigational product; NA = not applicable; ; Sc= Screening;
; V1 = Visit 1;

[a] Subjects who prematurely discontinue from the study at any time other than the Week 12 Visit and prior to the last scheduled study visit, including subjects who enter the Long-term Active-treatment Study (GED-0301-CD-004), will complete the Early Termination (ET) Visit (Section 6.3). The ET Visit should be completed as soon as possible after the decision is made to permanently discontinue the study treatment. Subjects who discontinue from the study at Week 12 will complete the Week 12 Visit.

[b] 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 (Section 6.4). If the ET Visit occurs ≥ 28 days 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.

[c] At the Week 12 Visit and thereafter, until the Week 52 Visit, subjects , will be eligible to early escape into the Long-term Active-treatment Study (GED-0301-CD-004), or may discontinue from the study. In order to be considered for the early escape at . Due to the delay in receiving the hematocrit sample results, beginning at the Week 12 Visit, and throughout the remainder of the study, the CDAI score will be evaluated by the site using the hematocrit results from the previous visit.

[d] Subjects who complete the GED-0301-CD-002 study at the Week 52 Visit, will have the option to enter the Long-term Active-treatment Study. Subjects entering the Long-term Extension Study will not have the Follow-up Visit.

[e] Pregnancy testing will be performed for FCBPs. Serum pregnancy tests will be performed at screening and urine pregnancy will be done at the remaining visits as described in Table 3.

[f] Contraception education is for Females of Child Bearing Potential (FCBP). The Investigator will educate all FCBP about the different options of contraceptive methods and their correct use at Screening and Baseline Visits. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before baseline).

[g] Details pertaining to clinical labs are provided in Section 6.5.3.

[h] The electronic Subject Daily Diary (Section 6.6.1) will be provided to subjects at the Screening Visit. Subject compliance with the completion of diary data should be assessed at each study visit during the Screening and Double-blind Treatment Period.

[i] The screening CDAI (Section 6.6.2) will be based on the Subject Daily Diary data collected during the Screening Period. Note that an abdominal exam is needed for CDAI assessment.

[j] The screening ileocolonoscopy should be performed following confirmation of the subject's eligibility, based on the CDAI score. Follow-up ileocolonoscopies will be done at Week 12 and Week 52 (Section 6.6.5). The ET ileocolonoscopy will not be repeated if performed within 8 weeks of the previous ileocolonoscopy.

6. PROCEDURES

The following procedures/assessments will be conducted according to the schedule indicated in the Table of Events (Table 3).

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days prior to the date of the first dose of IP (study randomization) unless noted otherwise below. Subjects may be allowed to re-screen with approval from the sponsor or designee.

6.1.1. Screening Visit

The following assessments will be performed at the Screening Visit as specified in Table 3, after informed consent has been obtained:

- Demographics including initials, date of birth, sex, race, and ethnicity-if allowed by local regulations
- Complete medical history including all relevant medical conditions diagnosed, and occurring prior to the Screening Visit, should be recorded.
- Prior and concomitant procedures including all procedures occurring ≤ 30 days before the Screening Visit
- Prior and concomitant medication evaluation including all medications (prescription and nonprescription, including vitamins) taken by the subject up to ≤ 30 days prior to the Screening Visit should be recorded. All medications taken by the subject at any time during the study must also be recorded. Other key medications and therapies, such as previous treatment for tuberculosis or relevant diseases, should also be recorded.
- Prior and concomitant CD medications taken by the subject and CD-related procedures performed, at any time prior to and during the study, should be recorded, including the stop dates for medications prohibited in the study.
- Adverse event assessment begins when the subject signs the informed consent form and is assessed continuously throughout the study, until 28 days following the last dose of IP. Refer to Section 10 for details pertaining to AEs.
- Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin β-hCG pregnancy test will be performed at the Screening Visit.
- Contraception education (Section 6.5.6)
- Vital signs including blood pressure, temperature, and heart rate
- Height and weight will be measured and recorded at screening; weight is to be done in street clothes, no shoes

- Complete physical examination (Section 6.5.1)
- 12-lead electrocardiogram (ECG) (Section 6.5.2)
- Stool culture analysis and assessment of Clostridium (C.) difficile toxin will be performed at the Screening Visit. Subjects with stool that is positive for any enteric pathogen or C. difficile toxin at the Screening Visit will be excluded from the study. Subjects who are initially positive for C. difficile toxin may re-screen for the study 8 weeks after the start of therapy, provided that the toxin results for C. difficile are negative (Section 6.5.4).
- Clinical laboratory evaluations will be performed by a central laboratory and are described below. Subject eligibility and clinical laboratory criteria are provided in Section 4.2. One laboratory re-test is allowed after obtaining Medical Monitor approval during the Screening Period. Details pertaining to the central laboratory assessments and panels are included in Section 6.5.3:
  - Hematology panel
  - Chemistry panel
  - Coagulation: prothrombin time (PT), activated partial thromboplastin time (APTT)
  - Urinalysis (dipstick)
    - Microscopic urinalysis (epithelial cells, red blood cells [RBC], white blood cells [WBC], crystals, bacteria, and casts) will be performed only if the dipstick urinalysis is abnormal.
- Subject Daily Diary (Section 6.6.1)
  - The electronic device to record the Subject Daily Diary will be provided to subjects at the Screening Visit. Subjects should enter diary data continuously throughout the study.
- Subjects will receive instructions pertaining to the use of the electronic device and the importance of diary compliance throughout the study.
  - Diary compliance must be assessed throughout the study.

During the Screening Period, the following assessments and procedures will be performed following the Screening Visit and prior to study randomization as specified in the Table of Events (Table 3):

- To be eligible for the study, the subject must have a 7-day average stool frequency score ≥ 3.5 or a 7-day average an abdominal pain score ≥ 1.5 extracted from the subject daily diary, during the Screening Period.
- CDAI score (Section 6.6.2)
  - The CDAI score is a key efficacy assessment in this study and will also be used to determine study eligibility. The subject self-assessment questionnaire items that are included in the CDAI scoring will be extracted from the Subject Daily Diary.

  - The screening CDAI score will be based on subject diaries collected during the Screening Period. If the screening CDAI score is ≥220 and ≤ 450, the subject will proceed with the screening endoscopy.

- Ileocolonoscopy is the type of endoscopy being performed during this study (Section 6.6.5) and the SES-CD is the instrument being used to assess endoscopy (Section 6.6.6).
  - The screening endoscopy should be performed after confirmation of a qualifying CDAI score and a qualifying 7-day average of stool frequency or abdominal pain.
  - The SES-CD is a key efficacy assessment based on endoscopic evaluation. During the study, the SES-CD will be evaluated by both the Investigator and by a central reader blinded to study treatment. The SES-CD score from the central reader will be used to determine study eligibility:
    - Subjects with a SES-CD ≥ 6 at screening, or the ileum segmental SES-CD ≥ 4 at screening, will be eligible for study randomization;
    - Subjects will be randomized upon notification of the qualifying SES-CD.
  - For subjects who will be re-screened, endoscopies performed as part of the original screening period, within 30 days prior to the re-screen date, and reviewed by a central reader, may be used to determine eligibility.

6.2. Double-blind Treatment Period

The subject will begin study treatment upon confirmation of eligibility. For all subsequent visits in the Double-blind Treatment Period, an administrative window of ± 3 days is permitted. The following evaluations will be performed at the frequency specified in Table 3. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Prior and concomitant procedures
- Prior and concomitant medications
- AE evaluation (continuously assessed)
- Electrocardiogram at the Week 12 and Week 52 Visits
- Contraception education (Section 6.5.6) at the Baseline Visit (Visit 2)
- A local urine pregnancy test will be performed on all FCBP. All local urine pregnancy test kits will be provided by the central laboratory. Urine and serum pregnancy tests should be performed if the FCBP has missed a menstrual period or the contraception method has changed at any time during the study.
- Vital signs and weight
- Complete physical examination (Section 6.5.1) at the Week 12 and Week 52 Visits
- Limited physical examination (Section 6.5.1) at the Baseline Visit, Week 24, and Week 36 Visits

- An abdominal examination to assess for the presence of an abdominal mass for the CDAI calculation will be performed at every visit. (Section 6.5.1)
- Clinical laboratory evaluations
- Subject Daily Diary Assessment
- CDAI assessment
  - Due to the delay in receiving the hematocrit sample results, beginning at the Week 12 Visit and thereafter until the Week 52 Visit, the CDAI score will be evaluated by the site using the hematocrit results from the previous visit.
- Ileocolonoscopy for SES-CD should be performed within the Visit window at Week 12 and Week 52.

- Dispense IP: The Principal Investigator (PI), Sub-investigator (Sub-I), or Study Coordinator (SC) should make an effort to witness subjects taking their first dose and record the date and time in the source document record. The IP (four tablets) should be taken QD by the subjects. Subjects will be instructed to take the IP in the morning, 30 minutes before breakfast, with a glass of water, and they will also be instructed to refer to the label for storage instructions.
- Return and count IP: A detailed record of the doses taken and doses missed between visits and at visits should be recorded in the Study Drug Record eCRF and the subject's source documents. Also, a record of the overall number of tablets dispensed and tablets returned at each visit must be maintained in the subject's source documents and recorded in the Drug Accountability eCRF.

6.2.1. Unscheduled Visits

Unscheduled visits, if needed, may occur at any time, in particular for safety reasons (or efficacy reasons) as deemed necessary by the Investigator or site staff, or for any reason that the subject must return to study center as it pertains to the study (eg, to pick up additional or replacement IP). All assessments contained in Table 3 will be made available to the site staff in the Unscheduled Visit eCRF, in order to perform the necessary unscheduled assessments and/or procedures.

6.3. Early Termination

An Early Termination (ET) evaluation will be performed for subjects who are withdrawn from study treatment for any reason at any time other than the Week 12 Visit, including subjects who early escape into the Long-term Active-treatment Study, as soon as possible after the decision to permanently discontinue study treatment has been made. (Subjects who discontinue from study treatment at Week 12 will complete the Week 12 Visit.)

The following evaluations will be performed as specified in Table 3:

- Prior and concomitant procedures
- Prior and concomitant medications
- AE evaluation (continuously assessed)
- 12-lead ECG
- A urine pregnancy test will be performed on all FCBP
- Vital signs and weight
- Complete physical examination
- Clinical laboratory evaluations
- Subject Daily Diary Assessment
- CDAI assessment
- Ileocolonoscopy (if not already done within 8 weeks of the previous colonoscopy)
- Return and count IP

6.4. Follow-up Period

All subjects will be followed for 28 days after the last dose of IP for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.1.

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.

The following evaluations will be performed at Follow-up Visit:

- Prior and concomitant procedures
- Prior and concomitant medications
- AE evaluation
- Vital signs and weight
- A urine pregnancy test will be performed on all FCBP
- Limited physical examination
- Clinical laboratory evaluations
- Subject Daily Diary assessment
- CDAI assessment

6.5. Safety Assessments

6.5.1. Physical Examination

A complete physical examination will include evaluation of the skin, nasal cavities, eyes, ears, abdomen, and respiratory, cardiovascular, neurological, lymphatic, and musculoskeletal systems. Gynecological and urogenital examinations will not be performed unless for cause.

Limited physical examinations will include evaluation of the skin, abdomen, and respiratory, cardiovascular, lymphatic, and musculoskeletal systems.

An abdominal examination will be performed at every visit (including those visits at which a complete or partial physical examination is not being performed) to assess the presence of an abdominal mass for the CDAI calculations.

6.5.2. Electrocardiogram

Subjects will have a 12-lead electrocardiogram (ECG) at the frequency specified in Table 3. Sites are to use their own local ECG machines and the automated ECG readings will be further interpreted by the Investigator by clinically correlating them with the subject's condition. The Investigator's clinical interpretation will be recorded in the eCRF as: normal; abnormal, not clinically significant; or abnormal, clinically significant.

6.5.3. Clinical Laboratory Assessments

Clinical laboratory evaluations will be performed by a central laboratory to include the following laboratory assessments performed at the frequency specified in Table 3:

- 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 (ALT)/serum glutamic pyruvic transaminase (SGPT), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, lactic dehydrogenase (LDH), magnesium, and complement activation (Bb, C3a and C5a).
- Coagulation assessment will include: prothrombin time (PT) and activated partial thromboplastin time (APTT)
- Urinalysis will be done at the central lab and will include specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen. Microscopic urinalysis (bacteria, casts, crystals, epithelial cells, RBC, and WBC) will be performed only if the dipstick urinalysis is abnormal.

Clinical laboratory evaluations are not required to be fasting. However, the site will record whether a clinical laboratory evaluation was fasting or nonfasting on the lab requisition form.

In subjects who develop new changes in liver function tests (eg, ALT or AST > 2 x the upper limit of normal [ULN], or Total Bilirubin [TBL] > 1.5 x ULN with normal baseline values, or ≥ 2 x the baseline values in subjects with abnormal baseline values), repeat testing should be performed within 48 to 72 hours. If abnormalities persist, subjects should be evaluated for causes of new elevations in ALT/AST or TBL (including but not limited to tests for hepatitis, liver imaging, history of Gilbert's syndrome). If there are persistent elevations in ALT or AST and/or TBL then close observation (including laboratory testing as appropriate) should be initiated and treatment could be temporarily interrupted or discontinued. Discontinuation or temporary interruption of study treatment should occur when criteria delineated in Appendix O are met. After treatment discontinuation or interruption, assessments should continue until a return of aminotransferases and/or TBL to normal or baseline levels, or until alternative explanation for the abnormal liver function tests (LFTs) is found.

6.5.4. Stool Assessment

Stool culture analysis and assessment of Clostridium (C.) difficile toxin will be performed at the Screening Visit. Subjects who are stool positive for any enteric pathogen or C. difficile toxin at the Screening Visit, will be excluded from the study. Subjects who are initially positive for C. difficile toxin may re-screen for the study 8 weeks after the start of therapy, provided that the toxin results for C. difficile are negative.

6.5.5. Clinically Significant Abnormal Findings

Clinically significant abnormal findings (clinical laboratory assessments, physical examination, ECG), with exception to the disease under study (CD), identified prior to first dose of IP will be recorded on the eCRF as medical history; clinically significant findings after the first dose of IP will be recorded as AEs.

6.5.6. Contraception Education

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for FCBP. The Investigator will educate all FCBP about the different options of contraceptive methods and their correct use at the Screening and Baseline Visits. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before baseline). A female of childbearing potential taking an oral contraceptive may need a backup or an alternative method of birth control based on Investigator judgment as the subject's Crohn's disease may potentially decrease the effectiveness of oral contraceptives.

There are no data on the effects of GED-0301 in pregnant women and data in animals are limited. Results of the animal and in vitro studies can be found in the IB. All FCBP must use 1 of the approved contraceptive options as described in the eligibility criteria while on IP and for at least 28 days after administration of the last dose of the IP. At the time of study entry, and at any time during the study when a subject's contraceptive measures or ability to become pregnant changes, the Investigator will educate the subject regarding contraception options and correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

6.6. Efficacy Assessments

6.6.1. Subject Daily Diary

During the Screening Visit, an electronic subject diary device will be given to each subject. The subject will receive instructions by the site personnel pertaining to the use of the electronic device and the importance of diary compliance throughout the study. On an ongoing basis, site personnel are expected to provide education and support to the subject about the use of the electronic device. In order to achieve consistent daily diary recording, the subject is instructed by the site personnel (at each visit if necessary) that he/she should enter diary data, each day, continuously throughout the study. Site personnel must also assess the subject's compliance with reporting of the daily diary data entries throughout the study.

The daily diary data will be extracted from the electronic devices and used for calculation of the CDAI efficacy parameters.

The electronic subject diary device will record the following information for the subject to assess his/her CD activity each day:

- Number of liquid or very soft stools per 24 hours
- Abdominal pain/cramps

- General well-being
- Fever over 100°F (37.8°C)
- Use of diphenoxylate/atropine, loperamide, or opiates for diarrhea

6.6.2. Crohn's Disease Activity Index

The CDAI (Appendix D) is the most commonly used measure in clinical studies evaluating the efficacy of new therapies in CD patients with predominantly inflammatory disease (Best, 1976; Sandborn, 2002). The daily diary will assess how CD affects the subject's quality of life and the effect of treatment on CD activity. The CDAI consists of a questionnaire with responses scored numerically and weighted. Scores (range 0 to 600) are then ranked according to severity of the disease. Mild active disease is defined by a score of ≥ 150 and ≤ 219, moderate active disease is defined by a score of ≥ 220 and ≤ 450, and severe disease is defined as a CDAI score > 450. Remission is defined as a CDAI score < 150.

The CDAI consists of 8 variables:

1. Total number of liquid or very soft stools (total for previous 7 days)
2. Abdominal pain/cramps rating (total for previous 7 days)
3. General well-being rating (total for previous 7 days)
4. Total number of listed categories the subject has experienced during the last 7 days
   - Arthritis or arthralgias
   - Iritis/uveitis
   - Erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
   - Anal fissures, fistulae, or abscess
   - Other fistula (specified by site personnel)
   - Fever higher than 100°F or 37.8°C during previous week
5. Antidiarrhea drug therapy taken (eg, loperamide, diphenoxylate, or opiates)
6. Abdominal mass presence
7. Anemia based on hematocrit value entered into formula:
   a. For men = 47 – hematocrit value
   b. For women = 42 – hematocrit value
8. Body weight in kilograms (kg) entered into formula:
   ([standard weight in kg – actual weight kg] / [standard weight in kg]) x 100%

6.6.5. Ileocolonoscopy

All eligible subjects are required to have ileocolonoscopies performed during the Screening Period, Week 12, and Week 52. The screening ileocolonoscopy should be performed if the subject's screening CDAI score is ≥ 220 and ≤ 450.

Subjects who discontinue from the study prior to the Week 52 Visit, will have the ileocolonoscopy done at the ET Visit, if an ileocolonoscopy has not been performed within 8 weeks of the previous ileocolonoscopy.

Video images of all endoscopic procedures will be captured and sent to a qualified centralized reader for calculation of the SES-CD to assess subject eligibility at screening, and to assess efficacy at Weeks 12 and 52. Additionally, the local SES-CD will be collected from the investigational sites. The site will receive a central reader SES-CD report during the Screening Period to determine if the SES-CD inclusion criterion is met.

For subjects at increased risk for colorectal cancer, pan-colonic surveillance with colonoscopy and biopsies should be done according to local guidelines.

6.6.6. Simple Endoscopic Score for CD

The SES-CD (Appendix E) is a validated endoscopic index that closely correlates with the Crohn's Disease Endoscopic Index of Severity and is often considered the standard for endoscopic evaluation in subjects with CD. However, the SES-CD is considered more suitable for clinical trials due to its simplicity and has been widely adopted for this purpose (Daperno, 2004).

6.7. Corticosteroid Tapering Procedure

Subjects are eligible to start corticosteroid tapering beginning at the Week 12 Visit, at the discretion of the Investigator, according to the following schedule:

- For prednisone doses > 10 mg (or equivalent), each week the daily dose is to be tapered by 5 mg until a dose of 10 mg/day is reached, after that each week the daily dose is to be tapered by 2.5 mg until discontinuation.
- For prednisone doses ≤ 10 mg (or equivalent), each week the daily dose is to be tapered by 2.5 mg until discontinuation.
- Subjects receiving budesonide should have their daily dose tapered by 3 mg every 3 weeks.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

GED-0301 will be provided as 40-mg film coated tablets. Placebo will be provided as identically appearing tablets.

7.2. Treatment Administration and Schedule

Subjects will receive GED-0301(160 mg QD) or placebo during the first 12 weeks of the study, followed by one of 3 dose regimens of GED-0301 (40 mg QD or 160 mg QD) or placebo QD, until the end of the study (Week 52 Visit). All subjects will receive 4 tablets daily during the Double-blind Treatment Period. Matched placebo tablets will also be provided. Subjects will be instructed to take the IP in the morning, 30 minutes before breakfast, with a glass of water. Treatment and administration schedule are described in Table 4.

Subjects who consent to participate in the PK substudy will be instructed to bring their IP to the study site where it must be administered after the collection of the predose PK blood sample. When the subject is providing a predose blood draw on the day of a PK substudy visit, the subject must be reminded to provide the date and time of his/her last dose from the day before the visit.

7.2.1. Dose Modification or Interruption

Dose modification is not permitted. Subjects will take their IP as determined by treatment arm. If a subject inadvertently does not take his or her medication for 4 or more consecutive days, Celgene or a Celgene designee must be contacted to decide whether the subject may remain in the study. Any inadvertent interruption in IP schedule will not alter the current dose or dose interval, nor will the length of the study be extended to account for days of IP missed. If a subject is unable or unwilling to restart IP at the prior dose and/or dose interval, then the subject will be evaluated by the Investigator for discontinuation from the Double-blind Treatment Period of the study, and enter the Follow-up Period.

7.2.2. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the IP (GED-0301). Overdose for this protocol, on a per-dose basis, is defined as ingestion of more than 4 tablets of GED-0301 (or matching placebo) within the same calendar day whether by accident or intentionally. Adverse events associated with an overdose must be collected on the AE page of the eCRF (see Section 10.1) for all overdosed subjects, but the overdose itself is not considered an AE. Other required or optional nonstudy drugs intended for prophylaxis of certain side effects, etc, are excluded from this definition.

7.3. Method of Treatment Assignment

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 double-blind, oral GED-0301 or

identically appearing placebo 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.

Subjects will receive double-blind, oral GED-0301 or identically appearing placebo daily (QD) as follows (Table 4):

- 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.

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, AZA, 6-MP, or 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.

At the Week 12 Visit and thereafter, until the Week 52 Visit, subjects who meet the criteria for early escape (Table 7) 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. Subjects who complete the GED-0301-CD-002 Study at the Week 52 Visit will have the option to enter the Long-term Active-treatment Study.

Designated study personnel at the investigational sites will be assigned password-protected, coded identification numbers, which give them authorization to access the IWRS to randomize subjects. The system will present a menu of questions by which the study personnel will identify the subject and confirm eligibility. When all questions have been answered, the IWRS will assign a randomization identification number. Confirmation of the randomization will be sent via fax to the investigational site, Celgene and/or its representative.

During the study visits, the pharmacy or authorized study personnel at the investigational site will dispense coded IP kits in accordance with the randomization number assigned by the IWRS.

Table 4: IP Dispensing Schedule: Double-blind Treatment Period

Week 0 Week 4 Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
GED-0301 160 mg QD	Placebo QD	GED-0301 160 mg QD	Placebo QD	GED-0301 160 mg QD	Placebo QD	GED-0301 160 mg QD	Placebo QD	GED-0301 160 mg QD	Placebo QD	GED-0301 160 mg QD
	Placebo QD	GED-0301 40 mg QD	Placebo QD	GED-0301 40 mg QD	Placebo QD	GED-0301 40 mg QD	Placebo QD	GED-0301 40 mg QD	Placebo QD	GED-0301 40 mg QD
	GED-0301 40 mg QD	GED-0301 40 mg QD	GED-0301 40 mg QD	GED-0301 40 mg QD	GED-0301 40 mg QD	GED-0301 40 mg QD	GED-0301 40 mg QD	GED-0301 40 mg QD	GED-0301 40 mg QD	GED-0301 40 mg QD
Placebo QD	Placebo QD	Placebo QD	Placebo QD	Placebo QD	Placebo QD	Placebo QD	Placebo QD	Placebo QD	Placebo QD	Placebo QD

IP = investigational product; QD= once daily.

7.4. Packaging and Labeling

GED-0301 tablets will be packaged in blister cards and or opaque high density polyethylene (HDPE) bottles fitted with induction seals and tamper evident child resistant caps. The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.5. Investigational Product Accountability and Disposal

The Investigator, or designee, is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying IP shipping order/packing list.

The Investigator, or designee, will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene.

The IP must be stored as indicated on the label. At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access.

Celgene (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6. Investigational Product Compliance

Study personnel will review the instructions printed on the package with the study subjects prior to dispensing the IP. Investigational product will be dispensed as noted in the Table of Events (Table 3). The subjects will be instructed to return the IP containers, including any unused IP, to the study site at each visit for tablet counts and reconciliation. Subjects will be asked whether they have taken their IP as instructed at each study visit. Any problems with IP compliance will be reviewed with the subject. If a subject misses 4 or more consecutive days of dosing, Celgene must be contacted to decide whether dosing should resume or whether the subject should be terminated from the study, and enter into the Follow-up Period.

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 75% of the doses between study visits) should be discussed with Celgene. Compliance is defined as taking between 75% and 120% of dispensed IP.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (prescription and non-prescription), treatments, and therapies taken by the subject from screening throughout their entire participation in the study, including those initiated prior to the start of the study, must be recorded on the subject's source document and on the appropriate page of the eCRF. The dose, unit, frequency, route, indication, date the medication was started, and date the medication was stopped (if not ongoing) must be recorded.

8.1. Permitted Concomitant Medications and Procedures

The following medications are allowed during the study:

- Oral aminosalicylates (SSZ or 5-ASA compounds), provided that treatment has been given at a stable dose for at least 2 weeks prior to the Screening Visit. The dose of oral aminosalicylates must remain stable through the duration of the study or early termination from the study. If oral aminosalicylates have been recently discontinued, treatment must have been stopped at least 2 weeks prior to the Screening Visit.
- Oral corticosteroids, provided that the dose (prednisone ≤ 20 mg/day or equivalent, budesonide ≤ 9 mg/day) has been stable for 3 weeks prior to the Screening Visit, and the dose must remain stable until the subject is eligible to start corticosteroids tapering (Section 6.7). If oral corticosteroids have been recently discontinued, discontinuation must have been completed at least 3 weeks prior to the Screening Visit.
- Immunosuppressants, such as AZA, 6-MP, or MTX, provided that treatment was initiated ≥ 12 weeks prior to the Screening Visit, must be at a stable dose for ≥ 8 weeks prior to the Screening Visit and remain stable for the duration of the study. If immunosuppressants have been recently discontinued, discontinuation must have been completed at least 8 weeks prior to the Screening Visit.
- Antibiotics used for the treatment of CD (eg, ciprofloxacin, metronidazole), provided that the dose has been stable for at least 2 weeks prior to the Screening Visit. If antibiotics have been recently discontinued, discontinuation must have been completed at least 2 weeks prior to the Screening Visit.
- Acetaminophen and low-dose aspirin for cardiovascular prophylaxis are allowed.

Note: The dose of concomitant CD medications noted above may not be increased during the study. No new CD therapy can be prescribed once the subject has been screened in the study.

8.2. Prohibited Concomitant Medications and Procedures

The following concomitant medications are prohibited during the Double-blind Treatment Period of the study, Screening Visit (Visit 1) through the Week 52 Visit, or the ET Visit for subjects who discontinue prematurely during the study:

- Use of any biologics are prohibited during the study and must be discontinued at least 8 weeks or 5 elimination half lives of the biologic, whichever is longer, prior to the Screening Visit. (See Table 8 for elimination half-life timeframes for biologics.)

- Use of bile acid sequestrants (eg, cholestyramine) is prohibited during the study and must be discontinued at least 3 weeks prior to the Screening Visit.
- Use of mycophenolic acid, tacrolimus, sirolimus, cyclosporine, thalidomide or apheresis (eg, Adacolumn®) is prohibited during the study and must be discontinued at least 8 weeks prior to the Screening Visit.
- Use of topical treatments with 5-ASA or corticosteroid enemas or suppositories is prohibited during the study and must be discontinued at least 2 weeks prior to the Screening Visit.
- Use of IV corticosteroids is prohibited during the study and must be discontinued at least 2 weeks prior to the Screening Visit.
- Administration of total parenteral nutrition (TPN) is prohibited and must be discontinued at least 4 weeks prior to the Screening Visit.
- Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) is prohibited.

In addition, subjects who require ileostomy, colostomy, any intestinal resection, or intra-abdominal surgery (related to CD) during the study will be discontinued from treatment.

8.3. Required Concomitant Medications and Procedures

There are no required concomitant medications.

Required procedures include ileocolonoscopy.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

Key elements of the statistical analyses for this study are described in this section; details will be documented in a Statistical Analysis Plan (SAP). The statistical analyses for this study will be the responsibility of the Biostatistics department of the sponsor or its designee.

This study will be conducted as a double-blind study with in-house blinding procedures. For the purpose of the final data analysis, the official, final Week 52 database will not be unblinded until medical/scientific review has been conducted, protocol violations have been identified, the data have been declared final and complete, and a SAP has been written and approved. The randomization schedule will be generated and implemented by the external vendor of the study interactive web response system (IWRS).

9.2. Study Population Definitions

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

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

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

9.3. Sample Size 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.

9.4. Background and Demographic Characteristics

Subjects' age, height, weight, and other continuous variables will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Protocol deviations/violations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

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 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.

9.6.1. Statistical Methods

Binary endpoints will be analyzed by the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. Subjects who have insufficient data for response determination for the time point under consideration will be considered nonresponders for that time point.

9.6.2. Multiplicity

Formal statistical tests are planned for the primary and secondary efficacy endpoints. In order to control the family-wise Type I error rate at the 0.05 level, formal statistical tests will be carried out using a gatekeeping closed testing procedure; details of this procedure, including the endpoints subjected to this procedure and their hierarchy, will be specified in the SAP.

For formal statistical tests that are planned but not performed as a result of the multiplicity adjustment procedure, as well as for any other comparisons that are not subjected to multiplicity adjustment, nominal 2-sided p-values (without adjustment for multiplicity) will be provided as a measure of the strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

9.7. Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, weight, and ECGs. No inferential testing for statistical significance will be performed.

TEAEs will be classified using the MedDRA classification system. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to IP. TEAEs leading to death or to discontinuation from treatment and serious TEAEs will also be tabulated. In the by-subject analysis, a subject having the same event more than once will be counted only once and by greatest severity.

Laboratory, vital signs, weight, and ECG data will be summarized descriptively by time point. In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal ranges at baseline versus postbaseline will be provided for laboratory tests.

9.8. Interim Analysis

No interim analysis is planned for this study.

9.9. Other Topics

[redacted]

9.9.3. Internal Celgene Safety Monitoring During the GED-0301 Program: Role of the Safety Management Team

In addition to ongoing safety monitoring conducted by Investigators and individual study personnel, cumulative and interval blinded AEs, SAEs, discontinuations due to AEs, and abnormal laboratory findings will be reviewed internally by the Safety Management Team (SMT). The review will follow the Council for International Organizations for Medical Sciences, Working Group VI (CIOMS VI) recommendations. The SMT is comprised of lead representatives from multiple Celgene functions engaged in the GED-0301 development program. The scope, conduct, processes, and accountabilities of the SMT are specified in the SMT charter.

9.9.4. External Safety Monitoring: Role of the Independent DMC

Safety monitoring will also be performed by an external, independent Data Monitoring Committee (DMC). The DMC will review unblinded data to evaluate safety during the study. The DMC is comprised of independent physician experts and a statistician for whom there is no identified conflict of interest. The DMC will be convened regularly, at least once a year, or ad hoc at the request of the SMT. The DMC scope, conduct, processes, and accountabilities are specified in a charter.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF. (See Section 7.2.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of daily life (ADLs) minimally or not affected
- No or minimal intervention/therapy may be required

Moderate

- Symptom(s) cause moderate discomfort
- Local or noninvasive intervention indicated
- More than minimal interference with ADLs but able to carry out daily social and functional activities.
- Drug therapy may be required

Severe (could be non-serious or serious)

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention
- Interference with ADLs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)
- Drug therapy is required

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in a female subject of childbearing potential are immediately reportable events.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within at least 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the Investigator at anytime thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant

initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to GED-0301 based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

11. DISCONTINUATIONS

Subjects can discontinue at any time at their own request or at the discretion of the investigator. Reasons for discontinuation of a subject from treatment include but are not limited to:

- Any safety reason (eg, adverse event, laboratory abnormality) which in the opinion of the Investigator or the sponsor (or designee) places the subject at significant risk should he/she continue participating in the study. Please refer to Appendix O for discontinuation criteria related to liver function test abnormalities.
- Surgical procedures related to Crohn's disease (eg, intestinal resection, ileostomy, colostomy, intra-abdominal surgery related to CD)
- Initiation of a biologic medication (eg, TNF-α blockers, natalizumab, vedolizumab, ustekinumab)
- Initiation of immunomodulatory agents for the treatment of CD, such as mycophenolic acid, tacrolimus, sirolimus, cyclosporine, thalidomide or apheresis (eg, Adacolumn®).

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Lack of efficacy
- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified in the eCRF)
- Pregnancy

The reason for discontinuation of treatment should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Lack of efficacy

- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the eCRF)
- Pregnancy

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study **unless,** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject. The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation. Emergency unblinding should only be performed by the Investigator through the IWRS by using an emergency unblinding personal identification number (PIN), and the Investigator should call IWRS for unblinded dose information.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc). In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.

14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Federal Drug Administration [FDA], European Medicines Agency [EMA]), Health Canada and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

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18. APPENDICES

APPENDIX A: TABLE OF ABBREVIATIONS

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
ASA	Aminosalicylic acid
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
AZA	Azathioprine
β-hCG	β-subunit of human chorionic gonadotropin
BUN	Blood urea nitrogen
CD	Crohn's disease
C. difficile	Clostridium difficile
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
C_{max}	Maximum plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CT	Computed tomography
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EFD	Embryo-fetal development
ER-25	Endoscopic response-25

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ER-50	Endoscopic response-50
ET	Early Termination
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Council for Harmonisation
IFN-γ	Interferon-gamma
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
LDA	Longitudinal data analysis
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
6-MP	6-mercaptopurine
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTX	Methotrexate

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PBO	Placebo
PK	Pharmacokinetics
PT	Prothrombin time
QD	Once daily
RBC	Red blood cell
ROW	Rest of World
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMT	Safety Management Team
SOP	Standard operating procedure
SSZ	Sulfasalazine
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TGF-β1	Transforming growth factor- beta 1
TNF-α	Tumor necrosis factor-alpha
UC	Ulcerative colitis
ULN	Upper limit of normal
US	United States
VAS	Visual Analogue Scale
WBC	White blood cell count

APPENDIX B: DEFINITIONS FOR EFFICACY OUTCOMES

Table 7: Definitions for Efficacy Outcomes

Efficacy Outcome	Definition
Clinical Remission	CDAI score < 150
Clinical Response	Decrease from baseline in CDAI ≥ 100 points
Endoscopic Response-50 (ER-50)	A reduction of at least 50% in SES-CD compared with baseline
Endoscopic Response-25 (ER-25)	A reduction of at least 25% in SES-CD compared with baseline
Endoscopic remission	SES-CD ≤ 2
Early Escape Criteria	Beginning at the Week 12 Visit and thereafter, until the Week 52 Visit, subjects will have the option to enter the Long-term Active-treatment Study (GED-0301-CD-004).

APPENDIX C: SUBJECT DAILY DIARY

Date	Number of *Liquid or Very Soft* Stools per 24 hrs	Abdominal Pain/Cramps 0 = None 1 = Mild - aware, but tolerable 2 = Moderate – interferes with usual activities 3 = Severe - incapacitating	General Well Being 0 = Generally Well 1 = Slightly Under Par 2 = Poor 3 = Very Poor 4 = Terrible	Fever over 100 °F (37.8 °C) Y = Yes N = No	Use of diphenoxylate/ atropine, loperamide, or opiates for diarrhea Y = Yes N = No
Sunday ___/___/___ mm dd yy					
Monday ___/___/___ mm dd yy					
Tuesday ___/___/___ mm dd yy					
Wednesday ___/___/___ mm dd yy					
Thursday ___/___/___ mm dd yy					
Friday ___/___/___ mm dd yy					
Saturday ___/___/___ mm dd yy					

APPENDIX D. CROHN'S DISEASE ACTIVITY INDEX (CDAI) SCORE

Crohn's Disease Activity Index (CDAI)

	SUM	X FACTOR	SUBTOTAL
TOTAL # OF *LIQUID* OR *VERY SOFT* STOOLS (total for previous 7 days)	=	x 2	=
ABDOMINAL PAIN/CRAMPS RATING (total for previous 7 days) 0 = None 1 = Mild - aware, but tolerable 2 = Moderate - interferes with usual activities 3 = Severe - incapacitating	=	x 5	=
GENERAL WELL BEING (total for previous 7 days) 0 = Generally Well 1 = Slightly Under Par 2 = Poor 3 = Very Poor 4 = Terrible	=	x 7 1	=
TOTAL # OF LISTED CATEGORIES the patient now has experienced during the last 7 days: A - Arthritis / Arthralgia B - Iritis / Uveitis Erythema Nodosum Pyoderma Gangrenosum C - Aphthous Ulcers D - Anal Fissure, *Fistula*, Abscess E - Other Fistula (specify:) F - Fever over 100 F (37.8 C)	=	x 20	=
ANTIDIARRHEAL DRUG THERAPY (ie: loperamide, diphenoxilate, opiates) 0 = None 1 = Yes	=	x 30	=
ABDOMINAL MASS: 0 = None 2 = Questionable 5 = Definite	=	x 10	=
ANEMIA: (Hct) M = 47 - = F = 42 - =	=	x 6	=
BODY WEIGHT: Std. Wt. = kg Actual Wt. = kg **Std. Wt. - Actual Wt.** x 100 % = ---------> **Std. Wt.**	=	x 1	=
	CDAI SCORE->		

Source: Best, 1976

APPENDIX E. SIMPLE ENDOSCOPIC SCORE FOR CROHN'S DISEASE (SES-CD)

	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Presence and size of ulcers (0-3)						
Extent of ulcerated surface (0-3)						
Extent of affected surfac (0-3)						
Presence and type of narrowings (0-3)						
					SES-CD =	

Definitions of the Simple Endoscopic Score for Crohn's Disease (SES-CD) variables

Variable	SES-CD values			
	0	*1*	*2*	*3*
Size of ulcers	None	Aphthous ulcers (Ø 0.1 to 0.5 cm)	Large ulcers (Ø 0.5 to 2 cm)	Very large ulcers (Ø > 2 cm)
Ulcerated surface	None	< 10%	10-30%	> 30%
Affected surface	Unaffected segment	< 50%	50-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Source: Daperno, 2004.

APPENDIX H. DEFINITION OF CD TREATMENT FAILURE AND INTOLERANCE

Budesonide

- Failure is defined as having signs and symptoms of active disease despite a history of receiving ≥ 8 weeks of treatment with budesonide at doses ≥ 9 grams
- Intolerance: similar to systemic corticosteroids

Systemic corticosteroids

- Failure is defined as having signs and symptoms of active disease despite a history of receiving at least one 4-week course regimen with prednisone ≥ 0.75 mg/kg mg daily orally or equivalent, or 1 week of intravenous corticosteroids. Where regional or local practice standards for the use of steroids in CD differ from this definition of failure, the local or regional standard should be used.
- Intolerance includes, but is not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia and infection.

Immunosuppressants

- Failure is defined as signs and symptoms of active CD despite a history of ≥ 8 weeks of treatment with azathioprine (≥1.5 mg/kg), or 6-mercaptopurine (≥0.75 mg/kg), or methotrexate (≥12.5 mg/week)
- Intolerance includes, but is not limited to nausea, vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia and infection

Biologics

- Failure is defined by:
    - an inadequate initial response (primary nonresponder) after at least 2 doses of induction therapy to: infliximab (doses of ≥5 mg/kg); adalimumab (doses of 160 mg followed by 80 mg); certolizumab (doses of 400 mg) or vedolizumab (doses of 300 mg) at least 2 weeks apart, or
    - recurrence of signs and symptoms, such as worsening of diarrhea, abdominal pain, rectal bleeding, or initiation or increased use of antidiarrheals (secondary nonresponders) after at least 2 doses of maintenance therapy to infliximab (doses of ≥5 mg/kg), adalimumab (doses of 40 mg), certolizumab (doses of 400 mg); or vedolizumab (doses of 300 mg).
- Intolerance to biologics may include fever, chills, rash, flush, itching, hypotension, urticaria, myalgia, arthralgias; which were related to the treatment.

APPENDIX M. HALF LIVES OF BIOLOGICS

Table 8: Elimination Half Lives of Biologics

Biologic	1 Elimination Half Life	5 Elimination HalfLives
Infliximab	10 days	50 days
Adalimumab	20 days	100 days
Certolizumab	14 days	70 days
Vedolizumab	25 days	125 days

* Note: The half-life information was obtained from the package insert of each above-mentioned biologics.

APPENDIX O: CRITERIA FOR TEMPORARY INTERRUPTION OF IP OR STUDY DISCONTINUATION BASED ON LIVER FUNCTION TEST ABNORMALITIES

Criteria for discontinuing or temporarily interrupting study treatment:

- When the baseline values were < 2 x upper limit of normal (ULN), discontinue if alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases to > 5 x baseline values.
- When the baseline values were ≥ 2 x ULN but < 5 x ULN, discontinue if ALT or AST increases to > 3 x baseline values.
- When ALT or AST increase > 2 x baseline values AND the increase is accompanied by a concomitant total bilirubin (TBL) increase to > 2 x baseline values.
- All patients who develop symptoms consistent with hepatic injury (eg, appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [> 5%]) in combination with elevations in liver enzymes.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName:
Title:
Date: Monday, 14 August 2017, 04:16 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Subject	Section(s) Affected	Change / Justification
Endpoint Harmonization	Protocol Summary, (Endpoints, Statistical Methods); Table 2 (Study Endpoints); Section 9.3 (Statistical Considerations, Sample Size and Power Considerations, Table 5 [previously Table 7])	The primary purpose of this protocol amendment is to harmonize and reprioritize the order of endpoints based on regulatory agency feedback. There is now one set of endpoints for all regions. The primary efficacy measure will be clinical remission (defined as a Crohn's Disease Activity Index [CDAI] score < 150) at Week 12. Key secondary efficacy measures will include: clinical remission at Week 52; endoscopic response-50 (ER-50, defined as a reduction of at least 50% compared with baseline in the Simple Endoscopic Score for Crohn's Disease [SES-CD]) at Week 52; clinical response (defined as a decrease from baseline in CDAI ≥ 100 points) at Week 12; steroid-free clinical remission at Week 52; sustained clinical remission at both Week 12 and Week 52; endoscopic response-25 (ER-25, defined as a reduction of at least 25% compared with baseline in SES-CD) at Week 12; and the evaluation of endoscopic remission (defined as SES-CD ≤ 2) at Week 52. The statistical sections were revised to support the hierarchy of endpoints as listed above.
Monitoring of liver function tests	Clinical Laboratory Assessments (Section 6.5.3); Criteria for Temporary Interruption of IP or Study Discontinuation Based on Liver Function Test Abnormalities (Appendix O)	Additional guidance has been added for subjects who develop new changes in liver function tests, including but not limited to repeat testing, evaluation for cause, and close observation. Criteria have also been provided to consider IP interruption or study discontinuation.
Discontinuation Criteria	Discontinuations (Section 11)	Text was updated to specify potential reasons for discontinuation, including but not limited to patient safety (eg, liver function test abnormalities), CD-

Subject	Section(s) Affected	Change / Justification
		related surgeries, initiation of biologics, and initiation of specific CD-related medications. The reasons for treatment and study discontinuation were updated to include lack of efficacy.

The amendment also includes several other minor clarifications and corrections:

Subject	Section(s) Affected	Change / Justification
Medical Monitor contacts	Medical Monitor Contact Information	Contact information now includes details for QuintilesIMS medical monitors by region.
Efficacy Measurements and Outcomes	Section 1.3.2 (Rationale for the Study Design); Appendix B (Definitions for Efficacy Outcomes, Table 7 [previously Table 9])	For simplification purposes, the definition of clinical remission is CDAI < 150 only. While clinical symptoms of stool frequency ≤ 3 and abdominal pain score ≤ 1 are still important endpoints to consider, the term "clinical remission" is now specific to CDAI. The title of Appendix B was changed to match the table title.
Exclusion Criteria	Section 4.3 (Exclusion Criteria)	Exclusion Criterion 24 was revised to further specify exceptions to the malignancy exclusion.
Ileocolonoscopy at Early Termination	Section 5 (Table of Events, Table 3 [previously Table 5]); Section 6.6.5 (Ileocolonoscopy)	Text was revised such that an ileocolonoscopy does not need to be performed at Early Termination if done within 8 weeks of the previous ileocolonoscopy.
Visit Windows	Section 5 (Table of Events, Table 3 [previously Table 5])	A 3-day visit window was added for the follow up visit, and the 3-day visit window was removed for the baseline visit. These updates were made to reflect the intended variance for visit scheduling.
Rescreening requests	Section 6.1 (Screening period)	Text was clarified to indicate that subjects may be allowed to rescreen with approval by the sponsor or designee.
Clostridium difficile testing	Section 6.1.1 (Screening Visit); Section 6.5.4 (Stool Assessment)	The process for C. difficile treatment and testing was revised as 2 months of consecutive negative toxin results are not necessary before rescreening. Subjects who test positive for the C. difficile toxin may

Subject	Section(s) Affected	Change / Justification
		undergo a rescreen 8 weeks after the start of treatment, provided that the toxin results for C. difficile are negative.
Abbreviations	Appendix A (Abbreviations and Specialist Terms, Table 6)	Abbreviations were added for total bilirubin
Criteria for Steroid Failure	Appendix H (Definition of CD Treatment Failure and Intolerance)	Based on feedback from sites, a note was added to clarify that where local or regional practice standards differ from protocol defined steroid failure criteria, local or regional standards should be used.
Typographical	Section 2	
	Section 6.3 (Early Termination)	Ileocolonoscopy was added to the list of assessments as it was inadvertently omitted.
	Throughout	Minor editorial corrections were made throughout the document.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Subject	Section(s) Affected	Change / Justification
Endpoint Hierarchy	Protocol Summary, (Endpoints, Statistical Methods); Tables 2-4 (Study Endpoints); Section 9.3 (Statistical Considerations, Sample Size and Power Considerations, Table 7)	The primary purpose of this protocol amendment is to prioritize the evaluation of clinical remission and endoscopic outcomes as primary and key secondary endpoints. Endpoints are now listed by two regions (United States [US] and Rest of World [ROW]) based on feedback from regulatory authorities. The primary efficacy measure will be clinical remission (defined as an average daily liquid or soft stool frequency ≤ 3 AND abdominal pain score ≤ 1 [US] or a Crohn's Disease Activity Index (CDAI) score < 150 [ROW]) at Week 12. The key secondary efficacy measures will include: the evaluation of endoscopic remission (defined as SES-CD ≤ 2) at Week 52; clinical remission based on CDAI score at Week 12 (US only); clinical remission (based on stool frequency/ abdominal pain and CDAI score for US, and CDAI score for ROW) at Week 52; clinical response (defined as a decrease from baseline in CDAI ≥ 100 points) at Week 12; endoscopic response-50 ([ER-50], defined as a reduction of at least 50% compared with baseline in SES-CD) at Week 52; sustained clinical remission at both Week 12 and Week 52; steroid-free clinical remission at Week 52; endoscopic response-25 ([ER-25], defined as a reduction of at least 25% compared with baseline in SES-CD) at Week 12; The statistical sections were revised to support the hierarchy of endpoints as listed above.

Subject	Section(s) Affected	Change / Justification
Inclusion Criteria	Protocol Summary (Study Population); Section 1.3.1 (Study Rationale and Purpose); Section 4.2 (Inclusion Criteria); Section 6.5.6 (Contraception Education); Section 6.6.4 Ilecolonoscopy; Appendix H (Definition of CD Treatment Failure and Intolerance)	Aminosalicylates were removed as one of the therapies that subjects may have failed to allow for study eligibility. Treatment with aminosalicylates is (a) often insufficient therapy for patients with CD, (b) generally not first-line therapy for patients with CD, and (c) usually prescribed in conjunction with other CD therapy. In addition, failed treatment with biologics was further specified to include infliximab, adalimumab, certolizumab or vedolizumab. Inclusion criteria were updated to clarify that the presence of active CD must be determined by ileocolonoscopy at screening (exclusive of other imaging procedures). Pan-colonic screening surveillance was removed as a requirement for inclusion for subjects with increased risk of colorectal cancer in CD, as there is no clear, global guidance with respect to screening programs for colorectal cancer. However, Section 6.6.4 now includes a statement indicating that subjects with increased risk of colorectal cancer should have undergone a colonoscopy with pan-colonic surveillance biopsies according to local guidelines. Clarification was added to the contraception options for inclusion, as follows: – The inclusion criterion requiring male subjects to use barrier contraception when engaging in sexual activity was removed. Based on additional PK results, there is minimal concern for GED-0301 entering blood at such high concentrations that it could get into semen. – Subjects taking an oral contraceptive may need a backup or alternative method of birth control based on Investigator judgment. The option to change or initiate an additional birth control method may be implemented in cases when the Investigator suspects that the effectiveness of oral contraceptives may be reduced based on the severity and extent of the subject's CD, which may affect gastrointestinal absorption or transit of oral contraceptives. These details were also added to Section 6.5.6 (Contraception Education).
Exclusion Criteria	Protocol Summary (Study Population), Section 4.3 (Exclusion Criteria); Section 6.6.4 (Efficacy Assessments, Ileocolonoscopy);	Exclusion criteria were revised to clarify the protocol requirements with respect to strictures. Strictures with prestenotic dilatation, requiring procedural intervention, or with obstructive symptoms, will be excluded. In addition, subjects with colonic strictures not passable with an adult colonoscope, or strictures in the ileum or ileocecal valve that are fibrotic in nature, will be excluded. Prior use of biologics is now specific to infliximab, adalimumab, certolizumab or vedolizumab.

Subject	Section(s) Affected	Change / Justification
	Section 8.2 (Prohibited Concomitant Medications and Procedures); Appendix M (Half Lives of Biologics, Table 10)	These specifics were added to exclusion criteria related to prior exposure with > 3 biologics. In addition, an exclusion criterion was added to prohibit subjects with prior exposure to biologics for the treatment of CD, approved or investigational, other than infliximab, adalimumab, certolizumab or vedolizumab. The exclusion of subjects with prior exposure to natalizumab was removed, as it is subsumed under the new exclusion criterion. Exclusion criteria now consider the duration of 5 elimination half-lives for biologics, in addition to the 8 week and 1 month wash-out periods for biologics and investigational drugs, respectively. Appendix M (Table 10) was added to provide the half-lives for biologics, ie, infliximab, adalimumab, certolizumab or vedolizumab. This additional detail accounts for the variance in half-lives for different biologics and the need, in these cases, for a longer wash-out period. All bile acid sequestrants are now excluded within 3 weeks prior to screening (previously limited to cholestyramine). This change is reflected in the exclusion criteria and in Section 8.2 (Prohibited Concomitant Medications and Procedures). It is now specified that subjects with a *confirmed* diagnosis of colorectal dysplasia are excluded from the study (with the exception of adenomatous colonic polyps that have been completely resected), in addition to subjects with a history of colorectal cancer. Clarification was added such that known serious infections are excluded without actively screening for exclusion of specific diseases (eg, tuberculosis, atypical mycobacterial disease, herpes zoster, or HIV).

The amendment also includes several other minor clarifications and corrections:

Subject	Section(s) Affected	Change / Justification
Medical Monitor contact	Medical Monitor Contact Information	Address for sponsor contact was updated.

Subject	Section(s) Affected	Change / Justification
Disease/ Compound Background	Protocol Summary (Indication); Section 1.2 (Compound Background)	Information was copied from the compound background section to the indication section to better describe the relationship between transforming growth factor – beta 1 (TGF-β1), Smads, and inflammatory bowel disease (IBD). Other edits were also made achieve consistency across the GED-0301 protocols.
Efficacy Measurements and Outcomes	Protocol Summary (Objectives); Section 1.3.2 (Rationale for the Study Design); Table 2 (Study Objectives); Appendix B (Table of Definitions, Table 9)	Clinical activity is now measured by average daily liquid or soft stool frequency and abdominal pain (as well as CDAI, as previously stated). The definition of clinical remission now includes an average daily liquid or soft stool frequency ≤ 3 AND abdominal pain score ≤ 1 (or CDAI < 150, as previously stated). Definitions for endoscopic response-25 (ER-25) and endoscopic response-50 (ER-50) were added. The terminology of mucosal healing was changed to endoscopic remission based on regulatory agency feedback. For simplification purposes, the definitions for clinical activity and endoscopic outcomes were removed from the primary and secondary objectives. The Week 12 time point was added to the primary objective. The secondary objectives were re-ordered to coincide with the order of the endpoints. Time points were removed from Appendix B (Table 9) as these are no longer part of the definitions for efficacy outcomes. In addition, the early escape definition in Table 9 was updated to indicate eligibility beginning at Week 12.
SES-CD scores	Protocol Summary (Study Design); Section 3.1 (Study Design); Section 7.3 (Method of Treatment Assignment)	To ensure a broad distribution of Crohn's Disease subjects, including those with more extensive and/or significant mucosal disease activity, the total number of subjects with a total SES-CD score ≥6 is targeted to comprise approximately 80% of the study population.
Options for completers and	Protocol Summary (Study Design), Section 3.1	Clarification was added to outline the treatment options for subjects at critical time points in the study. Subjects who complete the Week 52 Visit may enter the Long-term Active-treatment

Subject	Section(s) Affected	Change / Justification
subjects who meet early escape criteria	(Study Design); Figure 1 (footnote); Section 7.3 (Method of Treatment Assignment)	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.
Discontinuation Instructions	Protocol Summary (Study Design); Section 3.1 (Study Design); Figure 1; Section 3.1.2 (Early Termination Visit); Section 3.2 (End of Study); Table 5 (Table of Events); Section 6.3 (Early Termination)	Text was updated to indicate that subjects who discontinue at Week 12 (either because they meet early escape criteria or for any other reason) should complete the Week 12 Visit (instead of the Early Termination Visit). Clarification was also added to emphasize that subjects who prematurely discontinue from the study and do not enter into the Long-term Active-treatment study will have a 4-week Follow-up Visit.
Study Design Schematic	Figure 1	The figure was updated to remove the Week 2 time point and to indicate that no IP treatment is given during the Follow-Up period.
Contact Before Considering Subjects Lost to Follow up	Section 3.1.3 (Lost to Follow-up)	Language was revised such that the subject should be contacted through multiple (previously 3) telephone calls and/or emails and one registered letter before considering the subject lost to follow up.
Abdominal examination	Table 5 (Table of Events) footnote; Section 6.2 (Double Blind Treatment Period); Section 6.5.1 (Physical examination)	Language was added to clarify that an abdominal examination will be performed at every visit (including those visits in which a complete or limited physical exam is not being done) to assess the presence of an abdominal mass for the CDAI calculations. As a result, the statement regarding recording results for complete and physical examinations in source documents only was removed.
Screening procedures	Section 6.1 (Screening Period); Section 6.1.1	Additional provisions were made for screening procedures, including the ability to re-screen upon approval from the sponsor. In addition, for subjects who will be re-screened, endoscopies performed (a) as part of the original screening period, (b) within 30 days prior to the re-screen

Subject	Section(s) Affected	Change / Justification
	(Screening visit)	date, and (c) reviewed by a central reader, may be used to determine eligibility. Microscopic urinalysis also includes crystals and bacteria. These analytes were added to the screening urinalysis be consistent with information in Section 6.5.3 (Clinical Laboratory Assessments).
Clostridium(C.) difficile toxin	Section 6.1.1 (Screening visit), Section 6.5.4 (Stool assessment)	Additional clarity was provided regarding the need for negative *C. difficile* toxin results in order to be eligible for the study.
Hematocrit results	Section 6.2 (Double Blind Treatment Period), Table 5 (Table of Events)	Text was clarified to explain that due to the delay in receiving the hematocrit sample results, the CDAI score will be evaluated using the hematocrit results from the previous visit, beginning at the Week 12 Visit and thereafter until the remainder of the study.
CDAI components	Section 6.6.2 (Crohn's Disease Activity Index)	Under the list of categories the subject has experienced within the past 7 days, erythema nodosum and pyoderma gangrenosum were switched to the category with apthous ulcers (previously in the same category with iritis/uveitis).

Subject	Section(s) Affected	Change / Justification
Compliance with Investigational Product (IP)	Section 7.2.1 (Dose modification or interruption)	Text was revised to state that if a subject inadvertently does not take his or her medication for 4 or more consecutive days, Celgene must be contacted to decide whether the subject may remain in the study.
Overdose	Section 7.2.2 (Overdose)	The timeframe for overdose was revised to be within the same calendar day (instead of a 24 hour time period). Text was added to indicate that overdose also includes more than 4 tablets of matching placebo (in addition to GED-0301).
Concomitant Medications and Procedures	Sections 8.1 & 8.2 (Permitted/Prohibited Concomitant Medications and Procedures)	Timeframes for discontinuation of immunosuppressants (8 weeks) and antibiotics (2 weeks) were added to Section 8.1. A correction was also made to the text so that no new CD therapy can be prescribed once the subject has been screened (instead of randomized) in the study. Text was added to Section 8.2 to indicate that subjects who require ileostomy, colostomy, any intestinal resection, or intra-abdominal surgery (related to CD) during the study, will be discontinued from treatment.
Analysis model	Protocol Summary (Statistical Methods); Section 9.6.1 (Statistical Methods)	Revisions were made to indicate that a longitudinal data analysis (LDA) model will be used to analyze continuous endpoints. In this model, time is treated as a categorical value so that no restriction is imposed on the trajectory of the means over time. In addition, the model adjusts for stratification factors.

Subject	Section(s) Affected	Change / Justification
Male contraception	Section 10.4 (Pregnancy) ; Table 5 (Table of Events) ; Section 6.5.6 (Contraception Education)	Language was removed regarding male contraception, male contraception education, and partners of male subjects who become pregnant. These changes are based on the removal of the inclusion criterion requiring male subjects to use barrier contraception when engaging in sexual activity. Based on additional PK results, there is minimal concern for GED-0301 entering blood at such high concentrations that it could get into semen.
Removal of IVRS	Section 12.2 (Emergency Identification of Investigational Products)	Interactive Voice Response System (IVRS) was removed as an option as Interactive Web Response System (IWRS) is now the only method through which emergency unblinding is performed.
References and Appendices	Section 17 (References); Section 18 (Appendices)	References Boirivant, 2006; ; Liang, 2000; Lewis, 1997; Liu, 2009; Mehrotra, 2012) and appendices (Appendix A, Appendix B, Appendix H, Appendix M, were updated or added as appropriate.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Addition of Inclusion Criteria

The primary purpose of this protocol amendment is to add inclusion criteria

The rationale for this amendment is to align with

Revised Sections:

- Protocol Summary, Study Population
- Section 4.2, Inclusion Criterion # 7
- Section 6.1.1, Screening Procedures

Update of Exclusion Criterion #12

Exclusion Criterion #12 was updated to allow stable doses of antibiotics for the treatment of Crohn's disease (CD), provided that the dose has been stable for at least 2 weeks prior to the Screening Visit. In earlier GED-0301 studies; the use of antibiotics for the treatment of CD was prohibited. Following discussions with clinical investigators, the use of antibiotics may be commonly used as background therapy in subjects with CD and there is no reason to suspect a diminished effect of GED-0301 with its different mechanism of action. This change will support a broader subject population to be studied in this phase 3 trial.

Revised Sections:

- Protocol Summary, Study Population
- Section 4.3, Exclusion Criterion # 12
- Section 8.1, Permitted Concomitant Medications and Procedures
- Section 8.2, Prohibited Concomitant Medications and Procedures

Revision of Exclusion Criterion #13

Exclusion Criterion #13 was revised to exclude subjects with prior treatment with 3 biologics as opposed to 2 biologics.

The rationale is based on the expectation of responsiveness to GED 0301 (with a different mechanism of action then biologic therapy) in terms of clinical and endoscopic benefit, which is expected to be substantively similar in patients having been exposed to either 2 or 3 biologics. The intention, therefore, is to study a broader group of patients with prior biologic exposure. The target of 65% of the subjects in this trial to be naive to prior biologic therapy is unchanged.

Revised Sections:

- Protocol Summary, Study Population
- Section 4.3, Exclusion Criterion # 13

The amendment also includes several other minor clarifications and corrections:

- Update of Inclusion Criterion #9 to allow subjects who are at risk for colorectal cancer to have a colonoscopy within 2 years of the Baseline Visit.
- Update of Exclusion Criterion #22 to clarify that subjects treated with intravenous antibiotics for clinically significant infection prior to the Screening Visit, are excluded from the study. Subjects are permitted oral antibiotics to treat infection prior to the study.
- Update of Exclusion Criterion #24 to clarify that subjects with colonic polyps are permitted in the study.
- Clarification of subjects who require a Follow-up Visit. Subjects who escape into the Long-term Active-treatment Study will have the Early Termination Visit but not the Follow-up Visit.
- Correction of footnotes in Table 3.
- Correction to Table 3 (Week 52 Visit). Investigational product is not dispensed at Week 52.
- Correction to Table 3 (Early Termination Visit). Visit Number is Visit 16.
- Correction to Section 6.6.4, Ileocolonoscopy. Biopsies are not being done in this study. The word “biopsies” is deleted from this section.
- Correction of formatting in Section 6.2.(dispensing of IP).
- Correction to
- Correction to Appendix H, Definition of CD Treatment Failure and Intolerance