DISCLOSURE

REDACTED PROTOCOL AMENDMENT 1

GED-0301-CD-004

PHASE 3, LONG-TERM ACTIVE TREATMENT EXTENSION STUDY OF MONGERSEN (GED-0301) IN SUBJECTS WITH CROHN'S DISEASE

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A PHASE 3, LONG-TERM ACTIVE TREATMENT EXTENSION STUDY OF MONGERSEN (GED-0301) IN SUBJECTS WITH CROHN'S DISEASE

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PROTOCOL SUMMARY

Study Title

A Phase 3, long-term active treatment extension study of mongersen (GED-0301) in subjects with 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, an 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 inflammatory bowel disease (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 long-term safety of oral GED-0301 in subjects with CD

Secondary Objectives (Adult Subjects)

- There are no secondary objectives for adult subjects included in this study.

Secondary Objectives (Adolescent Subjects)

- To evaluate the efficacy of GED-0301 on clinical activity in subjects with CD
- To evaluate long-term endoscopic outcomes of GED-0301 in subjects with CD
- To evaluate the long-term changes in linear growth in response to GED-0301 in subjects with CD

Study Design

This is a Phase 3, double-blind, long-term active treatment extension study to evaluate the long-term safety of GED-0301 for 208 weeks in adult and adolescent subjects with CD who previously participated in either of the following two Phase 3 GED-0301 studies:

- Study GED-0301-CD-002 (Adult Subjects)

- Study GED-0301-CD-003 (Adult and Adolescent Subjects)

The purpose of this study is to assess long-term safety data of GED-0301 for a period of up to 208 weeks in adult subjects (ie, ≥ 18 years of age) who participated in the core Phase 3 GED-0301-CD-002 and GED-0301-CD-003 studies and adolescent subjects (ie, 12 to 17 years of age) who participated in the core Phase 3 GED-0301-CD-003 study.

Although all subjects will receive active treatment, this study is double-blinded for the entire 208 weeks for the purpose of preserving the blind of the subject's treatment allocation in the initial, core Phase 3 GED-0301 study.

Subjects from Study GED-0301-CD-002 who completed the study at Week 52, or who met the early escape criteria (Appendix H) and were discontinued during the time period beginning at Week 12 through Week 52, may be eligible to enter this study.

Subjects from Study GED-0301-CD-003 who completed the study at Week 12 may also be eligible to enter this long-term active treatment study.

Subjects who discontinued Studies GED-0301-CD-002 or GED-0301-CD-003 prior to the Week 12 Visit are not eligible for this study.

The study will consist of 3 periods:

- Screening Period – up to 4 weeks (ie, 1 day to 28 days depending on when long-term active treatment is available for the subject at the study center)
- Long-term Active Treatment Period – 208 Weeks (Week 0 to Week 208)
- Follow-up Period – 4 weeks (ie, no investigational product [IP] taken)

At Week 12, subjects will be evaluated to determine if they should be discontinued from the study based on clinical criteria. Subjects, who meet the following criteria, will be discontinued from the study at Week 12:

Subjects who complete this study through Week 208 will have a 4-week Follow-up Visit. Subjects who prematurely discontinue treatment from the study at any time prior to Week 208 will have an Early Termination (ET) Visit and a 4-week Follow-up Visit. The ET Visit should be scheduled as soon as possible after the last dose of IP. If the ET Visit occurs 28 days after the last dose of IP, then the Follow-up Visit is not required.

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

Study Population

The study population will consist of subjects with CD who previously participated in either of the following two Phase 3 GED-0301 studies (ie, GED-0301-CD-002 or GED-0301-CD-003) and have completed at least through the Week 12 Visit in each of those studies.

Length of Study

Subjects may participate for a maximum of 216 weeks with 3 different study periods: up to 4 weeks in the Screening Period; 208 weeks in the Long-term Active Treatment Period; and 4 weeks in the Follow-up Period.

The long-term active-treatment period of 208 weeks may be shortened in regions where GED-0301 becomes commercially available prior to study completion.

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 analysis, as prespecified in the protocol, whichever is the later date. There are no secondary objectives or endpoints for the adult subjects in this study.

Study Treatments

Subjects will receive blinded-active GED-0301 treatment during the 208-week Long-term Active Treatment Period. GED-0301 will be provided as 40-mg gastro-resistant, delayed release, pH-dependent tablets or matching placebo tablets in blister cards. All 160 mg once daily treatments are taken as four 40 mg tablets once daily in this study. See Appendix G for a full description of Study GED-0301-CD-004 treatment assignments. Subjects will be instructed to take 4 tablets in the morning, 30 minutes before breakfast with a glass of water.

This study is currently designed as a double-blind, active treatment extension study. Nevertheless, it should be noted that the dose regimens of GED-0301 could be adjusted or changed during this long-term active treatment study or this study could be changed to an open-label study, based on new information learned from any of the ongoing GED-0301 clinical studies. Any modifications to the dose regimens would be changed through a protocol amendment, which would require regulatory health authority and ethics committee approvals prior to implementation.

Overview of Key Safety Assessments

- Adverse events (AEs)
- Vital signs
- Physical examination
- Body weight
- Height (adolescent subjects)
- Electrocardiograms (ECGs)
- Clinical laboratory safety evaluations
- Pregnancy tests

Overview of Key Efficacy Assessments (Adolescent Subjects)

- Simple Endoscopic Score for Crohn's Disease (SES-CD) for previous GED-0301-CD-003 subjects
- Crohn's Disease Activity Index (CDAI)
- Pediatric Crohn's Disease Activity Index (PCDAI)

Statistical Methods

The safety and efficacy analyses will be based on the long-term active treatment population, which will consist of all subjects who enter the long-term active treatment study and receive at least 1 dose of IP during the long-term active treatment study.

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. The 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 post-baseline will be provided for laboratory tests.

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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. While the onset of CD is most commonly in the third decade of life, CD presents in up to 30% of cases before the age of 20 years (Kelsen, 2008) and around 10% of cases develop before the age of 17 years.

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, and is about 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. Childhood-onset CD is more severe and complicated and typically exhibits a higher disease activity index score compared to late-onset or adult CD (Mamula, 2003; Van Limbergen, 2008; Pigneur, 2010). The GI presentation of CD both in adults and in children is dependent mainly on the location and extent of disease involvement. The anatomic location of CD is similar in older children (> 8 years) and adults, most commonly involving the terminal ileum or any small bowel (Van Limbergen, 2008; Markowitz, 2009).

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 by 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 that are associated with intestinal activity (eg, peripheral arthritis, erythema nodosum, aphthous ulcers) and manifestations not associated with intestinal activity (eg, pyoderma gangrenosum, uveitis, spondylarthropathy, primary sclerosing cholangitis); non CD-specific autoimmune diseases which represent only a major susceptibility to autoimmunity (eg, hemolytic anemia, vitiligo, diabetes mellitus, psoriasis); and CD-related complications due to metabolic or anatomical abnormalities (eg, thromboembolic events, osteopathy, nephrolithiasis) (Vavricka, 2011; Bernstein, 2005). Adolescent patients with CD commonly present with growth and pubertal delay. In addition, extraintestinal manifestations of CD such as erythema nodosum, mouth ulceration, and large-joint lesions that may occur years before any GI symptoms develop have been observed in children with CD (Mamula, 2003). Additionally, patients with a history of prolonged 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 and integrin antagonists. 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). For pediatric patients, consensus guidelines recommend that corticosteroids should not be administered as maintenance therapy mainly due to the corticosteroid-induced adrenal suppression that can occur as early as one week after starting therapy. In children, where growth retardation can ensue, exclusive enteral nutrition (EEN) is employed as first-line therapy in some centers before using steroids with 5-aminosalicylates (Kansal, 2013; Ruemmele, 2014). However, compliance with long-term EEN treatment is challenging.

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 to respond to a TNF-α blocker, the response to a second TNF-α blocker is significantly lower. The TNF-α blockers may predispose patients 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 adolescent and adult patients with CD who do not respond, lose response, or are intolerant to currently available treatments.

1.2. Compound Background

Mongersen (GED-0301) inhibits the expression of Smad7, a key regulatory modulator of transforming growth factor-beta 1 (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 ulcerative colitis (UC) (Monteleone, 2001). This is associated with a reduction in phosphorylated (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 interferon-gamma [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 GED-0301.

GED-0301 is an investigational medicinal product in clinical development for the treatment of CD and UC. GED-0301 is an antisense oligodeoxynucleotide (21-mer) that is complementary to the sequence of the 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 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 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, an 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.

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 (Study GED-301-01-09) 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 conducted to date with GED-0301: 1) Study GED-301-01-09, a Phase 1, dose-escalating, safety and PK study of 7 days of oral administration of GED-0301 in subjects with active CD; 2) Study GED-301-01-11, a Phase 2 randomized, double-blind, placebo-controlled, dose-finding study of GED-0301 in subjects with active CD; and 3) Study GED-301-02-11, 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. A total of 139 subjects with CD have been exposed to oral GED-0301 at doses ranging from 10 mg to 160 mg, from 7 days to 14 days. 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 rationale and purpose of this study is to offer both adult and adolescent subjects in the core Phase 3 GED-0301 studies (ie, GED-0301-CD-002 and GED-0301-CD-003) an option to receive long-term extension treatment with GED-0301 and to obtain extended long-term safety data of GED-0301 for a period of up to 4 years.

As an additional safety measure, this study incorporates the Week 12 clinical criteria for discontinuing subjects who did not achieve a minimum level of improvement by Week 12. Subjects, who meet the following criteria, will be discontinued from the study at Week 12:

This study is double-blinded for the entire 208 weeks for the purpose of preserving the blind of the subject's treatment allocation in the initial, core Phase 3 GED-0301 study.

Subjects who have completed and achieved clinical improvement through Week 52 in Study GED-0301-CD-002, and through Week 12 in Study GED-0301-CD-003, are eligible to participate in this study. This would allow subjects who achieved a clinical benefit an opportunity to continue with GED-0301 treatment for an additional 208 weeks.

Likewise, subjects who did not achieve clinical improvement, met the early escape criteria (Appendix H) and were discontinued in Study GED-0301-CD-002 during the time period beginning at Week 12 through Week 52, and subjects who did not achieve clinical improvement, but were completers in Study GED-0301-CD-003 at Week 12 are also eligible to participate in this study. These subjects, who experienced an insufficient clinical improvement, are provided with the option for continued treatment at the highest maintenance dose of GED-0301 that will be used in the Phase 3 program.

In addition, placebo (PBO)-treated subjects from these Phase 3 studies are offered the opportunity to receive active GED-0301 for the first time, and potentially receive a clinical benefit.

This study will provide long-term active treatment up to 4 years and provide extended long-term safety data for oral GED-0301.

1.3.2. Rationale for the Study Design

The study is designed as a long-term extension study of up to 4 years for subjects who previously participated in the core GED-0301-CD-002 or GED-0301-CD-003 Phase 3 studies. This study is double-blinded for the purpose of preserving the blind of the subject's treatment allocation in the initial, core Phase 3 GED-0301 study, and providing extended long-term safety data for GED-0301 in these CD subjects through Year 4.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

The reason for the selected dose, schedule, and treatment regimens is to provide subjects with the same or highest blinded-active GED-0301 treatments based on whether the subject received clinical improvement from the core Phase 3 GED-0301 study treatment.

Subjects in Study GED-0301-CD-002 who achieved clinical improvement on their previous blinded-active GED-0301 treatment during the time period from Week 12 through Week 52 will continue on their same treatment for 208 weeks. Subjects who were receiving: 1) alternating GED-0301 40 mg once daily (QD) for 4 weeks, followed by PBO QD for 4 weeks; or 2) alternating GED-0301 160 mg QD for 4 weeks, followed by PBO QD for 4 weeks; or 3) continuous 40 mg GED-0301 QD will continue on this same blinded-active treatment regimen. Subjects who did not achieve clinical improvement on their above-mentioned, blinded-active GED-0301 treatments will be switched in this study to alternating GED-0301 160 mg QD for 4 weeks, followed by PBO QD for 4 weeks, through Week 208, as their long-term blinded-active treatment.

Subjects in Study GED-0301-CD-003 who achieved clinical improvement at Week 12 will receive alternating PBO QD for 4 weeks, followed by GED-0301 160 mg QD for 4 weeks, through Week 208 in this study. Subjects who did not achieve clinical improvement in Study GED-0301-CD-003 at Week 12 will receive alternating GED-0301 160 mg QD for 4 weeks, followed by PBO QD for 4 weeks, through Week 208, as their long-term blinded-active treatment in this study.

Previously blinded PBO-treated subjects who achieved clinical improvement will receive alternating GED-0301 160 mg QD for 4 weeks, followed by PBO QD for 4 weeks, through Week 208 in this study. Previously blinded PBO-treated subjects who did not achieve clinical improvement will receive blinded-active GED-0301 160 mg QD induction therapy for the first 12 weeks, and will continue on alternating PBO QD for 4 weeks, followed by GED-0301 160 mg QD for 4 weeks, through Week 208, as their long-term blinded-active treatment in this study.

Previously blinded GED-0301-treated subjects who did not achieve clinical improvement and PBO-treated subjects will be provided with the highest maintenance dose of GED-0301 being tested in the Phase 3 program, using the clinical safety and efficacy data from the prior GED-0301 studies (GED-301-01-09; GED-301-01-11; and GED-301-02-11). From these data, the highest maintenance treatment regimen tested will be alternating GED-0301 160 mg QD for 4 weeks, followed by PBO QD for 4 weeks. This study allows the subjects from the previously blinded treatment groups a chance to achieve clinical improvement by receiving extended GED-0301 therapy at this highest maintenance dose regimen.

All subjects will receive blinded-active GED-0301 treatment for 208 weeks, and the full description of the treatment assignments are detailed in Appendix G.

This study is currently designed as a double-blind, active treatment extension study. Nevertheless, it should be noted that the dose regimens of GED-0301 could be adjusted or changed during this long-term active treatment study or this study could be changed to an open-label study, based on new information learned from any of the ongoing GED-0301 clinical studies. Any modifications to the dose regimens would be changed through a protocol amendment, which would require regulatory health authority and ethics committee approvals prior to implementation.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives – Adult Subjects (≥ 18 years of age at screening of core study) from GED-0301-CD-002 and GED-0301-CD-003

Primary Objective
The primary objective of the study is to evaluate the long-term safety of oral GED-0301 in subjects with Crohn's disease (CD).
Secondary Objective(s)
There are no secondary objectives for adult subjects in this study.

Table 2: Study Endpoints – Adult Subjects from GED-0301-CD-002 and GED-0301-CD-003

Endpoint	Name	Description	Timeframe
Primary	Safety	• The evaluation of safety of GED-0301, assessed by the type, frequency and severity of adverse events, and its relationship to investigational product (IP), discontinuation due to adverse events, and clinically significant changes in electrocardiograms (ECGs), vital signs, and/or laboratory findings	Through Week 208 and 4 weeks postdose (as specified in the Table of Events, Table 5)
Secondary	Not applicable	• Secondary endpoints are not included for adult subjects in this study.	Not applicable

Table 2: Study Endpoints – Adult Subjects from GED-0301-CD-002 and GED-0301-CD-003 (Continued)

Endpoint	Name	Description	Timeframe

CD = Crohn's disease; ; ECG = electrocardiogram;

IP = investigational product;

Table 3: Study Objectives – Adolescent Subjects (12-17 years of age, inclusive) from GED-0301-CD-003

Primary Objective
The primary objective of the study is to evaluate the long-term safety of oral GED-0301 in adolescent subjects with Crohn's disease (CD).
Secondary Objective(s)
• To evaluate the efficacy of GED-0301 on clinical activity in subjects with CD • To evaluate long-term endoscopic outcomes of GED-0301 in subjects with CD • To evaluate the long-term changes in linear growth in response to GED-0301 in subjects with CD

Table 4: Study Endpoints – Adolescent Subjects from GED-0301-CD-003

Endpoint	Name	Description	Timeframe
Primary	Safety	The evaluation of safety of GED-0301, assessed by the type, frequency and severity of adverse events, and its relationship to investigational product (IP), discontinuation due to adverse events, and clinically significant changes in electrocardiograms (ECGs), vital signs, and/or laboratory findings	Through Week 208 and 4 weeks postdose (as specified in the Table of Events, Table 6)
Secondary	Efficacy	The proportion of subjects with clinical remission[a] at Week 40.	Week 40
		The proportion of subjects with endoscopic remission defined as SES-CD ≤ 2 at Week 40	Week 40
		The proportion of subjects who have clinical remission[a], defined as a PCDAI ≤ 10 points at Week 40.	Week 40
		The change from baseline (GED-0301-CD-003) in weight, height, body mass index (BMI), and height velocity z-scores (adjusted for chronological age) at Week 40	Week 40

Table 4: Study Endpoints – Adolescent Subjects from GED-0301-CD-003 (Continued)

Endpoint	Name	Description	Timeframe

Table 4: Study Endpoints – Adolescent Subjects from GED-0301-CD-003 (Continued)

Endpoint	Name	Description	Timeframe

BMI = body mass index; ; ECG = electrocardiogram;

IP = investigational product; PCDAI = Pediatric Crohn's Disease Activity Index; ; SES-CD = Simple Endoscopic Score for Crohn's Disease.

[a] Clinical remission is defined as the following: 1) Average daily liquid or soft stool frequency ≤ 3 AND abdominal pain score ≤1; 2) CDAI score < 150. Clinical remission using both definitions will be used for the analysis of this endpoint.

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a Phase 3, double-blind, long-term active treatment extension study to evaluate the long-term safety of GED-0301 for 208 weeks in adult and adolescent subjects with CD who previously participated in either of the following two Phase 3 GED-0301 studies:

- Study GED-0301-CD-002 (Adult Subjects)
- Study GED-0301-CD-003 (Adult and Adolescent Subjects)

The purpose of this study is to assess long-term safety data of GED-0301 for a period of up to 208 weeks in adult subjects (ie, ≥ 18 years of age) who participated in the core Phase 3 GED-0301-CD-002 and GED-0301-CD-003 studies and adolescent subjects (ie, 12 to 17 years of age) who participated in the core Phase 3 GED-0301-CD-003 study.

Although all subjects will receive active treatment, this study is double-blinded for the entire 208 weeks for the purpose of preserving the blind of the subject's treatment allocation in the initial, core Phase 3 GED-0301 study.

Subjects from Study GED-0301-CD-002 who completed the study at Week 52, or who met the early escape criteria (Appendix H) and were discontinued during the time period beginning at Week 12 through Week 52, may be eligible to enter this study.

Subjects from Study GED-0301-CD-003 who completed the study at Week 12 may also be eligible to enter this long-term active treatment study.

Subjects who discontinued Studies GED-0301-CD-002 or GED-0301-CD-003 prior to the Week 12 Visit are not eligible for this study.

This long-term active treatment study will consist of 3 periods:

- Screening Period – up to 4 weeks (ie, 1 day to 28 days depending on when long-term active treatment is available for the subject at the study center)
- Long-term Active Treatment Period – 208 Weeks (Week 0 to Week 208)
- Follow-up Period – 4 weeks (ie, no IP taken)

At Week 12, subjects will be evaluated to determine if they should be discontinued from the study based on clinical criteria. Subjects, who meet the following criteria, will be discontinued from the study at Week 12:

Subjects who complete this study through Week 208 will have a 4-week Follow-up Visit. Subjects who prematurely discontinue treatment from the study at any time prior to Week 208

will have an ET Visit and a 4-week Follow-up Visit. The ET Visit should be scheduled as soon as possible after the last dose of IP. If the ET Visit occurs 28 days after the last dose of IP, then the Follow-up Visit is not required.

At the Screening Visit in this study, all subjects who meet the inclusion criteria and do not meet the exclusion criteria will be eligible and assigned a subject identification number using a centralized interactive response technology system (IRTS).

Once the subject is eligible and registered in the IRTS, the assigned treatment is based on the clinical improvement criteria from the core GED-0301 study to determine the subject's course of treatment for the entire 208 weeks in this study.

Please note that all 160 mg once daily treatments are taken as four 40 mg tablets once daily in this study. That is, GED-0301-treated subjects who received one 160 mg tablet QD in GED-0301-CD-003 will receive four 40 mg tablets QD in this study.

Subjects will receive the following treatments:

Previously-treated GED-0301 subjects in Study GED-0301-CD-002 who met the clinical improvement criteria at Week 52:

- Will continue to receive their same blinded treatment, which will be:
  - Alternating PBO QD for 4 weeks and GED-0301 40 mg QD for 4 weeks, or
  - Continuous GED-0301 40 mg QD, or
  - Alternating PBO QD for 4 weeks and GED-0301 160 mg QD for 4 weeks.

Previously-treated GED-0301 subjects in Study GED-0301-CD-003 who met the clinical improvement criteria at Week 12:

- Will receive blinded treatment with:
  - Alternating PBO QD for 4 weeks and GED-0301 160 mg QD for 4 weeks.

Previously-treated PBO subjects who met the clinical improvement criteria:

  - At Week 52 in Study GED-0301-CD-002; or
  - At Week 12 in Study GED-0301-CD-003

- Will receive blinded treatment with:
  - Alternating GED-0301 160 mg QD for 4 weeks and PBO QD for 4 weeks.

Previously-treated GED-0301 or PBO subjects who did not meet the clinical improvement criteria:

  - At Week 12 through Week 52 in Study GED-0301-CD-002; or
  - At Week 12 in Study GED-0301-CD-003

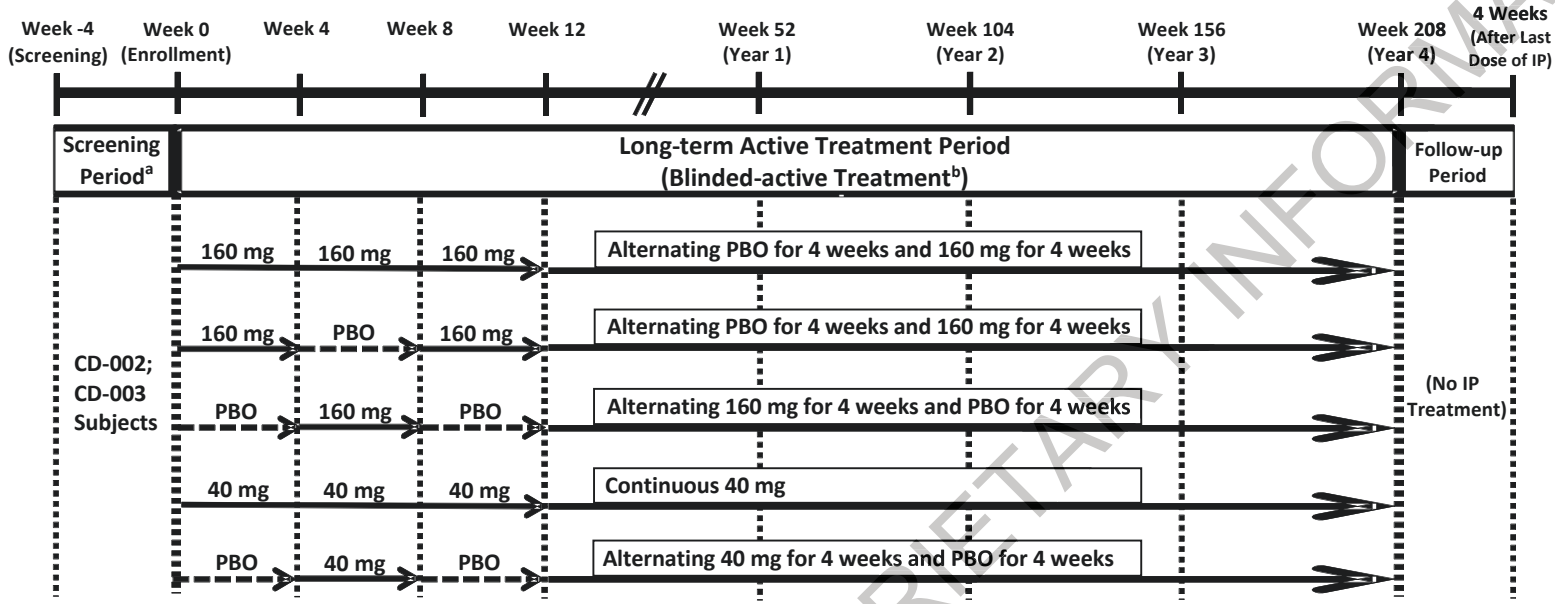
- Will receive blinded treatment with:
  - Alternating GED-0301 160 mg QD for 4 weeks and PBO QD for 4 weeks, if the subject previously received GED-0301 treatment, or
  - GED-0301 160 mg QD for 12 weeks, if the subject previously received PBO, and after Week 12, subjects will receive alternating PBO QD for 4 weeks and GED-0301 160 mg QD for 4 weeks.

See the overall study design (Figure 1) for an overview of the study blinded-active treatments. All subjects will receive a blinded-active GED-0301 treatment regimen for 208 weeks, and the full descriptions of the treatment assignments are detailed in Appendix G.

This study is currently designed as a double-blind, active treatment extension study. Nevertheless, it should be noted that the dose regimens of GED-0301 could be adjusted or changed during this long-term active treatment study or this study could be changed to an open-label study, based on new information learned from any of the ongoing GED-0301 clinical studies. Any modifications to the dose regimens would be changed through a protocol amendment, which would require regulatory health authority and ethics committee approvals prior to implementation.

The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 1: Overall Study Design



IP = investigational product; PBO = placebo

[a] The Screening Period can be 1 day to 28 days in duration depending on when active treatment (IP) is available for the subject.

[b] Blinded-active treatment is provided to eligible subjects from the core GED-0301-CD-002 and GED-0301-CD-003 studies during the Long-term Active Treatment Period for 208 weeks.

Please note: All 160 mg once daily treatments are taken as four 40 mg tablets once daily in the study. See Appendix G for full description on the Study GED-0301-CD-004 treatment assignments. No IP is dispensed during the Follow-up Period.

3.2. Study Duration for Subjects

Subjects may participate for a maximum of 216 weeks with 3 different study periods: up to 4 weeks in the Screening Period; 208 weeks in the Long-term Active Treatment Period; and 4 weeks in the Follow-up Period.

The long-term active-treatment period of 208 weeks may be shortened in regions where GED-0301 becomes commercially available prior to study completion.

3.3. 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 analysis, as prespecified in the protocol, whichever is the later date. There are no secondary objectives or endpoints for the adult subjects in this study and therefore no secondary analysis for adult subjects.

4. STUDY POPULATION

4.1. Number of Subjects

The number of subjects planned to enroll into this long-term active treatment study will be based on the number of eligible subjects who enter from the GED-0301-CD-002 and GED-0301-CD-003 studies, which include subject participation worldwide.

4.2. Inclusion Criteria

4.2.1. Inclusion Criteria for Adult Subjects

Adult subjects must satisfy the following criteria to be screened and enrolled in the study:

1. Subject is a male or female ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject must have completed through the Week 12 Visit in the core GED-0301 study **AND** either:
   - Completed participation through the last study treatment visit at Week 52 in Study GED-0301-CD-002 or at Week 12 in Study GED-0301-CD-003

   OR

   - Met the "early escape criteria" (Appendix H) and were discontinued beginning at the Week 12 Visit in Study GED-0301-CD-002.
5. Females of childbearing potential (FCBP)[1] must have a negative pregnancy test at screening and enrollment (Visits 1 and 2). FCBP must either practice true abstinence[2] from heterosexual contact or use one of the approved contraceptive options as described below while on IP and for at least 28 days after taking the last dose of IP:

[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] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Option 1: Any one of the following highly effective methods: hormonal contraception (oral[3], 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

4.2.2. Inclusion Criteria for Adolescent Subjects

Adolescent subjects must satisfy the following criteria to be screened and enrolled in the study:

1. Subject is a male or female, was 12 to 17 years of age at the time of obtaining assent/informed consent in the core GED-0301-CD-003 study and must affirmatively agree to participate in this study by signing an assent with a parent/legal guardian who can understand and voluntarily sign an ICF. Adolescent subjects who turn age 18 by the screening visit for the GED-0301-CD-004 study must also understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
2. Subject is able to swallow the IP tablets.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements, and a parent or legal guardian is willing to supervise adherence to the protocol requirements.
4. Subject must have completed through the Week 12 Visit in Study GED-0301-CD-003.
5. Females of childbearing potential (FCBP)[4] must have a negative pregnancy test at screening and enrollment (Visits 1 and 2). FCBP must either practice true abstinence[5]

[3] 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.

[4] 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).

[5] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

from heterosexual contact or use one of the approved contraceptive options as described below while on IP and for at least 28 days after taking the last dose of IP:

Option 1: Any one of the following highly effective methods: hormonal contraception (oral[6], 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 (Adult and Adolescent Subjects)

The presence of any of the following will exclude an adult and adolescent subject from screening and enrollment:

1. Subject had experienced a serious adverse event (SAE) related to the IP while participating in the core Phase 3 GED-0301 study.
2. Subject has any continuing serious medical condition, laboratory abnormality, or psychiatric illness that occurred while participating in the core Phase 3 GED-0301 study.
3. Subject has or had a flare or worsening of CD that, in the opinion of the Investigator, would not be in the best interest for the subject to participate in this long-term active treatment study.
4. Subject has initiated biologic agents, such as TNF-α blockers or integrin antagonists while, or after participating in the core Phase 3 GED-0301 study.
5. Subject has been diagnosed with colorectal cancer or confirmed diagnosis of colorectal dysplasia (with the exception of adenomatous colonic polyps that have been completely resected) while participating in the core Phase 3 GED-0301 study.
6. Subject has a newly diagnosed malignancy while participating in the core Phase 3 GED-0301 study. (However, subject may be allowed to enter into this study on a case by case basis after discussion with the Sponsor.)
7. Subject is pregnant or breastfeeding.
8. Subject has been newly diagnosed with substance abuse.
9. Subject has any new condition that may put the subject at risk or confound the ability to interpret data from the study.
10. Subject has developed a known hypersensitivity to oligonucleotides, GED-0301 or any ingredient in the IP.

[6] 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.

5. TABLE OF EVENTS

Table 5: Table of Events for Adult Subjects (Years 1 to 4)

	Screening Period	Long-term Active Treatment Period (Year 1)													
Visit Number	**1[a]**	**2[a]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Week	**-4 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Window	**-28 to 0 days**	**Day 0**	**(± 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)**
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion Criteria	X	X[a]	-	-	-	-	-	-	-	-	-	-	-	-	-
Safety Assessments [b]															
Prior / Concomitant Medications and Procedures	X[a]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X[a]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X[a]	X[a]	-	-	-	-	-	X	-	-	-	-	-	-	X
Contraception Education	X[a]	X[a]	-	-	-	-	-	X	-	-	-	-	-	-	X
Vital Signs / Weight	X[a]	X[a]	X	X	X	X	-	X	-	X	-	X	-	X	X
Complete Physical Examination	X[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Limited Physical Examination	-	X[a]	-	-	X	-	-	X	-	-	-	-	-	-	X
12-lead ECG	X[a]	-	-	-	X	-	-	X	-	-	-	-	-	-	X
Clinical Lab (Hematology) [c]	X[a]	X[a]	X	X	X	-	-	X	-	-	-	X[c]	-	-	X
Clinical Lab (Chemistry) [c]	X[a]	X[a]	-	-	X	-	-	X	-	-	-	X[c]	-	-	X
Clinical Lab (Coagulation) [c]	X[a]	X[a]	-	-	X	-	-	X	-	-	-	X[c]	-	-	X
Clinical Lab (Complement Activation Factor) [c]	X[a]	X[a]	-	-	X	-	-	X	-	-	-	X[c]	-	-	X
Clinical Lab (Urinalysis) [c]	X[a]	X[a]	-	-	X	-	-	X	-	-	-	X[c]	-	-	X

Table 5: Table of Events for Adult Subjects (Years 1 to 4) (Continued)

	Screening Period	Long-term Active Treatment Period (Year 1)													
Visit Number	**1[a]**	**2[a]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Week	**-4 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Window	**-28 to 0 days**	**Day 0**	**(± 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)**
Dosing															
Dispense IP	-	X	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

Table 5: Table of Events for Adult Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 2)												
Visit Number	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Visit Window	**(± 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)**
Safety Assessments [b]													
Prior / Concomitant Medications and Procedures	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
Pregnancy Test	-	-	-	-	-	-	X	-	-	-	-	-	X
Contraception Education	-	-	-	-	-	-	X	-	-	-	-	-	X
Vital Signs / Weight	X	-	X	-	X	-	X	-	X	-	X	-	X
Complete Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	-
Limited Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	X
12-lead ECG	-	-	-	-	-	-	-	-	-	-	-	-	X
Clinical Lab (Hematology)	-	-	-	-	-	-	X	-	-	-	-	-	X
Clinical Lab (Chemistry)	-	-	-	-	-	-	X	-	-	-	-	-	X
Clinical Lab (Coagulation)	-	-	-	-	-	-	X	-	-	-	-	-	X
Clinical Lab (Complement Activation Factor)	-	-	-	-	-	-	X	-	-	-	-	-	X
Clinical Lab (Urinalysis)	-	-	-	-	-	-	X	-	-	-	-	-	X

Table 5: Table of Events for Adult Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 2)												
Visit Number	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Visit Window	**(± 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)**
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

Table 5: Table of Events for Adult Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 3)												
Visit Number	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Visit Window	**(± 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)**
Safety Assessments [b]													
Prior / Concomitant Medications and Procedures	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
Pregnancy Test	-	-	-	-	-	X	-	-	-	-	-	-	X
Contraception Education	-	-	-	-	-	X	-	-	-	-	-	-	X
Vital Signs / Weight	-	X	-	-	-	X	-	-	-	X	-	-	X
Complete Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	-
Limited Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	X
12-lead ECG	-	-	-	-	-	-	-	-	-	-	-	-	X
Clinical Lab (Hematology)	-	-	-	-	-	X	-	-	-	-	-	-	X
Clinical Lab (Chemistry)	-	-	-	-	-	X	-	-	-	-	-	-	X
Clinical Lab (Coagulation)	-	-	-	-	-	-	-	-	-	-	-	-	X
Clinical Lab (Complement Activation Factor)	-	-	-	-	-	-	-	-	-	-	-	-	X
Clinical Lab (Urinalysis)	-	-	-	-	-	X	-	-	-	-	-	-	X

Table 5: Table of Events for Adult Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 3)												
Visit Number	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Visit Window	**(± 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)**
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

Table 5: Table of Events for Adult Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 4)														Follow-up Period
Visit Number	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**	**ET[g]**	**55**
Week	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**208**	**NA**	**FU**
Visit Window	**(± 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 Last Dose of IP (± 3 days)**
Safety Assessments [b]															
Prior / Concomitant Medications and Procedures	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
Pregnancy Test	-	-	-	-	-	-	X	-	-	-	-	-	X	X	X
Contraception Education	-	-	-	-	-	-	X	-	-	-	-	-	X	X	-
Vital Signs / Weight	-	-	X	-	-	-	X	-	-	-	X	-	X	X	X
Complete Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Limited Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
12-lead ECG	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Clinical Lab (Hematology)	-	-	-	-	-	-	X	-	-	-	-	-	X	X	X
Clinical Lab (Chemistry)	-	-	-	-	-	-	X	-	-	-	-	-	X	X	X
Clinical Lab (Coagulation)	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Clinical Lab (Complement Activation Factor)	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Clinical Lab (Urinalysis)	-	-	-	-	-	-	X	-	-	-	-	-	X	X	X

Table 5: Table of Events for Adult Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 4)														Follow-up Period
Visit Number	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**	**ET[g]**	**55**
Week	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**208**	**NA**	**FU**
Visit Window	**(± 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 Last Dose of IP (± 3 days)**
Dosing															
Dispense IP	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	-

; ECG = electrocardiogram; ; ET = early termination; ; FU = follow-up; IP = investigational product; NA = not applicable;

[a] Visit 1 and Visit 2 of the GED-0301-CD-004 study may be combined into a single visit, and may be combined with the last study visit from the core GED-0301 study. See Section 6.1.1 for further detailed information. If Visit 1 and Visit 2 from this study and the last study visit from the core GED-0301 study are done separately but all are within a 14-day period, certain evaluations do not need to be repeated. See Sections 6.1.1 and 6.2.

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

[g] Subjects who discontinue the study prior to Week 208 will have the ET Visit (ie, on the date of the last dose of IP, or very soon after the date of the last dose of IP), and have the Follow-up Visit, 28 days after the last dose of IP ± 3 days. If the ET Visit occurs 28 days after the last dose of IP, then the Follow-up Visit is not required.

Table 6: Table of Events for Adolescent Subjects (Years 1 to 4)

	Screening Period	Long-term Active Treatment Period (Year 1)													
Visit Number	**1[a]**	**2[a]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Week	**-4 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Window	**-28 to 0 days**	**Day 0**	**(± 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)**
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion Criteria	X	X[a]	-	-	-	-	-	-	-	-	-	-	-	-	-
Safety Assessments[b]															
Prior / Concomitant Medications and Procedures	X[a]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X[a]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X[a]	X[a]	-	-	-	-	-	X	-	-	-	-	-	-	X
Contraception Education	X[a]	X[a]	-	-	-	-	-	X	-	-	-	-	-	-	X
Vital Signs / Weight	X[a]	X[a]	X	X	X	X	-	X	-	X	-	X	-	X	X
Height (measured using a stadiometer)	X[a]	-	-	-	-	-	-	X	-	-	-	X	-	-	X
Complete Physical Examination	X[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Limited Physical Examination	-	X[a]	-	-	X	-	-	X	-	-	-	-	-	-	X
12-lead ECG	X[a]	-	-	-	X	-	-	X	-	-	-	-	-	-	X
Clinical Lab (Hematology)	X[a]	X[a]	X	X	X	X	X	X	X	X	X	X	-	-	X
Clinical Lab (Chemistry)	X[a]	X[a]	-	-	X	-	-	X	-	-	-	X	-	-	X
Clinical Lab (Coagulation)	X[a]	X[a]	-	-	X	-	-	X	-	-	-	X	-	-	X
Clinical Lab (Complement Activation Factors)	X[a]	X[a]	-	-	X	-	-	X	-	-	-	X	-	-	X
Clinical Lab (Urinalysis)	X[a]	X[a]	-	-	X	-	-	X	-	-	-	X	-	-	X

Table 6: Table of Events for Adolescent Subjects (Years 1 to 4) (Continued)

	Screening Period	Long-term Active Treatment Period (Year 1)													
Visit Number	**1[a]**	**2[a]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Week	**-4 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Window	**-28 to 0 days**	**Day 0**	**(± 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)**
Efficacy Assessments															
Subject Daily Diary	X	X[a]	X	X	X	X	X	X	X	X	X	X			
Crohn's Disease Activity Index (CDAI) [c]	-	X[a]	X	X	X	X	X	X	X	X	X	X			
Pediatric CDAI [c]	-	-	-	-	-	-	-	X	-	-	-	X			
ESR performed at the site, for Pediatric CDAI	-	-	-	-	-	-	-	X	-	-	-	X			
Ileocolonoscopy and SES-CD	-	-	-	-	-	-	-	-	-	-	-	X			
Dosing															
Dispense IP	-	X	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

Table 6: Table of Events for Adolescent Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 2)												
Visit Number	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Visit Window	**(± 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)**
Safety Assessments [b]													
Prior / Concomitant Medications and Procedures	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
Pregnancy Test	-	-	-	-	-	-	X	-	-	-	-	-	X
Contraception Education	-	-	-	-	-	-	X	-	-	-	-	-	X
Vital Signs / Weight	X	-	X	-	X	-	X	-	X	-	X	-	X
Height (measured using a stadiometer)	-	-	-	-	-	-	X	-	-	-	-	-	X
Complete Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	-
Limited Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	X
12-lead ECG	-	-	-	-	-	-	-	-	-	-	-	-	X
Clinical Lab (Hematology)	-	-	-	-	-	-	X	-	-	-	-	-	X
Clinical Lab (Chemistry)	-	-	-	-	-	-	X	-	-	-	-	-	X
Clinical Lab (Coagulation)	-	-	-	-	-	-	X	-	-	-	-	-	X
Clinical Lab (Complement Activation Factors)	-	-	-	-	-	-	X	-	-	-	-	-	X
Clinical Lab (Urinalysis)	-	-	-	-	-	-	X	-	-	-	-	-	X

Table 6: Table of Events for Adolescent Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 2)												
Visit Number	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Visit Window	**(± 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)**
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

Table 6: Table of Events for Adolescent Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 3)												
Visit Number	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Visit Window	**(± 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)**
Safety Assessments [b]													
Prior / Concomitant Medications and Procedures	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
Pregnancy Test	-	-	-	-	-	X	-	-	-	-	-	-	X
Contraception Education	-	-	-	-	-	X	-	-	-	-	-	-	X
Vital Signs / Weight	-	X	-	-	-	X	-	-	-	X	-	-	X
Height (measured using a stadiometer)	-	-	-	-	-	X	-	-	-	-	-	-	X
Complete Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	-
Limited Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	X
12-lead ECG	-	-	-	-	-	-	-	-	-	-	-	-	X
Clinical Lab (Hematology)	-	-	-	-	-	X	-	-	-	-	-	-	X
Clinical Lab (Chemistry)	-	-	-	-	-	X	-	-	-	-	-	-	X
Clinical Lab (Coagulation)	-	-	-	-	-	-	-	-	-	-	-	-	X
Clinical Lab (Complement Activation Factors)	-	-	-	-	-	-	-	-	-	-	-	-	X
Clinical Lab (Urinalysis)	-	-	-	-	-	X	-	-	-	-	-	-	X

Table 6: Table of Events for Adolescent Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 3)												
Visit Number	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**
Week	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Visit Window	**(± 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)**
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

Table 6: Table of Events for Adolescent Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 4)														Follow-up Period
Visit Number	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**	**ET[f]**	**55**
Week	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**208**	**NA**	**FU**
Visit Window	**(± 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 Last Dose of IP (± 3 days)**
Safety Assessments [b]															
Prior / Concomitant Medications and Procedures	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
Pregnancy Test	-	-	-	-	-	-	X	-	-	-	-	-	X	X	X
Contraception Education	-	-	-	-	-	-	X	-	-	-	-	-	X	X	-
Vital Signs / Weight	-	-	X	-	-	-	X	-	-	-	X	-	X	X	X
Height (measured using a stadiometer)	-	-	-	-	-	-	X	-	-	-	-	-	X	X	-
Complete Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Limited Physical Examination	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
12-lead ECG	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Clinical Lab (Hematology)	-	-	-	-	-	-	X	-	-	-	-	-	X	X	X
Clinical Lab (Chemistry)	-	-	-	-	-	-	X	-	-	-	-	-	X	X	X
Clinical Lab (Coagulation)	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Clinical Lab (Complement Activation Factors)	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Clinical Lab (Urinalysis)	-	-	-	-	-	-	X	-	-	-	-	-	X	X	X

Table 6: Table of Events for Adolescent Subjects (Years 1 to 4) (Continued)

	Long-term Active Treatment Period (Year 4)														Follow-up Period
Visit Number	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**	**ET[f]**	**55**
Week	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**208**	**NA**	**FU**
Visit Window	**(± 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 Last Dose of IP (± 3 days)**
Dosing															
Dispense IP	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; ; ESR = erythrocyte sedimentation rate; ET = early termination; ; FU = follow-up; IP = investigational product; NA = not applicable, PCDAI = Pediatric Crohn's Disease Activity Index; SES-CD = Simple Endoscopic Score for Crohn's Disease.

[a] Visit 1 and Visit 2 of the GED-0301-CD-004 study may be combined into a single visit, and may be combined with the last study visit from the core GED-0301 study. See Section 6.1.1 for further detailed information. If Visit 1 and Visit 2 from this study and the last study visit from the core GED-0301 study are done separately but all are within a 14-day period, certain evaluations do not need to be repeated. See Sections 6.1.1 and 6.2.

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

[c] Note that an abdominal examination is needed for CDAI, and PCDAI assessments.

[f] Subjects who discontinue the study prior to Week 208 will have the ET Visit (ie, on the date of the last dose of IP, or very soon after the date of the last dose of IP), and have the Follow-up Visit, 28 days after the last dose of IP ± 3 days. If the ET Visit occurs 28 days after the last dose of IP, then the Follow-up Visit is not required.

6. PROCEDURES

The following procedures/assessments will be conducted according to the schedule indicated in the Table of Events. Table 5 refers to the Table of Events for adult subjects, and Table 6 refers to the Table of Events for adolescent subjects.

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 enrollment) unless noted otherwise below. The duration of the Screening Period depends on when active treatment (ie, IP/study drug) is available for the subject at the study center.

6.1.1. Screening Visit

Visits may be completed separately, or combined into a single visit in the following scenarios:

- The Screening Visit 1 from this study and the last study visit from the core GED-0301 study may be combined and completed on the same day.
- The Screening Visit 1 and the Enrollment Visit 2 from this study may be combined and completed on the same day, if the GED-0301-CD-004 study drug is available for the subject at the study center.
- The Screening Visit 1 and the Enrollment Visit 2 from this study and the last study visit from the core GED-0301 study may be combined and completed on the same day, if the GED-0301-CD-004 study drug is available for the subject at the study center.

If 2 visits are combined into a single visit in this study, or if 2 or 3 visits are combined into a single visit from both studies (ie, the core GED-0301 study and this extension GED-0301 study), any visit assessments/procedures which are normally done separately at multiple visits are done only once and not repeated.

If the Screening Visit 1 from this study and the last study visit from the core GED-0301 study are both done separately but are within 14 days of each other, the following Visit 1 clinical and laboratory evaluations do not need to be repeated if they were done at the last study visit from the core GED-0301 study: hematology, chemistry, coagulation, complement activation factors, urinalysis, pregnancy test, ECG, and physical examination.

If all 3 visits (ie, Visit 1 and Visit 2 from this study and the last study visit from the core GED-0301 study) are done separately but all are within a 14-day period, the following clinical, and laboratory evaluations do not need to be repeated if they were done at the last study visit from the core GED-0301 study: hematology, chemistry, coagulation, complement activation factors, urinalysis, pregnancy test, , ECG, physical examination, CDAI,

After informed consent has been obtained, the following assessments will be performed at or following Screening Visit 1 and prior to study enrollment, as specified in the Table of Events

(Table 5 or Table 6), if they were not already completed at the last study visit from the core GED-0301 study:

- Demographics including initials, date of birth, gender, race, and ethnicity (if allowed by local regulations).
- Inclusion/exclusion criteria: Subjects must meet all inclusion criteria (Section 4.2) and must not have any of the conditions specified in the exclusion criteria (Section 4.3) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study (eg, if a female subject does not require pregnancy testing and birth control because of a hysterectomy, the date of the hysterectomy must be included in the core study's medical history).
- Prior and concomitant procedures evaluation: All procedures occurring at or after Screening Visit 1 should be recorded.
- Prior and concomitant medications evaluation: All ongoing medications from the core GED-0301 study will be electronically carried forward and should not be re-recorded in Prior and Concomitant Medications electronic case report form (eCRF) in this study. However, any new medications (prescription and nonprescription, including vitamins) taken by the subject at and after Screening Visit 1 or at any time during this study must be recorded. Additional instructions can be found in the eCRF Completion Guidelines.
- Adverse event evaluation: Adverse event (AE) 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. All ongoing AEs from the core GED-0301 study will be electronically carried forward and should not be re-recorded in the AE eCRF in this study. However, any new AEs or worsening AEs which occur at and after Screening Visit 1 or at any time during this study must be recorded. Worsening of a subject's CD should be considered as worsening of the disease under study, and should not be captured as an AE unless it meets any of the criteria of a serious adverse event (SAE). Refer to Section 10 for details pertaining to AEs. Additional instructions can be found in the eCRF Completion Guidelines.
- Pregnancy test: A pregnancy test is required for all female subjects of childbearing potential. A local urine pregnancy test will be performed at Screening Visit 1, if not done at the last study visit from the core GED-0301 study. All local urine pregnancy test kits will be provided by the central laboratory. Urine and confirmatory serum pregnancy (ie, serum pregnancy test of the beta-subunit of human chorionic gonadotropin [β-hCG]) tests should be performed if the FCBP has missed a menstrual period, or the contraception method has changed at any time during the study.
- Contraception education (Section 6.5.5)
- Vital signs and weight: Vital signs, including seated blood pressure, temperature, and heart rate will be taken. Weight (to be done in street clothes, no shoes) will also be measured and recorded, if not done at the last study visit of the core GED-0301 study.
- Height, only for the adolescent subjects and should be measured using a stadiometer.

- Complete physical examination (Section 6.5.1), if not done at the last study visit of the core GED-0301 study.
- 12-lead electrocardiogram (ECG) (Section 6.5.2), if not done at the last study visit of the core GED-0301 study.
- Clinical laboratory evaluations will be performed by a central laboratory and will include the following laboratory assessments, if not done at the last study visit of the core GED-0301 study. Details pertaining to the central laboratory assessments and panels are included in Section 6.5.3:
  - Hematology panel
  - Chemistry panel
  - Coagulation panel
  - Complement activation factor panel
  - Urinalysis panel
- Subject daily diary (Section 6.6.1)
  - A new or updated electronic device diary will be provided to the subject at Screening Visit 1 for the collection of the subject daily diary in this study.
  - Subject will receive instructions pertaining to the use of the electronic device and the importance of diary compliance through Week 40 for an adolescent subject.
  - In order to achieve consistent diary recording, the subject is instructed by the site personnel (at each visit if necessary) that he/she is required to enter diary data, each day, through Week 40 for an adolescent subject.
  - Site staff must assess the subject's diary compliance through Week 40 for an adolescent subject.

6.2. Treatment Period

The subject will begin study treatment upon confirmation of all eligibility and availability of IP at the study center. All subsequent visits after the Enrollment Visit (which is the Visit 2/Week 0 Visit) are scheduled based on the date of the Visit 2/Week 0 Visit ± 3 days, according to the timeframes specified in Table 5 for adult subjects and Table 6 for adolescent subjects. The Follow-up Visit is scheduled 28 days (4 weeks) after the date of the last dose of IP ± 3 days.

The following Visit 2 clinical and laboratory evaluations do not need to be repeated if they were completed within 14 days of Visit 1: hematology, chemistry, coagulation, complement activation factors, urinalysis, pregnancy test, and physical examination.

The following Visit 2 clinical, laboratory evaluations do not need to be repeated if they were completed within 14 days of the last study visit from the core GED-0301 study (or within 14 days of the combined Visit 1 and last study visit from the core GED-0301 study): hematology, chemistry, coagulation, complement activation factors, urinalysis,

pregnancy test, , physical examination, CDAI,

The following evaluations will be performed at the frequency specified in Table 5 for adult subjects and Table 6 for adolescent subjects. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Inclusion/exclusion criteria: Subjects must meet all inclusion criteria (Section 4.2) and must not have any of the conditions specified in the exclusion criteria (Section 4.3) to qualify for participation in the study, up through the day of enrollment at the Enrollment Visit 2.
- Prior and concomitant procedures evaluation (continuously assessed)
- Prior and concomitant medications evaluation (continuously assessed)
- AE evaluation (continuously assessed)
- Pregnancy test: A local urine pregnancy test will be performed on all FCBP at the Enrollment Visit, and the visits identified in Table 5 and Table 6. A local urine test will be performed by the site at the Enrollment Visit, prior to administration of IP, to ensure an immediate, negative test result. 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.
- Contraception education
- Vital signs and weight
- Height, only for the adolescent subjects and should be measured using a stadiometer.
- Physical examinations: The following physical examinations will be performed based on the Table of Events as specified in Table 5 and Table 6 and as described in Section 6.5.1:
  - Complete physical examination
  - Limited physical examination
    (A limited physical examination is not done, if Visit 1 and Visit 2 are combined and/or completed on the same day as the last study visit in the core GED-0301 study. In this case, only a complete physical examination is done.)
  - Abdominal examination
    (An abdominal examination for the abdominal mass assessment is completed for the CDAI, and PCDAI calculations when physical examinations are not done.)
- 12-lead ECG
- Clinical laboratory evaluations (Section 6.5.3) according to the timeframes in Table 5 and Table 6

  - Hematology panel
  - Chemistry panel
  - Coagulation panel
  - Complement activation factor panel
  - Urinalysis panel
- Subject daily diary assessment (Section 6.6.1):
  - Adolescent subjects complete subject daily diary through Week 40
- Crohn's Disease Activity Index (CDAI) assessment (Section 6.6.2)
  -
    - Adolescent subjects will be assessed for the CDAI through Week 40
- Pediatric Crohn's Disease Activity Index (PCDAI) assessment (Section 6.6.4)
  - The PCDAI score is an efficacy assessment only for adolescent subjects and is a self-assessment questionnaire. The subject self-assessment questionnaire items that are included in the PCDAI scoring will be extracted symptom data obtained from the subject at the scheduled visit.
- Erythrocyte sedimentation rate (ESR) only for adolescent subjects, performed locally at the site (Section 6.6.4.1) for the PCDAI calculation

- Dispense IP: The IP will be dispensed to the subject as specified in Table 5, Table 6 and Section 7.2. The subject should take the first dose in the office at the study site at the Enrollment Visit 2, and be witnessed by the site personnel. However, the IP can be dispensed to the subject at a combined Visit 1 and 2, if the GED-0301-CD-004 IP is available for the subject at the study center.
    - **The Principal Investigator, Sub-investigator or Study Coordinator should actually witness, if possible, the subject taking the first dose, and record date and time in the source document record.** The IP, four 40-mg tablets or matching placebo, should be taken by the subject once daily during the Long-term Active Treatment Period. Subjects will be instructed to take 4 tablets 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 5 for adult subjects and Table 6 for adolescent subjects 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 Visit

The Early Termination (ET) Visit evaluations will be performed for subjects who are early withdrawn from treatment, prior to Week 208, for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

These subjects who discontinue the treatment prior to Week 208 will have the ET Visit (ie, on the date of the last dose of IP, or very soon after the date of the last dose of IP), and have the Follow-up Visit, 28 days after the last dose of IP ± 3 days. If the ET Visit occurs 28 days after the last dose of IP, then the Follow-up Visit is not required.

The following evaluations will be performed at the frequency specified in the Table of Events (Table 5) for adult subjects and (Table 6) for adolescent subjects.

- Prior and concomitant procedures evaluation
- Prior and concomitant medications evaluation
- AE evaluation
- Pregnancy test: A local urine pregnancy test will be performed on all FCBP.
- Contraception education
- Vital signs and weight
- Height, only for the adolescent subjects and should be measured using a stadiometer
- Complete physical examination (Section 6.5.1)
- 12-lead ECG
- Clinical laboratory evaluations
  - Hematology panel
  - Chemistry panel
  - Coagulation panel
  - Complement activation factor panel
  - Urinalysis panel

- Return and count IP (Section 6.2)

6.4. Follow-up Period

All subjects will be followed for 28 days after the last dose of IP for the safety evaluations (eg, AE reporting) as well as for 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 discontinue the treatment prior to Week 208 will have the ET Visit (ie, on the date of the last dose of IP, or very soon after the date of the last dose of IP), and have the Follow-up Visit, 28 days after the last dose of IP ± 3 days. If the ET Visit occurs 28 days after the last dose of IP, then the Follow-up Visit is not required.

The following evaluations will be performed at the frequency specified in the Table of Events (Table 5 and Table 6) for the Follow-up Visit:

- Prior and concomitant procedures evaluation
- Prior and concomitant medications evaluation
- AE evaluation
- Pregnancy test: A local urine pregnancy test will be performed on all FCBP.
- Vital signs and weight
- Limited physical examination (Section 6.5.1)
- Clinical laboratory evaluations

- Hematology panel
- Chemistry panel
- Urinalysis panel

6.4.1. Study Completion

The study completion for an individual subject is defined as reaching the Visit 55/Follow-up Visit in the study, which includes completion of the IP treatment at the Week 208 Visit, and completion of the Follow-up Visit, which is 4 weeks (28 days) after last dose of IP ± 3 days. A subject who discontinues early prior to Week 208 is considered an early termination and will have the ET Visit (see Section 6.3) and a Follow-up Visit (see Section 6.4).

6.4.2. 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 eCRF.

6.5. Safety Assessments

6.5.1. Physical Examination

A complete physical examination will include evaluation of the skin, nasal cavities, eyes, ears, respiratory, cardiovascular, abdominal, 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, respiratory, cardiovascular, abdominal, 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, and PCDAI calculations.

Clinically significant abnormal findings (with the exception of the disease under study [CD]) identified prior to the very first dose of IP taken from the core study, should have been recorded on the Medical History eCRF in the core Phase 3 study. Any clinically significant findings identified during this study will be recorded as AEs on the AE eCRF.

6.5.2. Electrocardiogram

Subjects will have a 12-lead ECG at the frequency specified in Table 5 and Table 6. Sites are to utilize 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. "Abnormal, clinically significant" results if not related to medical condition or diagnosis, should be recorded as an AE on the AE eCRF.

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 5 and Table 6:

- 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.
- Chemistry serum 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, magnesium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, and lactate dehydrogenase (LDH).
- Coagulation panel will include: prothrombin time (PT) and activated partial thromboplastin time (APTT).
- Complement activation factor panel will include: compliment activation factors Bb, C3a and C5a.
- Urinalysis panel will include: specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen. The urinalysis will be completed at the central laboratory, not locally at the site. 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 laboratory requisition form.

Note: "Abnormal, clinically significant" results, if not related to a medical condition or diagnosis, should be recorded as an AE on the AE eCRF.

6.5.4. Clinically Significant Abnormal Findings

Clinically significant abnormal findings or results (clinical laboratory assessments, physical examinations, ECGs) if not related to a medical condition or diagnosis, which are identified prior to the very first dose of IP taken from the core study, should have been recorded on the Medical History eCRF in the core Phase 3 study. Clinically significant abnormal findings or results, not related to a medical condition or diagnosis, during this study should be recorded as AEs on the AE eCRF. Any clinically significant abnormal findings or results findings or results related to the disease under study, CD, should not be recorded an AE on the AE eCRF. Only if CD meets any of the criteria as an SAE, is it recorded on the AE eCRF.

6.5.5. 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 or abstinence, as appropriate, at the Screening and Enrollment Visits, throughout the study as necessary and re-emphasize contraception use every 6 months and at the Week 208 and ET Visits to ensure the subject continues her contraception methods through 28 days after the last dose of IP. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes during the study. The female subject's chosen form of contraception must be effective by the time the female subject is enrolled into the study (for example, hormonal contraception should be initiated at least 28 days before enrollment to study treatment). An FCBP 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 one of the approved contraceptive options, as described in the eligibility criteria, or must practice abstinence from heterosexual contact 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 an FCBP'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.

6.5.6. Cancer Surveillance

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

6.6. Efficacy Assessments

6.6.1. Subject Daily Diary

During Screening Visit 1, an electronic subject diary device (Appendix B) will be given to each subject. The subject (and the parents / guardians of adolescent subjects) 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 (and to the parents / guardians of adolescent subjects) 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 is required to enter diary data, each day, and through Week 40 if an adolescent subject in the study. Site personnel must also assess the subject's compliance with reporting of the daily diary data entries , and through Week 40 for an adolescent subject.

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

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 C) 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, whereas severe disease is defined as a CDAI score > 450. Remission is defined as a CDAI score < 150.

Clinical parameters needed for calculation of the CDAI will be collected by the subject via an electronic diary device and by the site at the scheduled visit via a separate electronic device.

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 arthralgia
   - Iritis or uveitis
   - Erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
   - Anal fissures, fistula, 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 in kg] / [standard weight in kg]) x 100%

6.6.4. Pediatric Crohn's Disease Activity Index (Adolescent Subjects)

The PCDAI (Appendix E) is an instrument that was developed and validated for numerical assessment of disease activity in children and adolescents with CD (Hyams, 1991). The PCDAI has a scoring range of 0 to 100. Mild disease corresponds to scores of 11 – 30; moderate to severe disease corresponds to scores > 30. Remission (ie, no disease activity) is defined as a PCDAI score ≤ 10.

The PCDAI includes subjective patient historical information, physical examination findings, objective laboratory parameters, data on weight gain/loss, and height velocity. The category of severity for each index item is assigned a score: 0 = normal; 5 = mild abnormality; 10 = severe

abnormality. The PCDAI also includes 3 laboratory parameters (ie, hematocrit, erythrocyte sedimentation rate and albumin level) which are part of the calculation. For hematocrit and erythrocyte sedimentation rate, the maximum score = 5. For albumin level, the maximum score = 10.

Clinical parameters needed for calculation of the PCDAI will be collected by the subject and the site at the scheduled visit via an electronic device.

The PCDAI consists of the following 11 variables:

1. Abdominal pain (1 week)
2. Stools per day (1 week)
3. Patient functioning / General well-being (1 week)
4. Weight
5. Height velocity (current visit height compared with height measured 6-12 months earlier expressed as a standard deviation score)
6. Abdominal tenderness, mass, guarding
7. Peri-rectal disease
8. Extra-intestinal manifestations (fever, arthritis, uveitis, erythema nodosum, pyoderma gangrenosum)
9. Hematocrit (%) for men/women
10. Erythrocyte sedimentation rate (mm/hr)
11. Albumin (g/dL)

6.6.4.1. Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate (ESR) will be tested only for adolescent subjects at visits when the PCDAI is performed at the frequency specified in Table 6. The ESR result is generated at the site from a supply kit provided by the central laboratory, and the site will record the ESR result into the appropriate electronic entry screen for calculating the PCDAI.

6.6.6. Ileocolonoscopy

All previous GED-0301-CD-003 subjects adolescents) will have an ileocolonoscopy performed during the Long-term Active Treatment Period at Week 40. An ileocolonoscopy is not required for previous GED-0301-CD-002 subjects.

Video images of all endoscopic procedures will be captured and sent to a qualified centralized reader for calculation of the SES-CD to assess efficacy at Week 40.

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

6.6.8. Simple Endoscopic Score for CD

The SES-CD (Appendix F) is a validated endoscopic index that closely correlates with the Crohn's Disease Endoscopic Index of Severity (CDEIS) 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).

6.6.9. Weight, Height, BMI, and Height Velocity (Adolescent Subjects)

Age-specific *z*-scores (based on chronological age and bone age) will be calculated for weight, height, body mass index (BMI), and height velocity. The *z*-scores are measurements of the deviation of the patient's growth parameter (weight, height, BMI, or height velocity) from the expected growth parameter of an age (chronological and bone) and sex-matched population. The *z*-score is calculated as the observed growth parameter – reference population parameter mean divided by the standard deviation of the reference population parameter. Height velocity will be calculated based on height measurements from the 6 to 12 months preceding the study according to the following formula: (Present Height [cm] - Previous Height [cm])/Interval (months) Between Measurements x 12.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

Mongersen (GED-0301) will be provided as 40-mg gastro-resistant, delayed release, pH-dependent tablets. Placebo will be provided as identically appearing tablets.

7.2. Treatment Administration and Schedule

Beginning at Week 0 through Week 12, subjects will receive blinded-active GED-0301 (160 mg QD or 40 mg QD) treatment as one of the following numbered treatment groups:

1) continuous 160 mg QD for 12 weeks;
2) 160 mg QD for 4 weeks, PBO QD for 4 weeks, 160 mg QD for 4 weeks;
3) PBO QD for 4 weeks, 160 mg QD for 4 weeks, PBO QD for 4 weeks;
4) continuous 40 mg QD for 12 weeks;
5) PBO QD for 4 weeks, 40 mg QD for 4 weeks, PBO QD for 4 weeks.

Beginning at Week 12 through Week 208, subjects from the above-numbered treatment groups will continue to receive blinded-active GED-0301 treatment for 196 weeks as the following:

1) alternating PBO QD for 4 weeks with 160 mg QD for 4 weeks, through Week 208;
2) alternating PBO QD for 4 weeks with 160 mg QD for 4 weeks, through Week 208;
3) alternating 160 mg QD for 4 weeks with PBO QD for 4 weeks, through Week 208;
4) continuous 40 mg QD, through Week 208;
5) alternating 40 mg QD for 4 weeks with PBO QD for 4 weeks, through Week 208.

Subjects will receive 1 blister card when IP is administered. Four tablets are taken once daily during the 208-week Long-term Active Treatment Period. Subjects will be instructed to take 4 tablets 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.

Please note: All 160 mg QD treatments are taken as four 40 mg tablets once daily in the study.

Treatment and administration schedules are described in Table 7, Table 8, Table 9, and Table 10.

The treatment described in each box is the treatment dispensed at a particular week visit. For example, if the subject was previously on PBO (with no clinical improvement) in the core GED-0301 study, the subject would receive the IP in this study as:

- blinded GED-0301 160 mg QD for a 4-week supply at the Week 0 Visit;
- blinded GED-0301 160 mg QD for a 4-week supply at the Week 4 Visit;
- blinded GED-0301 160 mg QD for a 4-week supply at the Week 8 Visit;
- blinded PBO QD for a 4-week supply at the Week 12 Visit;
- alternating blinded GED-0301 160 mg QD for a 4-week supply followed by blinded PBO QD for a 4-week supply at Week 16 through Week 208; and
- no IP at the Week 208 Visit.

Table 7: Investigational Product Dispensing Schedule for the Treatment Period at Year 1

Treatment Group from Core GED-0301 Study	Long-term Active Treatment Period (All Treatment is Blinded) (Year 1)													
	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**	**Week 52**
PBO (with no improvement)	160 mg QD	160 mg QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD
GED-0301 40 mg or 160 mg on/off, or 40 mg daily, or 160 mg QD for 12 weeks (with no improvement), or PBO (with improvement)	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD
GED-0301 160 mg on/off or 160 mg QD for 12 weeks (with improvement)	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD
GED-0301 40 mg daily (with improvement)	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD
GED-0301 40 mg on/off (with improvement)	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD

PBO = placebo; QD = once daily.

Table 8: Investigational Product Dispensing Schedule for the Treatment Period at Year 2

Treatment Group from Core GED-0301 Study	Long-term Active Treatment Period (All Treatment is Blinded) (Year 2)												
	Week 56	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**Week 100**	**Week 104**
PBO (with no improvement)	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD
GED-0301 40 mg or 160 mg on/off, or 40 mg daily, or 160 mg QD for 12 weeks (with no improvement), or PBO (with improvement)	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD
GED-0301 160 mg on/off or 160 mg QD for 12 weeks (with improvement)	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD
GED-0301 40 mg daily (with improvement)	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD
GED-0301 40 mg on/off (with improvement)	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD

PBO = placebo; QD = once daily.

Table 9: Investigational Product Dispensing Schedule for the Treatment Period at Year 3

Treatment Group from Core GED-0301 Study	Long-term Active Treatment Period (All Treatment is Blinded) (Year 3)												
	Week 108	**Week 112**	**Week 116**	**Week 120**	**Week 124**	**Week 128**	**Week 132**	**Week 136**	**Week 140**	**Week 144**	**Week 148**	**Week 152**	**Week 156**
PBO (with no improvement)	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD
GED-0301 40 mg or 160 mg on/off, or 40 mg daily, or 160 mg QD for 12 weeks (with no improvement), or PBO (with improvement)	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD
GED-0301 160 mg on/off or 160 mg QD for 12 weeks (with improvement)	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD
GED-0301 40 mg daily (with improvement)	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD
GED-0301 40 mg on/off (with improvement)	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD

PBO = placebo; QD = once daily.

Table 10: Investigational Product Dispensing Schedule for the Treatment Period at Year 4

Treatment Group from Core GED-0301 Study	Long-term Active Treatment Period (All Treatment is Blinded) (Year 4)												
	Week 160	**Week 164**	**Week 168**	**Week 172**	**Week 176**	**Week 180**	**Week 184**	**Week 188**	**Week 192**	**Week 196**	**Week 200**	**Week 204**	**Week 208**
PBO (with no improvement)	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	No IP
GED-0301 40 mg or 160 mg on/off, or 40 mg daily, or 160 mg QD for 12 weeks (with no improvement), or PBO (with improvement)	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	No IP
GED-0301 160 mg on/off or 160 mg QD for 12 weeks (with improvement)	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	PBO QD	160 mg QD	No IP
GED-0301 40 mg daily (with improvement)	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	40 mg QD	No IP
GED-0301 40 mg on/off (with improvement)	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	PBO QD	40 mg QD	No IP

IP = investigational product; PBO = placebo; QD = once daily.

7.2.1. Dose Modification or Interruption

Dose modification is not permitted. 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.

7.2.2. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the IP (mongersen [GED-0301] or matching PBO). Overdose for this protocol, on a per-dose basis, is defined as ingestion of more than the prescribed dose (ie, more than four tablets) 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.

Detailed information about any Celgene drug overdose in this study, regardless of whether the overdose was accidental or intentional, should be reported on the Investigational Drug Overdose eCRF page.

7.3. Method of Treatment Assignment

Eligible subjects will receive GED-0301 treatment for 4-week intervals during this 208-week Long-term Active Treatment Study as either: 1) four 40-mg tablets; 2) one 40-mg tablet and three PBO tablets; or 3) four PBO tablets.

Investigational product will be managed via an IRTS. Eligible subjects will enter the Long-term Active Treatment Period at the Enrollment Visit (Week 0/Visit 2), and will be assigned to receive IP as blinded-active treatment as described in Table 7, Table 8, Table 9, and Table 10, up through Week 208.

Designated study personnel at the investigational sites will be assigned password-protected, coded identification numbers, which give them authorization to access the IRTS to enroll 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 IRTS will assign an enrollment identification number. Confirmation of the enrollment 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 enrollment number assigned by IRTS.

7.4. Packaging and Labeling

GED-0301 tablets are packaged in blister cards fitted with induction seals and tamper-evident child-resistant seals.

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 5 and Table 6). 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 nonprescription), treatments, and therapies taken by the subject from screening throughout their entire participation in 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 for CD and Procedures

At any time during the study (from Screening Visit 1 through Week 208/Visit 54 and Follow-up/Visit 55), background concomitant CD medications, such as oral aminosalicylates, immunosuppressants and/or corticosteroids can be discontinued, adjusted or initiated, as clinically indicated at the discretion of the Investigator, with no required lead-in time prior to enrollment and with no dose restriction. The only exceptions are GED-0301-CD-003 subjects who were on stable doses of corticosteroids and achieved clinical improvement by Week 12 in Study GED-0301-CD-003. These subjects should follow the guidance for a corticosteroid tapering procedure (Section 8.1.1) upon entrance into this study.

8.1.1. Corticosteroid Tapering Procedure

GED-0301-CD-003 subjects who achieved clinical improvement by Week 12 in Study GED-0301-CD-003 are eligible to start corticosteroid tapering beginning at the Screening Visit 1 in Study GED-0301-CD-004, 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.

8.2. Prohibited Concomitant Medications and Procedures

The following concomitant medications are prohibited during the Screening Period and from the Enrollment Visit (ie, Week 0/Visit 2) through the last study treatment visit (ie, Week 208/Visit 54), or the ET Visit for subjects who discontinue prematurely during the study:

- Use of any biologic agents, including TNF-α blockers or integrin antagonists. If biologic agents are initiated, the subject must be discontinued from the study.

8.3. Required Concomitant Medications and Procedures

There are no required concomitant medications for any subjects and no required procedures for previous GED-0301-CD-002 subjects.

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 Sponsor or its designee.

9.2. Study Population Definitions

The safety and efficacy analyses will be based on the long-term active treatment population, which will consist of all subjects who enter the long-term active treatment study and receive at least 1 dose of IP during the long-term active treatment study.

9.3. Sample Size and Power Considerations

No sample size and power calculations are performed for this long-term active treatment study.

9.4. Background and Demographic Characteristics

Subjects' age, weight, and other continuous variables will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history 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. Protocol deviations/violations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

The efficacy endpoints will be summarized descriptively.

9.7. Safety Analysis

Safety 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.

Treatment-emergent adverse events will be classified using the MedDRA classification system. All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to IP. The 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

Unblinded analyses of safety data may be performed by a group independent of the study team and not involved with the study conduct. Unblinded group-level data may be distributed outside of this group; however, subject-level data will remain blinded.

9.9. Other Topics

9.9.1. 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 follows 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.

9.9.2. 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 IP 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. There is no known specific antidote for GED-0301 overdose. 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. Adverse events 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 AEs 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 nonserious 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 AE 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 AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the AE.

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 an SAE.

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 elevated β-hCG or positive pregnancy test in a female subject of childbearing potential, regardless of disease state) 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 email, phone or 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 SAEs made known to the Investigator at any time 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/Independent Ethics Committee (IRB/IEC) 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/IEC.

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 IB.

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, 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 IPs 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 (In Japan, Celgene KK shall notify the Heads of the Institutes in addition to the Investigators):

- 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;
- In Japan, measures taken in the foreign countries to ensure subject safety, study reports that indicate potential risk of cancer, etc., or biannual SAE report according to the local regulations.

Where required by local legislation, the Investigator shall notify his/her IRB/IEC 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/IEC. (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

11.1. Treatment Discontinuation

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

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

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

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

During the 208-week blinded-active treatment period, the blind must not be broken during the course of this period 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 IRTS by using an emergency unblinding personal identification number (PIN), and the Investigator should call IRTS 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/IEC 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 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/IEC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/IEC 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/IEC 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.

Investigational product 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/IEC and their occupation and qualifications. If the IRB/IEC 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/IEC 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/IEC 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/IEC and, if applicable, between a Coordinating Investigator and the IRB/IEC. 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/IEC prior to use.

13.7. Ongoing Information for Institutional Review Board/Independent Ethics Committee

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

- Information on serious or unexpected AEs 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/IEC, 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 IP 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-ROMs.

14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures. 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/IEC;
- Composition of the IRB/IEC;
- 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 case report forms (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. The 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 standard operating procedures (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 GCP 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 GCP 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/IECs, regulatory authorities (eg, United States Food and Drug Administration, European Medicines Agency, and 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.

17. REFERENCES

Baumgart DC, Sandborn WJ. Crohn's disease. Lancet 2012;380:1590-605.

Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology 2005 Sep;129(3):827-36.

Best WR, Becktel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index; national cooperative Crohn's disease study. Gastroenterology 1976;70(3):439-44.

Boirivant M, Pallone F, Di Giacinto C, Fina D, Monteleone I, Marinaro M, et al. Inhibition of Smad7 with a specific antisense oligonucleotide facilitates TGF-β1-mediated suppression of colitis. Gastroenterology 2006;131(6):1786-98.

Clark M, Colombel JF, Feagan BC, Fedorak RN, Hanauer SB, Kamm MA, et al. American gastroenterological association consensus development conference on the use of biologics in the treatment of inflammatory bowel disease, June 21-23, 2006. Gastroenterology 2007;133(1):312-39.

Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505-12.

Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis 2010 Feb;4(1):28-62.

Griffiths AM, Nicholas D, Smith C, Munk M, Stephens D, Durno C, et al. Development of a quality-of-life index for pediatric inflammatory bowel disease: dealing with differences related to age and IBD type. J Pediatr Gastroenterol Nutr 1999;28(4):S46-S52.

Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr 1991;12(4):439-47.

Kansal S, Wagner J, Kirkwood CD, Catto-Smith AG. Enteral nutrition in Crohn's disease: an underused therapy. Gastroenterol Res Pract 2013, Article ID 482108, 11 pages htt://dx.doi.org/10.1155/2013/482108.

Kelsen, J, Baldassano, RN. Inflammatory bowel disease: the difference between children and adults. Inflamm Bowel Dis 2008;14(Suppl 2):S9-S11.

Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32(9):920–4.

Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol 2009;104(2):465-83.

Loftus EV Jr, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. Aliment Pharmacol Ther 2002 Jan;16(1):51-60.

Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology 2004 May;126(6):1504-17.

MacDonald TT, Monteleone G. Immunity, inflammation and allergy in the gut. Science 2005;307(5717):1920-5.

Mamula P, Markowitz JE, Baldassano RN. Inflammatory bowel disease in early childhood and adolescence: special considerations. Gastroenterol Clin North Am 2003;32(3):967-95.

Markowitz J, Kugathasan S, Dubinsky M, Mei L, Crandall W, LeLeiko N, et al. Age of diagnosis influences serologic responses in children with Crohn's disease: a possible clue to etiology? Inflamm Bowel Dis 2009;15(5):714-9.

Monteleone G, Kumberova A, Croft NM, McKenzie C, Steer HW, MacDonald TT. Blocking Smad7 restores TGF-β1 signaling in chronic inflammatory bowel disease. J Clin Invest 2001;108(4):601-9.

Monteleone G, Caruso R, Pallone F. Role of Smad7 in inflammatory bowel diseases. World J Gastroenterol 2012;18(40):5664-8.

Pigneur B, Seksik P, Viola S, Viala J, Beaugerie L, Girardet JP, et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. Inflamm Bowel Dis 2010; 16(6):953-61.

Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis 2014;8(10):1179-207.

Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology 2002;122(2):512-30.

Van Limbergent J, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008;135(4):1114-22.

Vavricka SR, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol 2011Jan;106(1):110-9.

18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 11: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activities of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
APTT	Activated partial thromboplastin time
5-ASA	5-aminosalicylic acid
AST	Aspartate aminotransferase (SGOT)
β-hCG	Beta-subunit of human chorionic gonadotropin
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CIOMS VI	Council for International Organizations for Medical Sciences, Working Group VI
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EEN	Exclusive enteral nutrition
ESR	Erythrocyte sedimentation rate
ET	Early Termination
FCBP	Females of childbearing potential
GCP	Good Clinical Practice
GI	Gastrointestinal

Table 11: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICC	Intra-class correlation
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRTS	Interactive response technology system
IUD	Intrauterine device
kg	Kilograms
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mRNA	Messenger ribonucleic acid
p	Phosphorylated
PBO	Placebo
PCDAI	Pediatric Crohn's Disease Activity Index
PK	Pharmacokinetics
PT	Prothrombin time
QD	Once daily

Table 11: Abbreviations and Specialist Terms (Continued)

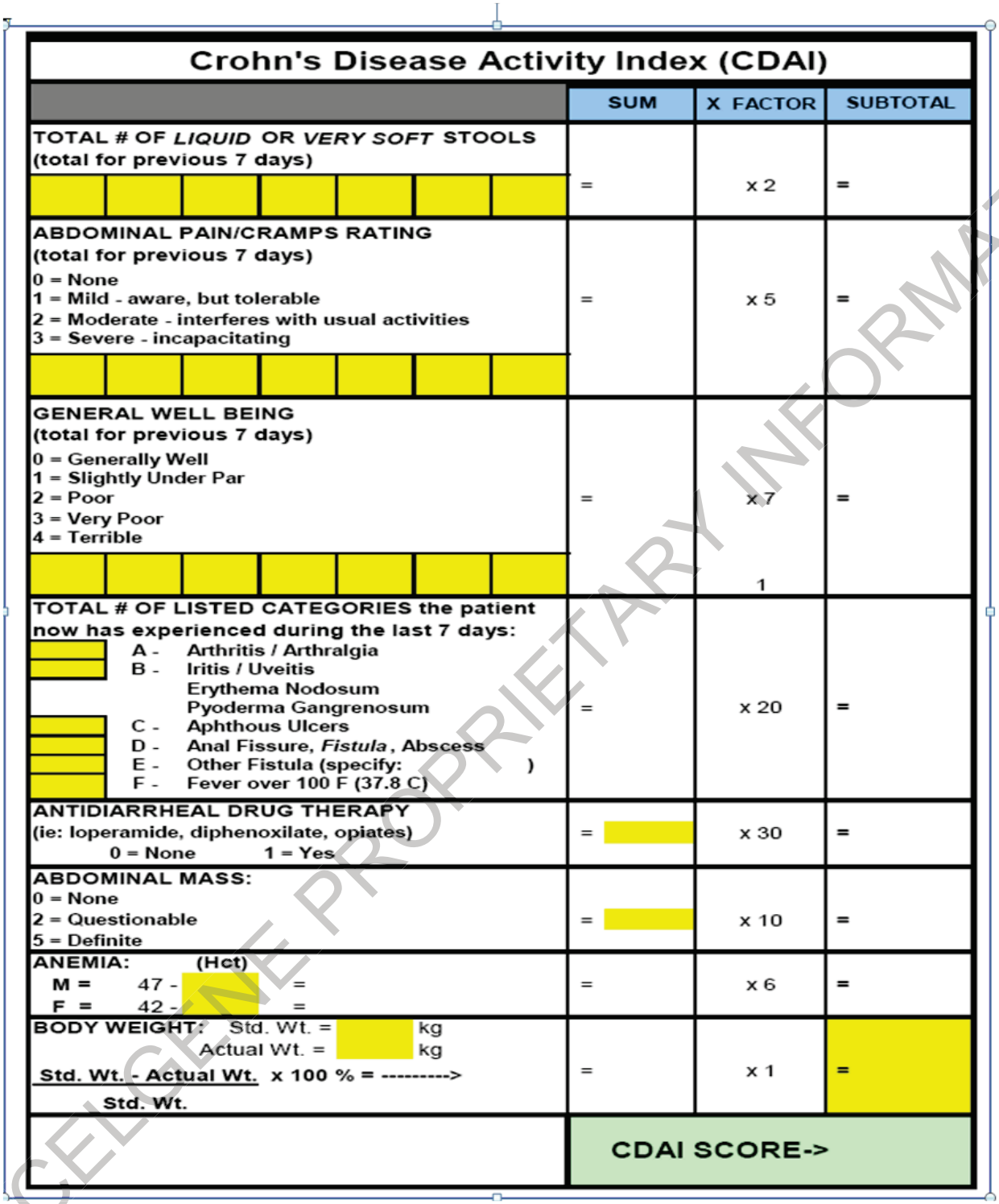
Abbreviation or Specialist Term	Explanation
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SES-CD	Simple Endoscopic Score for Crohn's Disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMT	Safety Management Team
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TGF-β1	Transforming growth factor-beta 1
TNF-α	Tumor necrosis factor-alpha
UC	Ulcerative colitis
VAS	Visual Analog Scale
WBC	White blood cell

APPENDIX B. SUBJECT DAILY DIARY

Instructions: You will be given an electronic diary. Your diary should be recorded daily and should reflect a 24-hour period. Please record your diary continuously throughout the study. The scores for abdominal pain and general well-being should reflect the average pain or well-being for that entire day. In case you experience fever, enter the temperature measured, if above 100°F. It you miss a day and you cannot recall all the information, complete the date and the information you do recall.

Date	Number of liquid or very soft stools per 24 hours	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 C. 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. PEDIATRIC CROHN'S DISEASE ACTIVITY INDEX

Pediatric Crohn's Disease Activity Index

Patient's study identification number: _____ **Score** **Subtotal**

One week			
Abdominal Pain	None	0	
	Mild – Brief, does not interfere with activities	5	
	Moderate/severe - Daily, longer lasting, affects activities, nocturnal	10	
Stools (per day)	0–1 liquid stool, no blood	0	
	Up to 2 semi-formed with small blood, or 2–5 liquid	5	
	Any gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	10	
Patient Functioning / General Well-Being	No limitation of activities, well	0	
	Occasional difficulty in maintaining age-appropriate activities, below par	5	
	Frequent limitation of activity, very poor	10	
Examination			
Weight	Weight gain or voluntary weight stable/loss	0	
	Involuntary weight stable, weight loss (1-9%)	5	
	Weight loss ≥10%	10	
Height Velocity†	≥ -1 SD	0	
	< -1 SD, > -2 SD	5	
	≤ -2 SD	10	
-or-			
Height†† (at diagnosis)	< 1 channel decrease	0	
	≥ 1, < 2 channel decrease	5	
	≥ 2 channel decrease	10	
Abdomen	No tenderness, no mass	0	
	Tenderness, or mass without tenderness	5	
	Tenderness, involuntary guarding, definite mass	10	
Perirectal Disease	None, asymptomatic tags	0	
	1–2 indolent fistula, scant drainage, no tenderness	5	
	Active fistula, drainage, tenderness, or abscess	10	
Extra-intestinal Manifestations†††	None	0	
	1 manifestation	5	
	≥ 2 manifestations	10	
Laboratory			
Hematocrit (%) **M = Male** **F = Female**	M/F ≤ 10 years: ≥ 33	0	
	M 11–14 years: ≥ 35		
	F 11–19 years: ≥ 34		
	M 15–19 years: ≥ 37		
	M/F ≤ 10 years: 28–32	2.5	
	M 11–14 years: 30–34		
	F 11–19 years: 29–33		
	M 15–19 years: 32–36		
	M/F ≤ 10 years: < 28	5	
	M 11–14 years: < 30		
	F 11–19 years: < 29		
	M 15–19 years: < 32		

Continued

APPENDIX E. PEDIATRIC CROHN'S DISEASE ACTIVITY INDEX (Continued)

Laboratory (Continued)			
ESR (mm / hr)	< 20	0	
	20–50	2.5	
	> 50	5	
Albumin (g / dL)	≥ 3.5	0	
	3.1–3.4	5	
	≤ 3.0	10	
		TOTAL PCDAI SCORE	

† Height velocity is calculated as cm / year based on current visit height compared to height over last 6–12 months. Height velocity is plotted on standardized curve (versus age) and expressed as SD score.
†† Height-channel represents lines on the standard percentile chart, for example, 10 – > 25 – > 50 percentile is 2 channels difference.
††† Extra-intestinal implies fever of ≥ 38.5ºC for 3 days over past week, definite arthritis, uveitis, Erythema nodosum, or Pyoderma gangrenosum.

Printed name of person entering scores

Signature of person entering scores **Date**

Source: Hyams, 1991.

APPENDIX F. 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 G. THE STUDY GED-0301-CD-004 TREATMENT TABLE

Core GED-0301 Study:	GED-0301 Treatment Received from Core GED-0301 Study:	Time Point in Core GED Study When Subject Eligible for CD-004:	Did Subject Meet the Clinical Improvement Criteria from the Core GED Treatment?	Treatment Regimen to Receive in Study GED-0301-CD-004:
CD-002	Blinded PBO QD through Week 52	At Week 12 Visit through Week 52 Visit	No	Blinded 160 mg QD for 12 weeks; followed by alternating blinded PBO QD for 4 weeks / blinded 160 mg QD for 4 weeks, through Week 208
CD-002	Blinded PBO QD through Week 52	Week 52 Visit	Yes	Alternating blinded 160 mg QD for 4 weeks / blinded PBO QD for 4 weeks, through Week 208
CD-002	Blinded 160 mg QD through Week 12; followed by alternating blinded PBO QD for 4 weeks / blinded 40 mg QD for 4 weeks through Week 52	At Week 12 Visit through Week 52 Visit	No	Alternating blinded 160 mg QD for 4 weeks / blinded PBO QD for 4 weeks, through Week 208
CD-002	Blinded 160 mg QD through Week 12; followed by alternating blinded PBO QD for 4 weeks / blinded 40 mg QD for 4 weeks through Week 52	Week 52 Visit	Yes	Alternating blinded PBO QD for 4 weeks / blinded 40 mg QD for 4 weeks, through Week 208

Please note: All 160 mg QD treatments are taken as four 40 mg tablets once daily in the study.

APPENDIX G. THE STUDY GED-0301-CD-004 TREATMENT TABLE (Continued)

Core GED-0301 Study:	GED-0301 Treatment Received from Core GED-0301 Study:	Time Point in Core GED Study When Subject Eligible for CD-004:	Did Subject Meet the Clinical Improvement Criteria from the Core GED Treatment?	Treatment Regimen to Receive in Study GED-0301-CD-004:
CD-002	Blinded 160 mg QD through Week 12; followed by continuous blinded 40 mg QD through Week 52	At Week 12 Visit through Week 52 Visit	No	Alternating blinded 160 mg QD for 4 weeks / blinded PBO QD for 4 weeks, through Week 208
CD-002	Blinded 160 mg QD through Week 12; followed by continuous blinded 40 mg QD through Week 52	Week 52 Visit	Yes	Continuous blinded 40 mg QD, through Week 208
CD-002	Blinded 160 mg QD through Week 12; followed by alternating blinded PBO QD for 4 weeks / blinded 160 mg QD for 4 weeks through Week 52	At Week 12 Visit through Week 52 Visit	No	Alternating blinded 160 mg QD for 4 weeks / blinded PBO QD for 4 weeks, through Week 208
CD-002	Blinded 160 mg QD through Week 12; followed by alternating blinded PBO QD for 4 weeks / blinded 160 mg QD for 4 weeks through Week 52	Week 52 Visit	Yes	Alternating blinded PBO QD for 4 weeks / blinded 160 mg QD for 4 weeks, through Week 208

Please note: All 160 mg QD treatments are taken as four 40 mg tablets once daily in the study.

APPENDIX G. THE STUDY GED-0301-CD-004 TREATMENT TABLE (Continued)

Core GED-0301 Study:	GED-0301 Treatment Received from Core GED-0301 Study:	Time Point in Core GED Study When Subject Eligible for CD-004:	Did Subject Meet the Clinical Improvement Criteria from the Core GED Treatment?	Treatment Regimen to Receive in Study GED-0301-CD-004:
CD-003	Blinded PBO QD through Week 12	Week 12 Visit	No	Blinded 160 mg QD for 12 weeks; followed by alternating blinded PBO QD for 4 weeks / blinded 160 mg QD for 4 weeks, through Week 208
CD-003	Blinded PBO QD through Week 12	Week 12 Visit	Yes	Alternating blinded 160 mg QD for 4 weeks / blinded PBO QD for 4 weeks, through Week 208
CD-003	Blinded 160 mg QD through Week 12	Week 12 Visit	No	Alternating blinded 160 mg QD for 4 weeks / blinded PBO QD for 4 weeks, through Week 208
CD-003	Blinded 160 mg QD through Week 12	Week 12 Visit	Yes	Alternating blinded PBO QD for 4 weeks / blinded 160 mg QD for 4 weeks, through Week 208

PBO = placebo; QD = once daily.

Please note: All 160 mg QD treatments are taken as four 40 mg tablets once daily in the study.

APPENDIX H. THE STUDY GED-0301-CD-002 EARLY ESCAPE CRITERIA

The GED-0301-CD-002 study "early escape criteria" definition:

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: Sunday, 08 January 2017, 01:30 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Addition of Adolescent Subjects into the GED-0301-CD-004 Study

The primary purpose of this protocol amendment is the addition of the adolescent subjects into this long-term active treatment extension study who previously participated in the Phase 3 GED-0301-CD-003 study. As a result, new sections were added to the protocol that apply specifically to adolescent subjects. Furthermore, the objectives, end points, inclusion/exclusion criteria, table of events, procedures and assessments sections were separated out for the adult and adolescent subjects throughout the protocol, where appropriate, to clearly indicate protocol information which applies specifically to adult versus adolescent subjects.

Revised Sections:

- Protocol Summary (Objectives)
    - Secondary Objectives (Adult Subjects)
    - Secondary Objectives (Adolescent Subjects) – newly added
- Protocol Summary (Study Design)
- Protocol Summary (Overview of Key Safety Assessments)
-
- Protocol Summary (Overview of Key Efficacy Assessments [Adolescent Subjects])
- Protocol Summary (Overview of Other Study Assessments)
- Protocol Summary (Statistical Methods)
- Section 1.1 (Disease Background)
- Section 1.3.1 (Study Rationale and Purpose)
- Section 1.3.2 (Rationale for the Study Design)
- Section 2 (Study Objectives and Endpoints)
    - Table 1 (Study Objectives – Adult Subjects [≥ 18 years of age at screening of core study] from GED-0301-CD-002 and GED-0301-CD-003)
    - Table 2 (Study Endpoints – Adult Subjects from GED-0301-CD-002 and GED-0301-CD-003)
    - Table 3 (Study Objectives – Adolescent Subjects [12-17 years of age, inclusive] from GED-0301-CD-003)
    - Table 4 (Study Endpoints – Adolescent Subjects from GED-0301-CD-003)
- Section 3.1 (Study Design)
- Section 4.2 (Inclusion Criteria)

  - Section 4.2.1 (Inclusion Criteria for Adult Subjects) – separated out to clearly identify the inclusion criteria specifically for adult subjects
  - Section 4.2.2 (Inclusion Criteria for Adolescent Subjects) – newly added to clearly identify the inclusion criteria specifically for adolescent subjects, with accompanied Footnotes #5, 6 and 7 regarding the adolescent pregnancy language

- Section 4.3 (Exclusion Criteria [Adult and Adolescent Subjects]) – identical for both adult and adolescent subjects and only the name of this section was changed for emphasis.
- Section 5 (Table of Events)
  - Table 5 (Table of Events for Adult Subjects) – separated out to identify the assessments/procedures for adult subjects
  - Table 6 (Table of Events for Adolescent Subjects) – newly added to identify the assessments/procedures for adolescent subjects
- Section 6 (Procedures)
- Section 6.1.1 (Screening Visit)
- Section 6.2 (Treatment Period)
- Section 6.2.1 (Unscheduled Visits)
- Section 6.3 (Early Termination Visit)
- Section 6.4 (Follow-up Period)
- Section 6.5.2 (Electrocardiogram)
- Section 6.5.3 (Clinical Laboratory Assessments)
- Section 6.6.1 (Subject Daily Diary)
- Section 6.6.4 (Pediatric Crohn's Disease Activity Index) – newly added
- Section 6.6.4.1 (Erythrocyte Sedimentation Rate) – newly added
- Section 6.6.6 (Ileocolonoscopy) – newly added
- Section 6.6.8 (Simple Endoscopic Score for CD) – newly added
- Section 6.6.9 (Weight, Height, BMI, and Height Velocity [Adolescent Subjects]) – newly added

- Section 8.1 (Permitted Concomitant Medications for CD and Procedures)
- Section 8.1.1 (Corticosteroid Tapering Procedure)
- Section 8.3 (Required Concomitant Medications and Procedures)
- Section 9.6 (Efficacy Analysis)
- Section 17 (References)
- Section 18 (Appendices)
    - Appendix A (Table of Abbreviations)
    - Appendix E (Pediatric Crohn's Disease Activity Index) – newly added
    - Appendix F (Simple Endoscopic Score for Crohn's Disease) – newly added

Revised Sections:

- Protocol Summary (Objectives)
    - Secondary Objectives (Adolescent Subjects)
- Protocol Summary (Study Design)
- Protocol Summary (Overview of Key Efficacy Assessments [Adolescent Subjects])
- Section 1.3.1 (Study Rationale and Purpose)
- Section 1.3.2 (Rationale for the Study Design)
- Section 2 (Study Objectives and Endpoints)
    - Table 1 (Study Objectives – Adult Subjects [≥ 18 years of age at screening of core study] from GED-0301-CD-002 and GED-0301-CD-003)

  - Table 2 (Study Endpoints – Adult Subjects from GED-0301-CD-002 and GED-0301-CD-003)
- Section 3.1 (Study Design)
- Section 5 (Table of Events)
  - Table 5 (Table of Events for Adult Subjects)
- Section 6.2 (Treatment Period)
  - Bullets for Ileocolonoscopy
- Section 6.3 (Early Termination Visit)
  - Bullets for Ileocolonoscopy
- Section 6.6.6 (Ileocolonoscopy) – newly added
- Section 6.6.8 (Simple Endoscopic Score for CD) – newly added
-
- Section 8.1 (Permitted Concomitant Medications for CD and Procedures)
- Section 8.3 (Required Concomitant Medications and Procedures)
- Appendix F – Simple Endoscopic Score for Crohn's Disease – newly added

Addition of the Week 12 Clinical Criteria for Discontinuation

The Week 12 clinical criteria were added for discontinuing subjects who did not achieve a minimum level of improvement by Week 12 in this active treatment extension study. Subjects who meet the following criteria will be discontinued from the study at Week 12:

Revised Sections:

- Protocol Summary (Study Design)
- Section 1.3.1 (Study Rationale and Purpose)
- Section 3.1 (Study Design)

Revision of Inclusion Criteria – Inclusion Criteria for Adult Subjects

- Inclusion Criterion #4 was revised to allow subjects to enter this study who had met the "early escape criteria" from Study GED-0301-CD-002 "at" the Week 12 Visit, rather than "after" the Week 12 Visit.
- Inclusion Criterion #4 was also updated to clarify that subjects must have completed the previous GED-0301 study through the Week 12 "Visit" in order to qualify for this study.

Revised Sections:

- Section 4.2 (Inclusion Criteria)
- Appendix H (The Study GED-0301-CD-002 Early Escape Criteria)

Revision of Inclusion Criterion #5 (Contraception Language)

The Inclusion Criterion #5 for female subjects was revised to state that females of childbearing potential (FCBP) must either practice true abstinence[1] from heterosexual contact or use one of the approved contraceptive options as described in Inclusion Criterion #5 while on investigational product (IP) and for at least 28 days after taking the last dose of IP. This is consistent with the new female contraception language for the GED-0301 Program.

In addition, the Inclusion Criterion #5 requiring male subjects to use barrier contraception when engaging in sexual activity was removed. Based on the pharmacokinetic results from previous and ongoing GED-0301 studies, there is minimal concern for GED-0301 entering blood at such high concentrations that it could present into semen and therefore, there is no cause for study drug exposure to female partners of male subjects.

Revised Sections:

- Section 4.2.1 (Inclusion Criteria for Adult Subjects)
- Section 6.5.5 (Contraception Education)
- Section 10.4 (Pregnancy)
- Section 10.4.2 (Male Subjects) – entire section was deleted since it no longer applies.

Revision of Exclusion Criteria

- Exclusion Criterion #4 was revised to emphasize that a subject is prohibited from entering this study who may have initiated biologic agents "while or after participating in the previous Phase 3 GED-0301 study."
- Exclusion Criterion #9 was added to exclude a subject who has any new condition that may put the subject at risk or confound the ability to interpret data from the study. As a result, the former Exclusion Criterion #9 was changed to Exclusion Criterion #10.

Revised Section:

- Section 4.3 (Exclusion Criteria [Adult and Adolescent Subjects])

The Early Escape Timing in Study GED-0301-CD-002 Changed from "After" to "At" Week 12 Visit

Sections throughout the protocol have added language emphasizing that subjects can enter this study who meet the "early escape criteria" and were discontinued from Study GED-0301-CD-002 beginning "at" the Week 12 Visit, rather than "after" the Week 12 Visit.

[1] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Revised Sections:

- Protocol Summary (Study Design)
- Section 1.3.1 (Study Rationale and Purpose)
- Section 1.3.3 (Rationale for Dose, Schedule and Regimen Selection)
- Section 3.1 (Study Design)
- Appendix G (The Study GED-0301-CD-004 Treatment Table)

Visit 1 and Visit 2 in GED-0301-CD-004 can be Combined and Completed on the Same Day as the Last Study Visit in the Core GED-0301 Study

Visit 1 and Visit 2 from this study may be combined and completed on the same day, if the GED-0301-CD-004 study drug is available for the subject at the study center. Also, Visit 1 and Visit 2 from this study and the last study visit from the core GED-0301 study can be combined into a single study visit and done on the same day, if the GED-0301-CD-004 study drug is available for the subject at the study center. If 2 visits are combined into a single visit in this study, or if 2 or 3 visits are combined into a single visit from both studies (ie, the core GED-0301 study and this extension GED-0301 study), any visit assessments/procedures which are normally done separately at multiple visits are done only once and not repeated.

The reason for this change is that it will allow the subject to receive study drug immediately at a combined Visit 1 and 2, and not have the subject come back to the study center for a separate Visit 2, if study drug is available at the study center.

Revised Sections:

- Section 5 (Table of Events)
    - Table 5 (Table of Events for Adult Subjects ([Years 1 to 4]) – Year 1
        - Assessments for the Visit 2 column contain an X[a], identifying the procedures which do not need to be repeated, if Visits 1 and 2 are combined into a single visit.
        - Visit window for Visit 1 was changed from -28 to -1 days to -28 to 0 days since Visit 1 and Visit 2 may be done on the same day.
    - Footnote "a" – was revised for clarification based on the above change
- Section 6.1.1 (Screening Visit)
- Section 6.2 (Treatment Period)
    - Limited physical examination – not done if Visits 1 and 2 are done on the same day
    - Dispense IP – the IP can be dispensed to the subject at a combined Visit 1 and 2, if the GED-0301-CD-004 IP is available for the subject at the study center.

If Visit 1 and Visit 2 in GED-0301-CD-004 and the Last Study Visit in the Core GED-0301 Study are Done Separately but Within a 14-Day Period, Certain Evaluations Not Repeated

If the Screening Visit 1 from this study and the last study visit from the core GED-0301 study are both done separately but are within 14 days of each other, the following Visit 1 clinical and laboratory evaluations do not need to be repeated if they were done at the last study visit from the core GED-0301 study: hematology, chemistry, coagulation, complement activation factors, urinalysis, pregnancy test, ECG, and physical examination.

If all 3 visits (ie, Visit 1 and Visit 2 from this study and the last study visit from the core GED-0301 study) are done separately but all are within a 14-day period, the following clinical, and laboratory evaluations do not need to be repeated if they were done at the last study visit from the core GED-0301 study: hematology, chemistry, coagulation, complement activation factors, urinalysis, pregnancy test, , ECG, physical examination, CDAI,

The reason for this change is that it will decrease subject and site burden and will prevent unnecessary repeat of study assessments if the above-mentioned study visits are completed separately within a 14-day period.

Revised Sections:

- Section 5 (Table of Events)
    - Footnote "a" – was revised for clarification based on the above change
- Section 6.1.1 (Screening Visit)
- Section 6.2 (Treatment Period)

Visit 1 Serum Pregnancy Test is No Longer Required

A Visit 1 serum pregnancy test is no longer needed and has been replaced by a local urine pregnancy test. The reason is that Visit 1 in this study is a basically a continuation of the core GED-0301 study and only a local urine test is required.

Revised Section:

- Section 6.1.1 (Screening Visit) – Sub-bullet Pregnancy test

Inclusion of Section 8.1.1 (Corticosteroid Tapering Procedure)

The corticosteroid tapering procedure was added solely for previous GED-0301-CD-003 subjects who were on stable doses of corticosteroids and achieved clinical improvement by Week 12 in Study GED-0301-CD-003. These subjects should follow the guidance for a corticosteroid tapering procedure (Section 8.1.1) upon entrance into this study.

Revised Sections:

- Section 8.1 (Permitted Concomitant Medications for CD and Procedures)
- Section 8.1.1 (Corticosteroid Tapering Procedure) – newly added section

Inclusion of Section 9.9.2 (External Safety Monitoring: Role of the Independent DMC)

Safety monitoring for this study will be performed by an external, independent Data Monitoring Committee (DMC), along with the other Phase 3 GED-0301 studies, as part of the external safety monitoring for the GED-0301 Program. This section was intended to be included in the original protocol, but was inadvertently missed.

Revised Section:

- Section 9.9.2 (External Safety Monitoring: Role of the Independent DMC) – newly added section

Subject Dosing Instructions (Emphasis that Subjects Take 4 Tablets of IP Each Day)

Sections of the protocol were updated with clearer subject dosing instructions; emphasizing that "4 tablets" of the investigational product (IP) must be taken each day. That is, subjects will be instructed to take "4 tablets" in the morning, 30 minutes before breakfast with a glass of water.

Revised Sections:

- Protocol Summary (Study Treatments)
- Section 6.2 (Treatment Period; sub-bullet Dispense IP)
- Section 7.2 (Treatment Administration and Schedule)

All 160 mg Daily Treatments are Taken as Four 40 mg Tablets

Sections of the protocol have an added statement emphasizing that all 160 mg once daily (QD) treatments are taken as "four 40 mg tablets" daily in the study.

Revised Sections:

- Section 3.1 (Study Design)
- Figure 1 (Overall Study Design)
- Section 7.2 (Treatment Administration and Schedule)
- Appendix G (The Study GED-0301-CD-004 Treatment Table)

Change in the Cancer Surveillance Language

The language in this section had changed since there is no clear, global guidance with respect to screening programs for colorectal cancer. Therefore, Section 6.5.6 was updated to include a general statement indicating that subjects with increased risk of colorectal cancer should have undergone a colonoscopy with pan-colonic surveillance biopsies according to local guidelines. In Section 5, Table 5 (Table of Events), Footnote b, the text was revised to emphasize the same information.

Revised Sections:

- Section 5 (Table of Events, formerly Table 3)
- Section 6.5.6 (Cancer Surveillance)

Changes in the Appendices

The appendices were changed for multiple reasons: 1) to add the adolescent-specific key clinical efficacy assessments; 2)

Revised Sections:

- Appendix E – Pediatric Crohn's Disease Activity Index was added and the Inflammatory Bowel Disease Questionnaire was removed.
- Appendix F – Simple Endoscopic Score for Crohn's Disease was added .

The amendment also includes several other minor clarifications and corrections:

- For the Medical Monitor/Emergency Contact Information (Page 2 of the Protocol), the medical monitor title and contact information was updated.
- International Conference on Harmonisation has been corrected throughout the protocol to: International Council for Harmonisation.
- Throughout several sections and tables within the protocol document, the words "previous" or "prior" GED-0301 study was changed to "core" GED-0301 study for clarification and consistency purposes.
- In the Protocol Summary (Indication), Section 1.1 (Disease Background), Section 1.2 (Compound Background), Section 1.2.1 (Nonclinical Experience) and Section 1.2.2.2 (Clinical Safety), the text was updated to be consistent in documentation throughout the GED-0301 Program. As a result of the changes, Section 1.1.1 (Transforming Growth Factor-Beta 1 Signaling Pathway in Crohn's Disease) was no longer required and therefore deleted. In Section 17 (References), the references (Ballas, 2001) and (Ottenhof, 2011) were removed since the text in the Protocol Summary (Indication) and Section 1.2 (Compound Background) were updated and these references are no longer applicable.

- In the Protocol Summary (Study Design) and Section 3.1 (Study Design), text was added in Paragraph 3 in each section to emphasize that this study can only accept adult subjects from Study GED-0301-CD-002, since both adult and adolescent subjects are included in Study GED-0301-CD-003.
- In the Protocol Summary (Study Population), text was added to emphasize that this study can only accept subjects from the Study GED-0301-CD-002 or Study GED-0301-CD-003 if they have completed at least through the Week 12 "Visit" in each of those studies.
- In the Protocol Summary (Study Treatments), Section 1.3.3 (Rationale for Dose, Schedule and Regimen Selection) and Section 3.1 (Study Design), text was added in the applicable paragraph to emphasize that any modifications to the dose regimens in the study would be changed through a protocol amendment, which would require regulatory health authority and ethics committee approvals prior to implementation.
- In Section 1.2 (Compound Background) and Section 17 (References), the appropriate reference (Boirivant, 2006) was added to support the statement regarding Smad7, as a key regulatory modulator of transforming growth factor-beta 1 (TGF-β1).
- In Section 3.1 (Study Design) and Figure 1 (Overall Study Design), the descriptions of the treatment groups were updated to more clearly describe the treatment; for example, "alternating" PBO for 4 weeks "and" 160 mg for 4 weeks.
- In Section 3.1 (Study Design) and Section 5 (Table 5 and Table 6) Footnote "a" for each table, new text was added to further emphasize that the Visit 1 assessments and procedures in this study are not repeated if the early termination (ET) or last study treatment visit from the previous GED-0301 study and Visit 1 from this study are completed on the same day.
- In Section 3.2 (Study Duration for Subjects) and Protocol Summary (Length of Study), a paragraph was added to point out that the long-term active-treatment period of 208 weeks may be shortened in regions where GED-0301 becomes commercially available prior to study completion.
- In Section 3.3 (End of Study), the word "secondary" was added to the applicable sentence since there are secondary endpoints from the adolescent population as part of the study analysis. Also, a sentence was added to further clarify that there are no secondary objectives or endpoints for the adult subjects in this study and therefore no secondary analysis for adult subjects.
- In Section 4.2.1 (Inclusion Criteria for Adult Subjects), Footnote #4 was added to Inclusion Criterion #5 stating that subjects taking an oral contraceptive may need a backup or alternative method of birth control based on Investigator judgment. Section 6.5.5 (Contraception Education) was also updated with this information. 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 Crohn's disease (CD), which may affect gastrointestinal absorption or transit of oral contraceptives.

- In Section 4.3 (Exclusion Criteria [Adult and Adolescent Subjects]), Exclusion Criterion #5 has additional language to clarify that subjects are excluded when they have a "confirmed diagnosis of" colorectal dysplasia.
- In Section 5, Table 5 (Table of Events, formerly Table 3), the abdominal examination for the abdominal mass assessment was removed from the table since it had caused some confusion. Even though removed, the abdominal examination for the abdominal mass assessment is performed at each visit when the CDAI assessments are required. Therefore, in Section 5, Table 5 (Table of Events) Footnote d and Section 6.5.1 (Physical Examination), text was revised to emphasize that 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, and PCDAI calculations.
- In Section 6.4.2 (Lost to Follow-up), some of the content was changed to provide more flexibility on how and how many times a site may contact a subject if lost to follow-up. This language is consistent now with all the Phase 3 GED-0301 studies.
- In Section 6.6.1 (Screening Visit), the text in the two sub-bullets "prior concomitant medications evaluation" and "adverse event evaluation" were revised to emphasize that ongoing concomitant medications and ongoing AEs from the core GED-0301 study will be electronically carried forward and do not need to be recorded in the appropriate eCRFs for this study.
- In Section 6.6.2 (Crohn's Disease Activity Index), some of the content was corrected or updated to emphasize that clinical parameters needed for calculation of the CDAI will be collected by the subject via an electronic diary device and by the site at the scheduled visit via a separate electronic device. Also, 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 aphthous ulcers (previously in the same category with iritis/uveitis).
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- In Section 7.1 (Description of Investigational Products) and Protocol Summary (Study Treatments), the text in the first sentence was updated to emphasize that GED-0301 will be provided as 40-mg "gastro-resistant, delayed release, pH-dependent" tablets and are not regular "coated" tablets.
- In Section 7.2 (Treatment Administration and Schedule), the title names of Tables 4 to 7 (Investigational Product Dispensing Schedule for the Treatment Periods at Year 1, Year 2, Year 3, and Year 4, respectively) were changed to better define the intended purpose, which is to identify visits when IP dispensing occurs, not when dosing occurs.
- In Section 7.2.2 (Overdose), the timeframe for overdose as previously defined was revised to be within the same calendar day and no longer within a 24-hour period.
- In Section 7.3 (Method of Treatment Assignment), the table numbers were updated from Table 4 to Tables 7 to 10.
- In Section 7.4 (Packaging and Labeling), the text was corrected to state that blister cards with child-resistant seals are used in this study and not opaque high-density polyethylene bottles with child-resistant caps.
- In Section 17 (References), the following references were added based on the addition of new information or assessments related to the addition of the adolescent population content within the protocol: ; Daperno, 2004; Griffiths, 1999; Hyams, 1991; Kansal, 2013; Kelsen, 2008; Lewis, 1997; Mamula, 2003; Markowitz, 2009; ; Pigneur, 2010; Ruemmele; 2014; ; ; Van Limbergen, 2008;
- In Section 18 (Appendices), Appendix A (Table of Abbreviations) was updated with the removal of 4 abbreviations (ie, AS ODN, CpG, DNA and RNase) since text within the protocol was updated and these abbreviations are no longer applicable. The abbreviation DMC was added since Section 9.9.2 (External Safety Monitoring: Role of the Independent DMC) within the protocol was added. Also, other abbreviations were added based on the addition of the new pediatric and adolescent information.