DISCLOSURE

REDACTED PROTOCOL AMENDMENT 4

CC-10004-UC-001

A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) FOR TREATMENT OF SUBJECTS WITH ACTIVE ULCERATIVE COLITIS

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A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) FOR TREATMENT OF SUBJECTS WITH ACTIVE ULCERATIVE COLITIS

INVESTIGATIONAL PRODUCT:	**Apremilast**
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SPONSOR NAME / ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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PROTOCOL SUMMARY

Study Title

A Phase 2, randomized, placebo-controlled, multicenter study to investigate the efficacy and safety of apremilast (CC-10004) for treatment of subjects with active ulcerative colitis.

Indication

Active ulcerative colitis (UC).

Objectives

Primary Objective

To evaluate the clinical efficacy of apremilast (30 mg twice daily [BID] and 40 mg BID), compared with placebo, in subjects with active UC.

Secondary Objectives

- To evaluate the safety and tolerability of apremilast (30 mg BID and 40 mg BID), compared with placebo, in subjects with active UC
- To evaluate the long-term safety in subjects with active UC, receiving apremilast (30 mg BID or 40 mg BID)

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Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy and safety of 2 doses of apremilast in subjects with active UC (defined as a total Mayo score [TMS] of ≥ 6 to ≤ 11, with an endoscopic subscore ≥ 2).

Approximately 165 subjects (55 subjects per arm) will be randomized in a 1:1:1 ratio to receive oral apremilast (30 mg BID or 40 mg BID), or identically appearing placebo BID for up to 12 weeks, followed by 40 weeks of blinded treatment with apremilast (30 mg BID or 40 mg BID). At the end of 52 weeks in the study, subjects who have a Mayo endoscopy score ≤ 1 will have the opportunity to participate in the Extension Phase and will receive apremilast for an additional 52 weeks.

Treatment assignment will be stratified via an Interactive Voice Response System (IVRS)/or an Interactive Web Response System (IWRS) based on (1) concomitant use of oral corticosteroids and (2) previous exposure to immunosuppressants (eg, 6-mercaptopurine [6-MP], azathioprine [AZA], or methotrexate [MTX]). The number of subjects with previous exposure to immunosuppressants is targeted to comprise no more than 50% of the subjects enrolled, and no less than 30%.

The study will consist of 5 phases:

- Screening Phase – up to 4 weeks
- Double-blind Placebo-controlled Phase – Weeks 0 to 12
- Blinded Active-treatment Phase – Weeks 12 to 52
- Extension Phase – Weeks 52 to 104
    - The 52-week extension is an active-treatment phase and henceforth will be referred to as the Extension Phase for the remainder of the document. The Extension Phase was blinded prior to the implementation of Amendment 4. Following the implementation of Amendment 4, the Extension Phase will be open-label and all subjects will receive 30 mg BID as of their next visit.
- Post-treatment Observational Follow-up Phase – The 4-week period after the last dose of investigational product (IP)

Double-blind Placebo-controlled Phase

Eligible subjects will enter the Double-blind, Placebo-controlled Phase at the Baseline Visit (Week 0/Visit 2). Subjects will be randomly assigned to study treatment as described above. With the aim to mitigate potential dose-related side effects associated with apremilast, such as

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headache and gastrointestinal (GI) disturbances, apremilast-treated subjects will be dose-titrated in 10-mg/day increments over the first 8 days of treatment. All subjects will receive blister cards of identical appearance to maintain blinding (Table 5). Subjects will continue to receive the treatment assigned at baseline for 12 weeks.

Blinded Active-treatment Phase

Following 12 weeks of treatment, subjects will enter the Blinded Active-treatment Phase. At the Week 12 visit, subjects will be evaluated for clinical improvement based on the TMS. The endoscopy subscore assessed by the investigator will be used for the calculation of the Week 12 TMS.

Subjects who achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive the following IP between the Week 12 Visit and the Week 52 Visit:

- Subjects who were randomized to apremilast (30 mg BID or 40 mg BID) at baseline will continue to receive the treatment assigned at baseline.
- Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments over the first 8 days of treatment (Table 5).

Subjects who do not achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive the following IP until the Week 52 Visit:

- Subjects who were randomized to apremilast 30 mg BID at baseline will be re-assigned apremilast 40 mg BID, with no dose titration.
- Subjects who were randomized to apremilast 40 mg BID at baseline will continue to receive apremilast 40 mg BID.
- Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments over the first 8 days of treatment (Table 5).

In order to maintain the blind for the treatment assigned at baseline, all subjects will receive blister cards of identical appearance during the titration period beginning at Week 12. However, for subjects continuing on the dosage of apremilast assigned at baseline, and for subjects who are not undergoing dose titration (as noted above), the IP included in the "titration" portion of the blister card will include the total daily dose of apremilast (30 or 40 mg BID) and will not include the dose titration.

Extension Phase

At the end of the Blinded Active-treatment Phase (Week 52), subjects who have a Mayo endoscopy score ≤ 1 will have the opportunity to participate in the Extension Phase. Subjects participating in the Extension Phase will receive apremilast for an additional 52 weeks (Weeks 52 to 104). With the implementation of Amendment 4, subjects entering the Extension Phase will receive apremilast 30 mg BID. Subjects currently in the Extension Phase who are receiving apremilast 40 mg BID will be switched to 30 mg BID at the next scheduled visit.

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Post-treatment Observational Follow-up Phase

All subjects are required to spend 4 weeks in the Post-treatment Observational Follow-up Phase following the last dose of IP.

Study Population

The study population consists of female and male subjects 18 years and older at the time of signing the informed consent form (ICF). The major eligibility criteria are:

- Diagnosis of UC with a duration of at least 3 months, prior to the Screening Visit
- TMS ≥ 6 to ≤ 11 prior to randomization in the study (Section 6.7)
- Mayo endoscopic subscore ≥ 2 prior to randomization in the study
- Subjects must have had a therapeutic failure, been intolerant to, or have a contraindication to at least one of the following: oral aminosalicylates (ie, 5-aminosalicylic acid [5-ASA] compounds or sulfasalazine [SSZ]), budesonide, systemic corticosteroids, or immunosuppressants (eg, 6-mercaptopurine [6-MP], azathioprine [AZA], or methotrexate [MTX])
- Subjects receiving oral aminosalicylates may continue their use during the study, provided that treatment started at least 6 weeks prior to screening, and has been at a stable dose for at least 14 days prior to the Screening Visit.
- Subjects receiving oral corticosteroids may continue their use, provided that the dose (prednisone ≤ 20 mg/day or equivalent, budesonide ≤ 9 mg/day) has been stable for 3 weeks prior to the Screening Visit and must remain stable until the subject is eligible to start corticosteroids tapering, beginning at the Week 12 Visit.

Length of Study

Subjects will spend up to 112 weeks in this study: up to 4 weeks in the Screening Phase; 12 weeks in the Double-blind Placebo-controlled Phase and 40 weeks in the Blinded Active-treatment Phase. Subjects who participate in the Extension Phase will spend an additional 52 weeks in the study. All subjects are required to spend 4 weeks in the Post-treatment Observational Follow-up Phase.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

Study Treatments

Subjects will receive one of two dose regimens of apremilast in the Double-blind Placebo-controlled Phase (30 mg BID or 40 mg BID), or placebo BID. During the Blinded Active-treatment Phase, subjects will receive apremilast 30 mg BID or 40 mg BID. With the implementation of Amendment 4, subjects who participate in the Extension Phase will receive apremilast 30 mg BID. Subjects currently receiving 40 mg BID in the Extension Phase will be switched to 30 mg BID at the next scheduled visit. Apremilast will be provided in blister cards as 10-mg, 20-mg, or 30-mg tablets in the clinical image. Matched placebo tablets will also be

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provided. Tablets will be taken by mouth twice daily, morning and evening, approximately 12 hours apart, with no food restrictions.

Overview of Efficacy Assessments

- TMS at baseline, Week 12, and Week 52, or at the Early Termination Visit if the Early Termination Visit occurs prior to Week 52
- Modified Mayo score (based on stool frequency, rectal bleeding, and endoscopy) at baseline, Week 12, and Week 52
- PMS during the Screening Phase and at all visits through the Week 52 Visit, and for subjects participating in the Extension Phase, through Week 104 and at the Observational follow-up Visit.
- Endoscopy (flexible rectosigmoidoscopy) during the Screening Phase, Week 12, and Week 52 or at the Early Termination Visit if the Early Termination Visit occurs prior to Week 52
- Colonoscopy, as opposed to rectosigmoidoscopy, is required at screening only if one was not performed within 12 months prior to the Screening Visit.

Overview of Safety Assessments

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Body weight
- Electrocardiograms (ECG)
- Clinical laboratory safety evaluations
- Pregnancy tests

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1. INTRODUCTION

1.1. Apremilast

Apremilast (CC-10004) is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) that works intracellularly to modulate a network of pro- and anti-inflammatory mediators. Phosphodiesterase 4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. Inhibition of PDE4 elevates intracellular cAMP levels, which in turn downregulates the inflammatory response by modulating the expression of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-23, IL-17, and other pro-inflammatory cytokines. Elevation of cAMP also increases anti-inflammatory cytokines. These pro- and anti-inflammatory mediators have been implicated in inflammatory bowel disease (IBD), psoriasis and psoriatic arthritis (PsA) (Schafer, 2010). Apremilast is currently under clinical development for the treatment of inflammatory autoimmune disorders, such as PsA, psoriasis, ankylosing spondylitis (AS), Behçet disease (BD), and atopic dermatitis. Detailed information about apremilast can be found in the Investigator's Brochure (IB).

Ulcerative colitis (UC) is an intestinal inflammatory condition that is characterized by T-cell activation, and is associated with an atypical Type 2 helper T-cell (T_h2) response mediated by non-classic natural killer (NK) T-cells producing IL-5 and IL-13. Ulcerative colitis has been associated with the production of pro-inflammatory cytokines, such as IL-1β, IL-6, TNF-α, and TNF-like ligand 1 (TL1A) (Danese, 2011). In addition, other helper T-cell lineages have been recently characterized, including T_h17 cells that produce the proinflammatory cytokine IL-17. Levels of IL-17 have been found to be increased in the mucosa of patients with IBD (Fujino, 2003).

TNF-α has been shown to play a role in the pathogenesis of UC and Crohn's disease (CD). Specifically, elevated levels of TNF-α have been found in the stool, lamina propria, and blood of patients with active disease and treatment with TNF-α neutralizing antibodies reduces UC and CD disease activity. One pathway through which TNF-α damages the gut is through upregulation of matrix metalloproteinase (MMP) production by gut myofibroblasts, leading to extracellular matrix breakdown, tissue destruction, and ulcer formation. In pokeweed mitogen-stimulated gut lamina propria mononuclear cells (LPMCs) from normal subjects, apremilast significantly reduced TNF-α production by 63% ($p < 0.001$). Additionally, apremilast significantly inhibited CD and UC patient LPMC-MMP-3 production in vitro ($p < 0.001$). The reduction in LPMC-MMP-3 production by apremilast was characterized by a significant inhibition of LPMC-MMP-3 mRNA and protein production in a dose-dependent manner within the concentration range of 2 to 100 µM (Gordon, 2009). Apremilast has also shown beneficial effects in the 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis mouse model of IBD. Administration of apremilast at the dose of 2.5-mg/kg resulted in a reduction of diarrhea and the severity of the mucosal damage in the distal large intestine to a degree similar to the positive control, 5-ASA; first-line therapy in the standard of care for IBD. Apremilast had a positive trophic effect on intestinal mucosal crypt morphology, particularly by increasing crypt width. Apremilast also reduced the loss of body weight induced by TNBS, in a dose-dependent manner. Together, these nonclinical results highlight the potential of apremilast in the treatment of IBD.

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As such, apremilast may act to suppress the existing inflammatory response by downregulating the expression of TNF-α, IL-5, IL-13 and IL-17 and other inflammatory cytokines present within the gastrointestinal (GI) tract, along with the inhibition of further recruitment of immune cells into inflamed tissue (Sandborn, 2003).

1.2. Ulcerative Colitis

Ulcerative colitis is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. It is one of the most common forms of IBD.

The worldwide incidence of ulcerative colitis is 1.2 to 20.3 cases per 100,000 persons per year, and its prevalence is 7.6 to 246.0 cases per 100,000 per year (Danese, 2011). The highest incidence and prevalence of IBD are seen in the populations of Northern Europe and North America, and the lowest incidence and prevalence are in continental Asia, where UC is by far the most common form of IBD (Danese, 2011). Although the etiology of UC remains unknown, a dysregulation or overstimulation of the mucosal immune system appears to play a critical role in the pathophysiology of intestinal inflammation and contributes to mucosal ulceration (Ordás, 2012). Clinical characteristics include rectal bleeding, diarrhea, and abdominal pain, as well as extraintestinal manifestations involving the skin, liver, and other sites (Danese, 2011). Patients with UC often have a poor quality of life and are at risk for disease flares leading to hospitalizations and/or surgeries.

The main objectives of treatment in patients with UC are to induce and maintain the remission of symptoms and mucosal inflammation in order to improve patients' quality of life. Treatment of UC currently involves pharmacological treatment and surgery, which is indicated when pharmacological treatment fails or when a surgical emergency (eg, perforation of the colon) occurs. Treatment takes into consideration the level of clinical activity combined with the extent of disease (proctitis, left-sided disease, extensive disease, or pancolitis). Pharmacological treatment usually involves aminosalicylates and glucocorticoids as an initial approach. Various immunosuppressants, as well as biologic tumor necrosis factor (TNF) blockers, are used in refractory or severe disease. Although these drugs can provide clinical benefit, they have important limitations. Aminosalicylates are only modestly effective. Glucocorticoids can cause unacceptable adverse events (AEs) and do not provide a benefit as maintenance therapy. Additionally, immunosuppressant use has been restricted to maintenance therapy and is also associated with significant potential toxicities. The TNF blockers, although efficacious, predispose patients to serious infections (including opportunistic infections) and possibly malignancies, (Clark, 2007; Kornbluth, 2010). Because apremilast specifically inhibits PDE4, which increases intracellular cyclic adenosine monophosphate (cAMP) and this modulates multiple pro-inflammatory and anti-inflammatory mediators, such as TNF-α, IL-12, and IL-23, it is believed there may be a role for this drug in the treatment of UC.

The additional burden caused by comorbidities induced by adverse effects of some of these drugs indicates that an unmet medical need exists for effective and well-tolerated orally active agents for inducing and maintaining remission in patients with active UC.

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1.3. Nonclinical Studies

1.3.1. In Vitro Activity

In lipopolysaccharide (LPS)-challenged peripheral blood mononuclear cells (PBMCs), apremilast inhibited, in order of decreasing potency interferon-γ inducible protein-10 (IP-10), interferon-γ (IFN-γ), monokine induced by interferon-γ (MIG), TNF-α, IL-12p70, macrophage inflammatory protein-1α (MIP-1α), monocyte chemotactic protein-1 (MCP-1), and granulocyte macrophage colony-stimulating factor (GM-CSF) production. Reduction of TNF-α, IFN- γ, IL-12, and IL-23 expression occurred at the messenger ribonucleic acid (mRNA) level. It also inhibited IFN-γ and IL-2 production by PBMCs stimulated with staphylococcal enterotoxin B. In purified human Natural Killer (NK) cells, apremilast inhibited production of TNF-α and GM-CSF. Production of IL-8 and leukotriene B4 by polymorphonuclear neutrophils (PMN), and TNF-α production by human epidermal keratinocytes (HEK), were also blocked by apremilast in vitro. Apremilast was tested in a model of psoriasis using normal human skin xenotransplanted onto beige-severe combined immunodeficient (SCID) mice and triggered with human psoriatic NK cells. Orally administered apremilast (5 mg/kg/day) significantly reduced epidermal thickness and proliferation, and decreased the general histopathologic appearance of psoriasiform features. Staining for TNF-α, human leukocyte antigen DR (HLA-DR), and intercellular cell adhesion molecule-1 (ICAM-1) in lesional skin was also qualitatively reduced by apremilast treatment (Schafer, 2010).

1.3.2. In Vivo Anti-inflammatory Activity in Animals

1.3.2.1. 2,4,6-Trinitrobenzene Sulfonic Acid (TNBS)-induced Colitis Mouse Model of IBD

In the 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis mouse model of IBD, apremilast reduced body weight loss in a dose-dependent manner. At the 2.5-mg/kg dose, apremilast reduced diarrhea and the severity of the mucosal damage in the distal large intestine to a degree similar to the positive control, 5-aminosalicylic acid (5-ASA; IBD treatment option). Apremilast had a positive trophic effect on intestinal mucosal crypt morphology, particularly by increasing crypt width CCI . Supplemental experimentation demonstrated that, IFN-γ, IP-10, and monokine gene expression levels did not correlate with colitis severity. Nevertheless, these in vivo data highlight the beneficial effects of apremilast, ie, reducing the damage to the colonic mucosa, in the TNBS-induced colitis model. Also, the efficacy of apremilast was comparable with that of 5-ASA (anti-inflammatory agent). Together, these results highlight the potential of apremilast in the treatment of UC.

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1.4. Clinical Summary

1.4.1. Clinical Pharmacology

The pharmacokinetic (PK) disposition of apremilast has been characterized extensively in healthy subjects and subjects with PsA, psoriasis, asthma, and rheumatoid arthritis (RA). In healthy subjects under fasting conditions, following oral administration, apremilast was rapidly absorbed with maximum plasma concentrations occurring approximately 2.5 hours postdose and with an absolute bioavailability of approximately 73%. CCI [redacted] Coadministration with food did not alter the extent of absorption; therefore, apremilast can be administered with or without food.

In vitro data indicated that human plasma protein binding of apremilast was approximately 68%. Apremilast was primarily eliminated as metabolites formed via multiple metabolic pathways including both cytochrome P450 (CYP)-mediated oxidative metabolism (and subsequent glucuronidation) and non-CYP-mediated hydrolysis, with less than 3% excreted unchanged in urine and a terminal elimination half-life of approximately 6 to 9 hours. Apremilast did not inhibit CYP enzymes in vitro, suggesting that it is unlikely to inhibit the metabolism of coadministered CYP substrates. There were no clinically significant interactions with ketoconazole, MTX, or an oral contraceptive containing ethinyl estradiol and norgestimate, when apremilast was coadministered with these drugs. Pharmacokinetic studies were conducted in

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subjects with hepatic impairment and subjects with renal impairment. Hepatic impairment does not affect the PK of apremilast, while severe renal impairment increases apremilast exposure area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) by approximately 88%.

Apremilast at doses higher than 30 mg BID has been evaluated previously in healthy volunteers in a multiple dose PK and safety study (CC-10004-PK-007), in which 9 subjects received 40 mg BID for 14 days; and in a thorough QT study (CC-10004-PK-008) in which 57 subjects received 50 mg BID for 4.5 days. Results from the thorough QT study did not show any evidence of prolongation of the heart rate-corrected QT interval (QTc), indicating that apremilast in this dose range does not pose a risk for prolongation of the QT interval.

1.4.2. Safety

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As of the cut-off date, 42 clinical studies have been completed, including:

- 24 Phase 1 studies (19 studies in healthy subjects, 1 study in subjects with moderate or severe hepatic impairment, 1 study in subjects with severe renal impairment, 1 study in subjects with mild to moderate renal impairment, and 1 study in subjects with PsA or RA),
- 10 Phase 2 studies (5 studies in subjects with psoriasis, 1 study in subjects with PsA, 1 study in subjects with RA, 1 study in subjects with BD, 1 study in subjects with AD, and 1 study in subjects with asthma),
- 7 Phase 3 studies (3 studies in subjects with psoriasis and 4 studies in subjects with PsA), and
- 1 Phase 4 study (in subjects with psoriasis).

A total of 7 clinical studies are currently ongoing:

- 1 Phase 1 study (in healthy subjects),
- 2 Phase 2 studies (1 in pediatric subjects with psoriasis and 1 in subjects with UC), and
- 4 Phase 3 studies (1 study in subjects with PsA, 1 study in subjects with psoriasis of the scalp, 1 study in subjects with BD, and 1 study in subjects with AS).

In completed and ongoing apremilast Phase 2 or Phase 3 studies, the most commonly observed treatment emergent adverse events (TEAEs) [ie, those reported in > 5% of subjects] have been diarrhea, nausea, headache (including tension headache), upper respiratory tract infections, and nasopharyngitis. The majority of TEAEs of diarrhea, nausea, headache occurred within the first 2 weeks of treatment and most resolved within 4 weeks.

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The majority of reported TEAEs were mild or moderate in severity and resolved while subjects continued apremilast treatment. The incidence of SAEs was low and comparable between apremilast and placebo treatment groups in the placebo-controlled periods and was not driven by any single preferred term or any specific individual organ toxicity. The safety profile of apremilast is comparable in the psoriasis and PsA indications. The overall safety profile in subjects with AS, BD, and RA is similar to the safety profile in the psoriasis and PsA indications.

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1.4.3. Dose Justification

Oral doses of apremilast at 30 mg BID and 40 mg BID were selected for this study after consideration of the nonclinical pharmacology results and clinical study results in two Phase 1 PK studies (CC-10004-PK-007 and CC-10004-PK-008), two Phase 2 dose-ranging studies in PsA (CC-10004-PSA-001) and psoriasis (CC-10004-PSOR-005). In the CC-10004-PSOR-005 study, a clear dose response in efficacy assessments was observed between placebo, and 10, 20, and 30 mg BID in the psoriasis population. The CC-10004-PSOR-005 study and CC-10004-PK-008 study demonstrated that drug exposure increased proportionally with dose (from 10 mg BID to 30 mg BID, and from 30 mg BID to 50 mg BID, respectively). Additionally, apremilast has been tolerated with no overt safety concerns in a thorough QTc study (CC-10004-PK-008) with doses up to 50 mg BID.

Since the dose response had not been characterized in subjects with ulcerative colitis prior to the start of this study, two dose regimens were chosen (30 mg BID and 40 mg BID). The 30 mg BID regimen was chosen due to its demonstrated efficacy and its acceptable safety and tolerability profiles in subjects with PsA and psoriasis. The 40 mg BID regimen was chosen to further explore the potential therapeutic effect of apremilast and to evaluate the dose-response relationship in this population. Apremilast at doses higher than 30 mg BID have been evaluated previously in healthy subjects in a multiple dose PK and safety study (CC-10004-PK-007), in which 9 subjects received 40 mg BID for 14 days; and in a thorough QT study (CC-10004-PK-008) in which 57 subjects received 50 mg BID for 4.5 days. In both studies, an increase in the incidence of AEs was noted with increasing apremilast doses. The majority of reported AEs were mild to moderate in intensity. The most frequently reported AEs were nausea, headache, decreased appetite, diarrhea, vomiting, and abdominal pain. There was no evidence of dose-related changes in vital signs, physical examinations and clinical laboratory findings. In pooled data from Phase 3 PsA studies, the proportion of subjects reporting diarrhea, nausea, and headache increased in a treatment- and dose-dependent manner, with the highest incidence occurring in the first 2 weeks of treatment. The majority of reported AEs were mild or moderate in severity and resolved with continued therapy. The incidences of SAEs and other clinical/laboratory parameters were similar between the dose groups.

Of note, available information from several compounds that are approved or were in development for IBD at the time of study start suggested that higher doses or more frequent dosing are required for the treatment of patients with IBD compared to patients with RA, PsA and/or psoriasis such as adalimumab (Humira®) (Humira, 2013), tofacitinib (Xeljanz®)

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(Sandborn, 2012, Xeljanz, 2012), and golimumab (Simponi®) (Simponi, 2013). Risk minimization measures such as ongoing safety review and Data Monitoring Committee (DMC) oversight were implemented to ensure that the safety of the subjects is adequately monitored.

The results from the first 12 weeks of this study indicated that subjects with active UC treated with apremilast 30 mg BID achieved meaningful improvements in symptoms of UC (remission), endoscopy, CCI compared to placebo. Subjects treated with apremilast 40 mg BID achieved meaningful improvements in symptoms of UC (response) CCI compared to placebo. An acceptable safety profile was observed in both the apremilast 30 mg and 40 mg BID dose groups. Based upon the similarity of the clinical, endoscopic CCI endpoints in subjects treated with apremilast 30 mg and 40 mg BID and the plateau of dose response, as well as the extensive marketed safety experience with this dose, the 30 mg BID dose was determined to be the minimum dose that provides the maximum treatment response with an acceptable safety profile.

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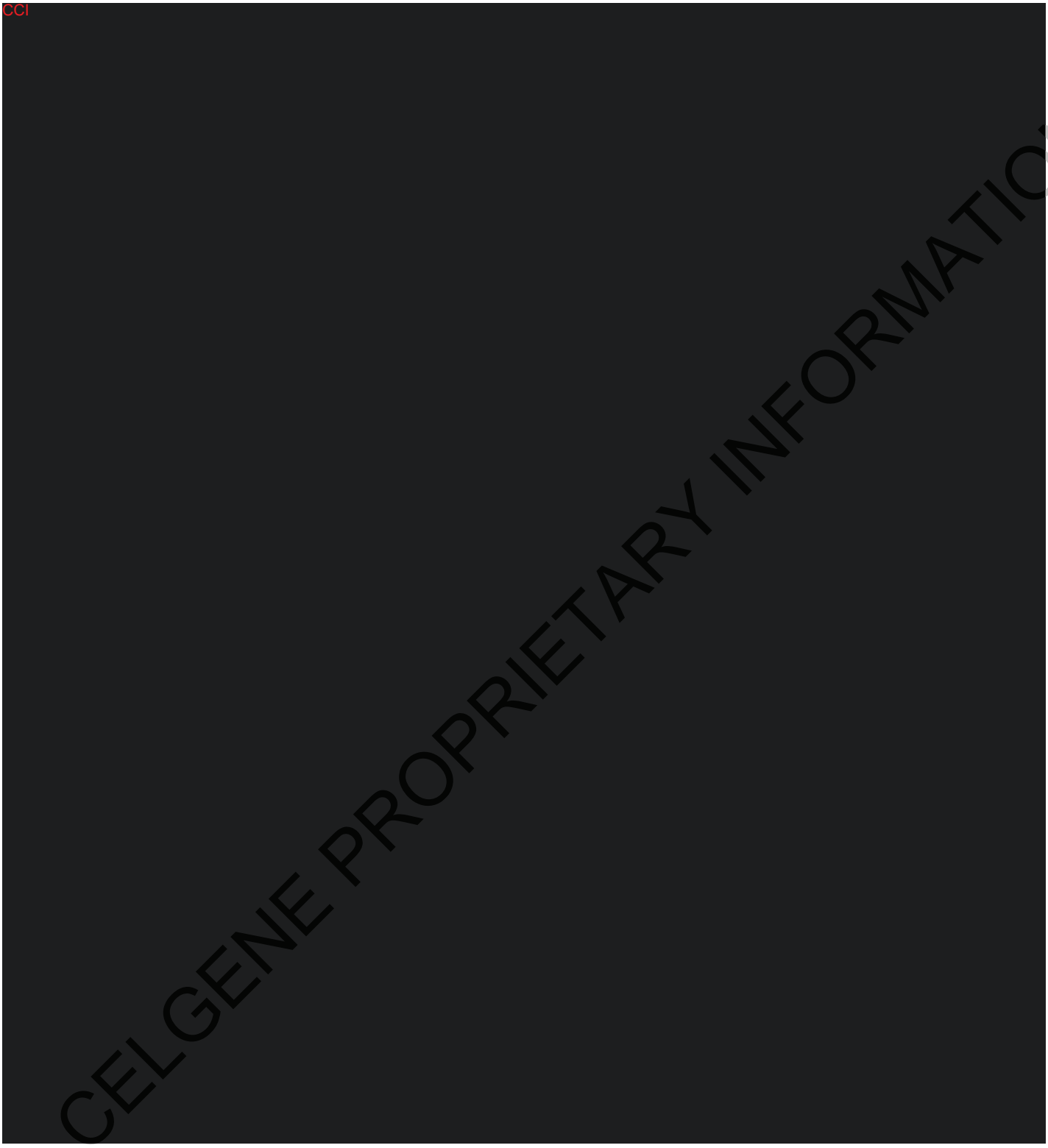

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2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of apremilast (30 mg BID and 40 mg BID), compared with placebo, in subjects with active ulcerative colitis (UC).

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of apremilast (30 mg BID and 40 mg BID), compared with placebo, in subjects with active UC
- To evaluate the long-term safety in subjects with active UC, receiving apremilast (30 mg BID or 40 mg BID)

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3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint of this study is the proportion of subjects achieving a clinical remission in the TMS at Week 12, defined as a TMS of ≤ 2, with no individual subscore > 1

3.2. Secondary Endpoints

3.2.1. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The proportion of subjects achieving clinical response at Week 12, defined as a decrease from baseline in the TMS of at least 3 points and at least 30%, along with a reduction in the rectal bleeding subscore (RBS) of at least 1 point or an absolute RBS of ≤ 1
- The proportion of subjects achieving endoscopic remission at Week 12, defined as a Mayo endoscopic subscore of 0
- The proportion of subjects achieving endoscopic response at Week 12, defined as a decrease from baseline of at least 1 point in the Mayo endoscopic subscore
- The proportion of subjects achieving a RBS ≤ 1 at Week 12
- The proportion of subjects achieving clinical remission in the modified Mayo Score (range: 0 to 9, based on stool frequency (SFS), RBS and endoscopy) at Week 12, defined as a score of 2 points or lower, with no individual subscore exceeding 1 point
- The proportion of subjects achieving clinical response in the modified Mayo Score at Week 12, defined as a decrease from baseline at least 2 points and at least 25%, along with a reduction in the RBS of at least 1 point or an absolute RBS of ≤ 1 point
- The proportion of subjects achieving clinical remission at Week 8, defined as a PMS of ≤ 2, with no individual subscore > 1
- The proportion of subjects achieving clinical response at Week 8, defined as a decrease from baseline in the PMS of at least 2 points and at least 25%, along with a reduction in the RBS of at least 1 point or an absolute RBS of ≤ 1 point

3.2.2. Secondary Safety Endpoints

The following safety parameters will be evaluated for the duration of the study:

- Type, frequency, severity, and relationship of AEs to IP
- Number of subjects who discontinue IP due to any AE
- Frequency of clinically significant changes in physical examination, vital signs, and/or laboratory findings

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4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy and safety of 2 doses of apremilast in subjects with active UC (defined as a total Mayo score [TMS] of ≥ 6 to ≤ 11, with an endoscopic subscore ≥ 2).

Approximately 165 subjects (55 subjects per arm) will be randomized in a 1:1:1 ratio using an Interactive Voice Response system (IVRS) or an Interactive Web Response System (IWRS) to receive oral apremilast (30 mg BID or 40 mg BID), or identically appearing placebo BID for up to 12 weeks, followed by 40 weeks of blinded treatment with apremilast (30 mg BID or 40 mg BID). At the end of 52 weeks in the study, subjects who have a Mayo endoscopy score ≤ 1 will have the opportunity to participate in the Extension Phase and will continue to receive apremilast for an additional 52 weeks.

Treatment assignment will be stratified via IVRS/IWRS based on concomitant use of oral corticosteroids and previous exposure to immunosuppressants (eg, 6-MP, AZA, or MTX). The number of subjects with previous exposure to immunosuppressants is targeted to comprise, no more than 50% of the subjects enrolled, and no less than 30%.

The study will consist of 5 phases:

- Screening Phase – up to 4 weeks
- Double-blind Placebo-controlled Phase – Weeks 0 to 12
- Blinded Active-treatment Phase – Weeks 12 to 52
- Extension Phase – Weeks 52 to 104
    - The 52-week extension is an active treatment phase and henceforth will be referred to as the Extension Phase for the remainder of the document. The Extension Phase was blinded prior to the implementation of Amendment 4. Following the implementation of Amendment 4, the Extension Phase will be open-label and all subjects will receive 30 mg BID as of their next visit.
- Post-treatment Observational Follow-up Phase – The 4-week period after the last dose of investigational product (IP).

Double-blind Placebo-controlled Phase

Eligible subjects will enter the Double-blind Placebo-controlled Phase for 12 weeks, at the Baseline Visit (Week 0, Visit 2). Subjects will be randomly assigned to study treatment as described above. With the aim to mitigate potential dose-related side effects associated with apremilast, such as headache and gastrointestinal (GI) disturbances, apremilast-treated subjects will be dose-titrated in 10-mg/day increments over the first 8 days of treatment (Table 5). All subjects will receive blister cards of identical appearance to maintain blinding. Subjects will continue to receive the treatment assigned at baseline for 12 weeks.

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Blinded Active-treatment Phase

Following 12 weeks of treatment, subjects will enter the Blinded Active-treatment Phase for 40 weeks. At the Week 12 visit, subjects will be evaluated for clinical improvement based on the TMS. The endoscopy subscore assessed by the investigator will be used for the calculation of the Week 12 TMS.

Subjects who achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive the following IP between the Week 12 Visit and the Week 52 Visit:

- Subjects who were randomized to apremilast (30 mg BID or 40 mg BID) at baseline will continue to receive the treatment assigned at baseline.
- Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments over the first 8 days of treatment (Table 5).

Subjects who do not achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive the following IP until the Week 52 Visit:

- Subjects who were randomized to apremilast 30 mg BID at baseline will be re-assigned apremilast 40 mg BID, with no dose titration.
- Subjects who were randomized to apremilast 40 mg BID at baseline will continue to receive apremilast 40 mg BID.
- Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments over the first 8 days of treatment (Table 5).

In order to maintain the blind for the treatment assigned at baseline, all subjects will receive blister cards of identical appearance during the titration period beginning at Week 12. However, for subjects continuing on the dosage of apremilast assigned at baseline, and for subjects who are not undergoing dose titration (as noted above), the IP included in the "titration" portion of the blister card will include the total daily dose of apremilast (30 or 40 mg BID) and will not include the dose titration.

Extension Phase

At the end of the Blinded Active-treatment Phase (Week 52), subjects who have a Mayo endoscopy score ≤ 1 will have the opportunity to participate in the Extension Phase. Subjects participating in the Extension Phase will receive apremilast for an additional 52 weeks (ie, Weeks 52 to 104). Subjects entering the Extension Phase will receive apremilast 30 mg BID as of their next visit. Subjects currently in the Extension Phase who are receiving apremilast 40 mg BID will be switched to 30 mg BID at the next scheduled visit.

Post-treatment Observational Follow-up Phase

All subjects are required to spend 4 weeks in the Post-treatment Observational Follow-up Phase following the last dose of IP.

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4.1.1. Internal Celgene Safety Monitoring During the Apremilast Program

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) on a regular basis. 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 apremilast development program.

4.1.2. Internal Data Safety Monitoring Board During the Study

Unblinded safety data has been reviewed regularly by an internal data safety monitoring board (iDSMB) at Celgene that is independent of the study team. With the implementation of Amendment 4, all subjects will be in the Extension Phase and will receive open-label apremilast 30 mg BID at their next visit. Therefore, the iDSMB is no longer necessary to support CC-10004-UC-001.

4.1.3. External Safety and Efficacy Monitoring During Apremilast Program

Monitoring has been performed by an independent, external DMC assessing both safety and efficacy as outlined in the DMC charter. The DMC was comprised of 3 independent external trialists and an independent, external statistician, for whom there was no identified conflict of interest. The DMC was convened approximately every 6 months. Following the meeting with the DMC on 27 Oct 2017 the DMC continued to recommend that the study could continue as planned.

After all subjects completed the 12-week Placebo-controlled Phase, Celgene determined that the DMC was no longer necessary to support the CC-10004-UC-001 study since the safety profile of apremilast in UC is similar to that observed in the approved indications and no new safety signal emerged in CC-10004-UC-001.

4.2. Study Design Rationale

This study represents the first investigation of apremilast in subjects with UC. This study will provide information on the safety and clinical efficacy in the UC population prior to advancing to larger clinical trials, as well as provide critical information for the design of future studies in this population.

The purpose of this study is to determine whether apremilast is effective and safe in the treatment of subjects with active UC. The primary measure of efficacy will be clinical remission determined by the TMS during the Double-blind Placebo-controlled Phase at Week 12. Clinical remission is defined as a TMS ≤ 2, with no individual subscore > 1, at Week 12. The TMS is a widely accepted standard for the evaluation of patients with UC and is commonly used as an endpoint in clinical trials (Rutgeerts, 2005). The laboratory results, AEs, vital signs, electrocardiograms (ECGs), pregnancy tests and physical examinations will be monitored to evaluate safety.

A schematic diagram illustrating the study design is shown in Figure 1.

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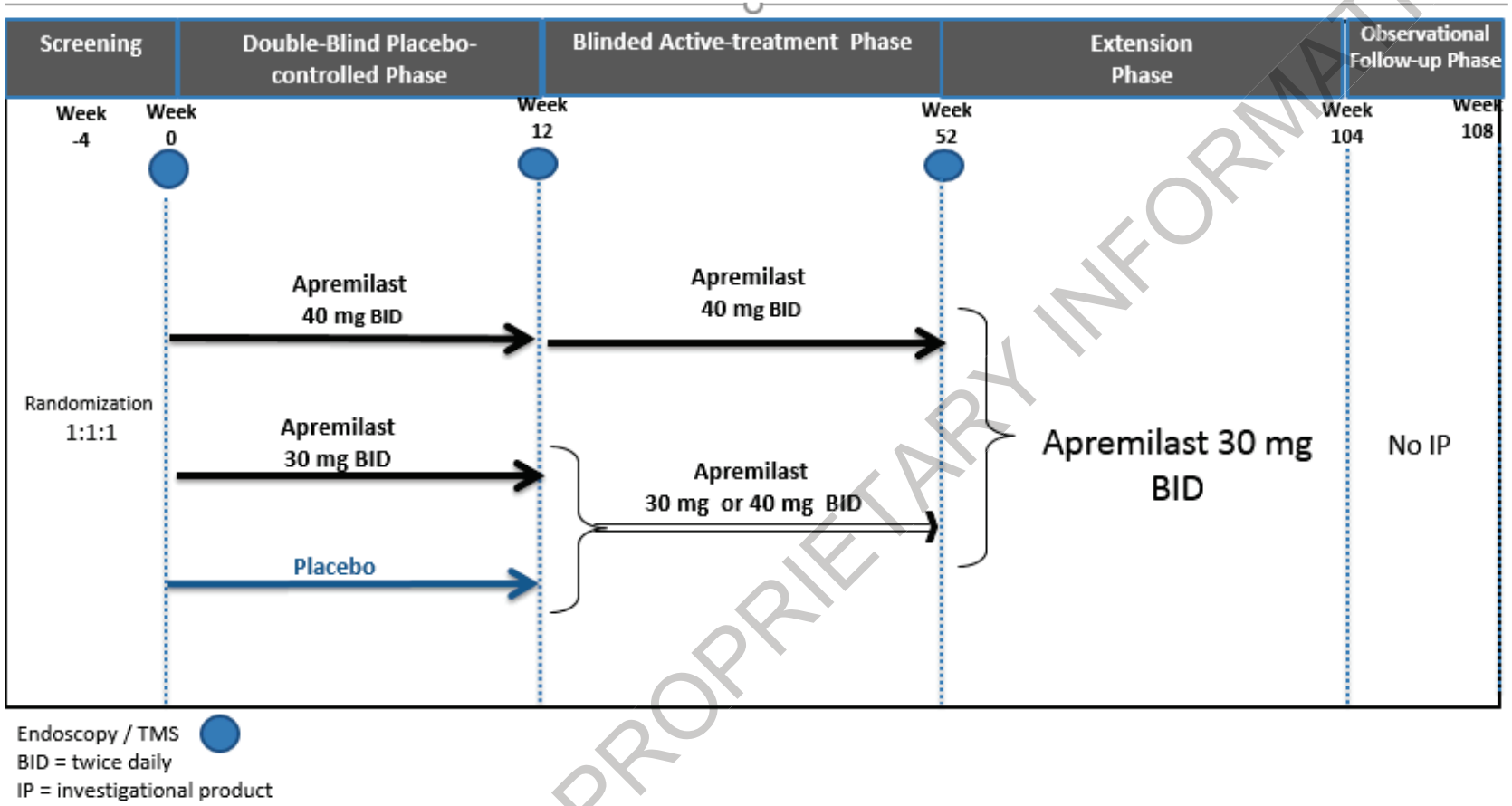
Figure 1: Overall Study Design



Subjects who achieve at least 20% decrease from baseline in the total Mayo score (TMS) at Week 12 will receive the following study treatment until the Week 52 Visit:
Subjects assigned apremilast (30 mg BID or 40 mg BID) at baseline will continue to receive the treatment assigned at baseline; Subjects assigned placebo at baseline will be re-randomized to receive apremilast (30 mg or 40 mg BID).
Subjects who do not achieve at least 20% decrease from baseline in the TMS at Week 12 will receive the following IP until the Week 52 Visit:

- Subjects assigned apremilast 30 mg BID at baseline will be re-assigned to receive apremilast 40 mg BID
- Subjects assigned apremilast 40 mg BID at baseline will continue to receive apremilast 40 mg BID. Subjects assigned placebo at baseline will be re-randomized to receive apremilast (30 mg or 40 mg BID)

At the end of 52 weeks in the study, subjects who have a Mayo endoscopy score ≤ 1 will have the opportunity to participate in the Extension Phase and receive apremilast 30 mg BID. Subjects currently in the Extension Phase who are receiving apremilast 40 mg BID will be switched to 30 mg BID at the next scheduled visit.
All subjects are required to spend 4 weeks in the Post-treatment Observational Follow-up Phase following the last dose of IP.

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4.3. Study Duration

Subjects will spend up to 112 weeks in this study: up to 4 weeks in the Screening Phase; 12 weeks in the Double-blind Placebo-controlled Phase and 40 weeks in the Blinded Active-treatment Phase. Subjects who participate in the Extension Phase will spend an additional 52 weeks in the study. Subjects are required to spend 4 weeks in the Post-treatment Observational Follow-up Phase following the last dose of IP.

4.4. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as prespecified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

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5. TABLE OF EVENTS

Table 4: Table of Events

	Screen-ing Phase	Double-blind Placebo-controlled Phase					Blinded Active-treatment Phase					Extension Phase			ET	Post-treatment Observational Follow-up Phase
Visit Number	**1**	**2 Baseline Visit**	**3**	**4**	**5**	**6[a]**	**7**	**8**	**9**	**10**	**11[b]**	**12**	**13**	**14**	**ET[c]**	**15[d]**
Week	**-4 to -1**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**12 (± 3 days)**	**16 (± 3 days)**	**24 (±3 days)**	**36 (±3 days)**	**48 (± 3 days)**	**52 (±3 days)**	**68 (±7 days)**	**86 (±7 days)**	**104 (±7 days)**	**ET (±3 days)**	**Obs. Follow-up (± 7 days)**
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	--
Inclusion / Exclusion Criteria	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior / Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test and Contraception Education[e]	X	X	-	-	-	X	-	-	-	-	X	X	X	X	X	-
Hepatitis B and C Tests	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical Lab Evaluations	X	X	-	-	-	X	-	-	X	-	X	X	X	X	X	-
Stool Culture / Microbiology	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Height	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vital Signs / Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X	-	-	-	-	X	-	-	-	-	X	-	-	X	X	-
Limited Physical Exam	-	X	-	-	-	-	-	X	-	-	-	X[f]	X[f]		-	X
Adverse Events[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Table 4: Table of Events (Continued)

	Screen-ing Phase	Double-blind Placebo-controlled Phase					Blinded Active-treatment Phase					Extension Phase			ET	Post-treatment Observational Follow-up Phase
Visit Number	**1**	**2 Baseline Visit**	**3**	**4**	**5**	**6[a]**	**7**	**8**	**9**	**10**	**11[b]**	**12**	**13**	**14**	**ET[c]**	**15[d]**
Week	**-4 to -1**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**12 (± 3 days)**	**16 (± 3 days)**	**24 (±3 days)**	**36 (±3 days)**	**48 (± 3 days)**	**52 (±3 days)**	**68 (±7 days)**	**86 (±7 days)**	**104 (±7 days)**	**ET (±3 days)**	**Obs. Follow-up (± 7 days)**
Psychiatric Evaluation[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	-	-	-	-	X	-	-	-	-	X	-	-	X	X	-
CCI [redacted]																
Subject Diary for UC Disease Activity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone Contact: Remind subjects who are participating in the Extension Phase to complete diaries 1 week before each visit.	-	-	-	-	-	-	-	-	-	-	-	X	X	X	X	X
PGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Partial Mayo Score (PMS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy (Flexible Rectosigmoidoscopy/ colonoscopy[j]	X	-	-	-	-	X	-	-	-	-	X	-	-	-	X[k]	-

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Table 4: Table of Events (Continued)

	Screen-ing Phase	Double-blind Placebo-controlled Phase					Blinded Active-treatment Phase					Extension Phase			ET	Post-treatment Observational Follow-up Phase
Visit Number	**1**	**2 Baseline Visit**	**3**	**4**	**5**	**6[a]**	**7**	**8**	**9**	**10**	**11[b]**	**12**	**13**	**14**	**ET[c]**	**15[d]**
Week	**-4 to -1**	**0 (Day 1)**	**2 (± 3 days)**	**4 (± 3 days)**	**8 (± 3 days)**	**12 (± 3 days)**	**16 (± 3 days)**	**24 (±3 days)**	**36 (±3 days)**	**48 (± 3 days)**	**52 (±3 days)**	**68 (±7 days)**	**86 (±7 days)**	**104 (±7 days)**	**ET (±3 days)**	**Obs. Follow-up (± 7 days)**
Total Mayo Score (TMS)	-	X	-	-	-	X	-	-	-	-	X	-	-	-	X[k]	-
CCI [redacted]																
SF-12v2 (Short Form 12-item Health Survey, version 2)	-	X	-	-	-	X	-	-	-	-	X	-	-	X	-	-
CCI [redacted]																
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	-

ECG=Electrocardiogram; ET= Early Termination Visit; CCI [redacted]; IP = Investigational Product; Obs. Follow-up=Post-treatment Observational Follow-up Phase; CCI [redacted]; PGA= Physicians Global Assessment; PMS= Partial Mayo Score; TMS= Total Mayo Score; UC= ulcerative colitis.

[a] Subjects will be evaluated based on the TMS at the Week 12 Visit and will receive blinded active IP for an additional 40 weeks (Section 4.1).

[b] At the Week 52 Visit, subjects who have a Mayo endoscopy score ≤1 will have the opportunity to participate in an Extension Phase and will receive apremilast 30 mg BID. With the implementation of Amendment 4, subjects currently in the Extension Phase who are receiving apremilast 40 mg BID will be switched to 30 mg BID at the next scheduled visit.

[c] Subjects who discontinue from the study prior to the Week 52 Visit, or prior to the Week 104 Visit for subjects participating in the Extension Phase, will have the Early Termination Visit. Subjects who complete the Week 52 Visit and do not participate in the Extension Phase will not have the Early Termination Visit.

[d] The Post-treatment Follow-up Visit will be conducted approximately 4 weeks after the last dose of IP for all subjects.

[e] The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization). Contraception education is for males and Females of Child Bearing Potential (FCBP). Pregnancy testing will be performed 7 times during the study for FCBP. Serum pregnancy tests will be performed at Screening and urine pregnancy testing will be done at the Baseline Visit, Week 12, Week 52 (or at the Early Termination Visit if prior to the Week 52 Visit) and all visits during the Extension Phase. In addition, urine pregnancy testing will be done at the Early Termination

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Visit. Urine pregnancy test kits will be provided to the site. The investigator will educate all FCBP about the different options of contraceptive methods and their correct use at Screening and Baseline Visits. The subject will be re-educated every time their contraceptive measures/methods or their ability to become pregnant changes. A pregnancy test(s) should be administered if the FCBP subject misses a menstrual period.

f During the Extension Phase, a limited physical exam may be performed to evaluate an adverse event, or for any reason, at the discretion of the investigator.

g When reviewing adverse events, evaluation of vasculitis (Section 6.6.5) and/or psychiatric evaluation (Section 6.6.6) are to be assessed as appropriate.

h Evaluate the need for referral to a Psychiatrist and other actions, including discontinuation, as required per protocol Section 6.6.6.

[redacted]

j The screening endoscopy will consist of a colonoscopy or flexible rectosigmoidoscopy. Colonoscopy is required at screening only for those subjects who have not had a colonoscopy within 12 months prior to the Screening Visit. Rectosigmoidoscopies will be repeated at Week 12 and Week 52 (or at the Early Termination Visit if prior to the Week 52 Visit). Rectosigmoidoscopy will not be repeated if within 4 weeks of the previous endoscopy. Rectosigmoidoscopy is not required during the Extension Phase.

k The following procedures and assessments are not required at the Early Termination Visit for subjects who discontinue the study during the Extension Phase: rectosigmoidoscopy, [redacted]; calculation of the TMS, [redacted].

[redacted]

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6. PROCEDURES

The following procedures/assessments will be conducted according to the schedule indicated in the Table of Events (Table 4).

6.1. Informed Consent

An Informed Consent Form (ICF) must be signed by the subject before any study-related assessments are performed. CCI [redacted] Details of the informed consent process may be found in Section 14.3.

6.2. Contraception Education

The risks to a fetus or to a nursing child from apremilast are not known at this time. In animal studies, there were more miscarriages in female mice and monkeys who were given high doses of apremilast than in those who were not given apremilast. In addition, baby mice from the apremilast-treated mothers weighed less than normal baby mice. Results of the animal and in vitro studies can be found in the IB.

All females of childbearing potential (FCBP[1]) must use one of the approved contraceptive options as described in Section 7.2 while on investigational product and for at least 28 days after administration of the last dose of the IP.

At the time of study entry, and at any time during the study when a 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.

6.3. Medical and Disease History

Relevant medical history should be recorded, including caffeine consumption, smoking and alcohol history, as well as previous relevant surgeries. Disease history includes history of UC (ie, the disease under study).

6.4. Inclusion/Exclusion Criteria

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations are expected to be completed during the 28-day Screening Phase, prior to the date of the first dose of IP (study randomization). Subjects must meet all inclusion criteria (Section 7.2) and must not have any of the conditions specified in the exclusion criteria (Section 7.3) to qualify for participation in the study. Subjects may be allowed to re-screen upon discussion with the Sponsor. The subject's source documents must support his/her qualifications for the study

[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).

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(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 medical history).

6.5. Prior/Concomitant Medications and Therapies

All medications (prescription and nonprescription, including vitamins) taken by the subject up to 30 days prior to the Screening Visit (Visit 1) should be recorded, including the stop dates for medications prohibited in the study. All medications taken by the subject at any time during the study must also be recorded. Other key medications and therapies, such as previous treatment for tuberculosis or relevant diseases, should also be recorded.

6.6. Safety Assessments

6.6.1. Serum and Urine Pregnancy Tests for Females of Childbearing Potential

A serum pregnancy test with a sensitivity of ≤ 25 mIU/mL will be required for FCBP at screening. A urine pregnancy test will be performed on all FCBP at the Baseline Visit, Week 12, Week 52 and at all visits during the Extension Phase. In addition, a urine pregnancy test will be done at the Early Termination Visit. A urine pregnancy test kit will be provided by the central laboratory. Pregnancy tests should be performed if the FCBP has missed a menstrual period or the contraception method has changed.

6.6.2. Hepatitis B and C

The hepatitis screen includes testing for hepatitis B surface antigen and antibody, hepatitis B core antibodies (IgG/IgM), and antibodies to hepatitis C. Blood will also be drawn at screening for confirmatory hepatitis C testing to be completed for subjects who test positive for hepatitis C antibodies.

6.6.3. Vital Signs, Height, and Weight

Vital signs, including temperature, pulse, and seated blood pressure, will be taken during the visits indicated in Table 4. Height will be measured and recorded at screening; weight will also be measured and recorded at screening and then as indicated in Table 4. Body mass index (BMI) will be calculated at screening.

6.6.4. Complete and Limited Physical Examinations

Complete physical examinations will include evaluation of the skin, nasal cavities, eyes, ears, respiratory, cardiovascular, abdominal, neurological, lymphatic, and musculoskeletal systems. Limited physical examinations will include evaluation of the skin, respiratory, cardiovascular, lymphatic, and musculoskeletal systems. Results of the complete and limited physical examinations will be recorded only in the source documents.

Clinically significant abnormal findings (with the exception of the disease under study [UC]) identified prior to first dose of IP will be recorded on the electronic case report form (eCRF) as medical history; clinically significant findings after the first dose of IP will be recorded as AEs.

Note: Gynecological and urogenital examinations will not be performed unless for cause.

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6.6.5. Vasculitis Assessment

The PDE4 inhibitors, including apremilast, have been shown to produce inflammatory perivascular histopathological changes in animal studies (eg, rodent toxicology studies). The investigator should be watchful for any signs and symptoms of vasculitis at all times. Any suspicion of vasculitis must be thoroughly investigated by taking pertinent patient history, doing a physical examination, reviewing AEs, and performing diagnostic procedures as clinically indicated. A subject with signs and symptoms of possible vasculitis should receive a thorough evaluation as described above, managed as medically appropriate, and continued with follow-up until the signs and symptoms of vasculitis have resolved.

6.6.6. Psychiatric Evaluation

Depression has been reported with the use of apremilast. Details are provided in the IB (Section 4.3.7.2.2).

The investigator should advise subjects, their caregivers, and families of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur, to contact the investigator.

During the study (post randomization), any subject who is identified by the investigator (and/or appropriate site staff) as having a suicide attempt, or major psychiatric illness requiring hospitalization, must be immediately withdrawn from the study and referred for further medical and/or psychiatric care. If a subject is discontinued, the subject should return for the Post-treatment Observational Follow-up Visit after the Early Termination Visit.

At any time during the study (post randomization), the investigator (and/or appropriate site staff) should evaluate any subject who has thoughts of suicide to determine if the subject truly has suicide ideation. In such case, the subject will be referred to a psychiatrist for evaluation and treatment as appropriate. The subject may remain on IP until after the psychiatric evaluation, which should be completed within 3 weeks of the referral time. If the psychiatrist deems the subject not to be a risk for suicide, the subject may remain in the study, but if a risk of suicide is confirmed, the subject must be discontinued from the study. If the subject is discontinued, the subject should return for the Post-treatment Observational Follow-up Visit.

A copy of the psychiatric evaluation report must reside in the subject's source document.

6.6.7. Stool Culture / Microbiology

Stool culture analysis and assessment of *Clostridium difficile* toxin will be performed at the Screening Visit. A portion of the sample collected at screening will be retained for confirmatory testing to be completed for subjects who test positive for *Clostridium difficile* antigen. Subjects who are positive for *C. difficile* toxin may rescreen for the study after they have successfully completed therapy and had 2 months of consecutive negative tests for *C. difficile*.

6.6.8. Twelve-lead Electrocardiogram

The 12-lead ECG will be performed after the subject has been supine for approximately 3 minutes. Sites are to utilize their own local ECG machines for the study 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:

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normal; abnormal, not clinically significant; or abnormal, clinically significant. "Abnormal, clinically significant" results should be recorded in the Medical History eCRF if found prior to first dose of IP or in the AE eCRF if found after the first dose of IP.

6.6.9. Clinical Laboratory Evaluations

A central laboratory will be used for this study. Clinical laboratory evaluations will include:

- Hematology: complete blood count (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count and differential, absolute WBC counts, platelet count)
- Serum chemistries: total protein, albumin, calcium, phosphorous, glucose, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, lactic dehydrogenase (LDH), magnesium
- Urinalysis: dipstick urinalysis (specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen)
  - Microscopic urinalysis (epithelial cells, RBC, WBC, and casts) will be performed only if the dipstick urinalysis is abnormal

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

6.6.10. Adverse Events

Adverse events (Section 11.1) will be recorded by the investigator from the time the subject signs informed consent to 28 days after the last dose of IP. The AEs, including 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. Worsening of a subject's UC, including UC flare, should be considered as worsening of disease under study, and should not be captured as an AE. Worsening or exacerbation of UC, including UC flare, meeting the definition of an SAE should be reported as an SAE.

6.6.10.1. Adverse Events of Special Interest

6.6.10.1.1. Diarrhea

Diarrhea and loose stools have been reported as AEs in subjects receiving PDE4 inhibitors, including apremilast. Since diarrhea is a cardinal symptom of UC, it may be difficult to evaluate the potential effect of apremilast in the frequency and consistency of stools in this subject population. In order to help characterize diarrhea as an adverse reaction, and differentiate from symptoms of intestinal inflammation, ongoing review of the Subject Diary for Ulcerative Colitis (Section 6.7.1) and the Bristol Stool Chart (Appendix G) for the frequency and consistency of

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the stools, respectively, will be conducted and analyzed CCI [redacted]. Diarrhea will only be documented as an AE when reported by the subject and assessed by the investigator as a new event or worsening of pre-existing diarrhea.

6.6.10.1.2. Weight Loss

Subjects with UC may experience weight loss as part of the disease process. In addition weight loss has been observed with apremilast. Therefore, as part of the ongoing safety surveillance for this study, the decrease in subject weight as compared to baseline will be evaluated throughout the study. Subjects with an unexplained weight loss ≥ 7.5% from baseline will be discontinued from the study.

6.7. Efficacy Assessments

6.7.1. Subject Diary for Ulcerative Colitis Disease Activity

Subjects will be provided with the Subject Diary for UC Disease Activity CCI [redacted] at study visits in order to record the following information:

- Normal number of stools per day (when not having a flare)
- Number of toilet visits for defecation (per day)
- Presence of blood in the stools (if any)
- Description of blood in the stools (if any)
- Abdominal pain/cramps
- General well-being

Diaries will be completed from screening until the Week 52 Visit or Early Termination Visit, and the Observational Follow-up Visit. Subjects who participate in the Extension Phase will complete diaries for 7 days prior to each scheduled visit, or Early Termination Visit, and the Observational Follow-up Visit.

The information extracted will be used for calculation of the Mayo score. In order to encourage consistent diary recording, subjects are required to enter diary data continuously throughout the study. The method of diary data collection will be electronic data capture.

6.7.2. Endoscopy

The screening endoscopy may consist of either a flexible rectosigmoidoscopy or a colonoscopy. A colonoscopy is required during the Screening Phase only for those subjects who have not had a colonoscopy within 12 months prior to the Screening Visit. Subsequent endoscopies (rectosigmoidoscopies) will be performed on Week 12 and Week 52, or at the Early Termination Visit if the Early Termination Visit occurs prior to Week 52. The flexible rectosigmoidoscopy will not be repeated within 4 weeks of the previous rectosigmoidoscopy. Rectosigmoidoscopy is not required during the Extension Phase or at the Early Termination Visit for subjects who discontinue the study during the Extension Phase.

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Images of all endoscopic procedures (flexible rectosigmoidoscopy/colonoscopy) will be captured and sent to a centralized reader for their assessment, which will be used for the calculation of the TMS.

The screening endoscopy that is assessed by the central reader will be used to calculate the TMS to determine study eligibility. The Week 12 endoscopy assessment performed by the investigator will be used to calculate the TMS for the determination of subjects who do not achieve at least a 20% decrease from baseline in the TMS, at the Week 12 Visit. The Week 52 endoscopy assessment performed by the investigator will be used to determine eligibility for entry into the Extension Phase (Mayo endoscopy score ≤1).

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6.7.3. Total Mayo Score

The TMS is an instrument designed to measure disease activity of UC. The Mayo score ranges from 0 to 12 points (Rutgeerts, 2005). It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease (Appendix B):

- Stool Frequency Subscore (SFS)
- Rectal Bleeding Subscore (RBS)
- Endoscopy Subscore
- Physician's Global Assessment (PGA)

The frequency of the TMS assessment is described in the Table of Events (Table 4). During the Screening Phase, if the subject's Mayo score, excluding the endoscopy subscore (PMS), is ≥ 4 points, appropriate endoscopy examination (flexible rectosigmoidoscopy or colonoscopy) will be performed to assess the TMS. Diary data used to calculate the TMS is described in Section 6.7.1.

If the subject scores ≥ 2 on the endoscopic subscore at screening, and meets all other inclusion/exclusion criteria, the subject will be randomized. The endoscopy should be performed within the Visit window. Documented results from the screening endoscopy must be available for the investigator's interpretation prior to randomization.

Clinical response is defined as a decrease from baseline in TMS of at least 3 points, and at least a 30% decrease in the TMS, with an accompanying decrease in the RBS of at least 1 point or absolute RBS of 0 or 1. Clinical remission is defined as TMS ≤ 2 points, with no individual subscore exceeding 1 point. Endoscopic response is defined as a 1-point or greater decrease

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from baseline in the endoscopy subscore. Endoscopic remission is defined as endoscopy subscore of 0.

6.7.4. Modified Mayo Score

A modification to the total Mayo score will be implemented in this study. This modified Mayo score will be based on the stool frequency, rectal bleeding and endoscopy subscores of the total mayo score, and will exclude the PGA subscore, since this is a global measure that is subjective in nature. The modified Mayo Score ranges from 0 to 9 points. Clinical response is defined as a decrease from baseline in modified Mayo Score of at least 2 points and at least 25%, with an accompanying decrease in the RBS of at least 1 point or an absolute RBS of 0 or 1. Clinical remission is defined as a modified Mayo Score of 2 points or lower, with no individual subscore exceeding 1 point.

6.7.5. Partial Mayo Score

The PMS is the sum of the RBS, SFS, and PGA, and ranges from 0 to 9 points. Clinical response is defined as a decrease from baseline in PMS of at least 2 points and at least 25%, with an accompanying decrease in the RBS of at least 1 point or an absolute RBS of 0 or 1. Clinical remission is defined as a PMS of 2 points or lower, with no individual subscore exceeding 1 point. The PMS will be assessed as described in Table 4, Table of Events.

6.7.6. Physician Global Assessment

The PGA is done as part of the Mayo score. It acknowledges three other criteria: the subject's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status.

6.8. Disease and Health-related Quality of Life Assessments

6.8.1. The Medical Outcome Study Short Form 12-item Health Survey V2

The Medical Outcome Study Short Form 12-item Health Survey, version 2 (SF-12v2) (Appendix C) is a self-administered instrument consisting of 12 items from the original Short Form Health Survey SF-36, across all dimensions. The 12 items include the self assessment of health, physical functioning, physical role limitation, mental role limitation, social functioning, mental health, and pain (Ware, 1996). The instrument was designed to reduce respondent burden while achieving minimum standards of precision. Version 2 of the Survey allows for the calculation of an 8-scale profile in addition to the two summary scores.

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6.12. Dosing

6.12.1. Investigational Product Dispensing and Counting

After the subject has satisfied all inclusion and exclusion criteria, IP will be dispensed as specified by the IWRS/IVRS. The tear-off label from each blister card should be pasted into the drug accountability document in each subject's record. Subjects must be instructed to return all previously issued empty blister cards and/or unused IP at the time that new IP is issued. A detailed record of tablets issued and returned at each visit must be maintained in the subject's record.

6.12.2. Site Instructions for Dosing the Subject

At each visit, the site staff should make every effort to witness the subject taking the first dose from the new blister card and should record the date and time in the subject's source record. If the subject is seen in the late afternoon or evening, the subject should take the AM tablets at the site, and should skip the PM tablets on that date if it is less than 7 hours before the subject's scheduled bed time. Taking the AM tablets will ensure that subjects who are randomized to an apremilast dose group will receive the active dose from the dose titration card.

6.13. Early Termination Visit

The Early Termination Visit is based on the subject's withdrawal from the study prior to Week 52. For subjects participating in the Extension Phase, the Early Termination Visit is based on the subject's withdrawal from the study after Week 52 and prior to Week 104. Participation in the study is completely voluntary. Subjects are also free to withdraw from the study at any time if they feel they are not benefiting from the study in order to receive rescue therapy and/or receive treatment with standard medical care. In addition, the investigator may discontinue the subject from the study at any time based on his/her assessment of clinical efficacy and/or safety. The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. When a subject withdraws or is discontinued from the study, every effort should be made to complete as many safety and efficacy assessments as reasonably appropriate. Refer to Table 4 for the assessments to be performed at the Early Termination Visit.

6.13.1. 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 at least two 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.

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6.14. Study Completion

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

For the purpose of analysis, study completion for an individual subject is defined as reaching the Week 52 Visit. For subjects participating in the Extension Phase, completion of the Extension Phase for an individual subject is defined as completing the Week 104 Visit. Subjects not meeting this definition will be considered early termination subjects. All subjects are required to return for the Post-treatment Observational Follow-up Visit approximately 4 weeks after the last dose of IP.

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7. STUDY POPULATION

7.1. Number of Subjects and Sites

Approximately 165 subjects will be enrolled in this study at approximately 80 sites.

7.2. Inclusion Criteria

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

1. Male or female aged 18 and over at the time of signing the informed consent.
2. Must understand and voluntarily sign an informed consent form prior to any study related assessments/procedures being conducted.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Diagnosis of UC with duration of at least 3 months prior to the Screening Visit.
5. TMS ≥ 6 to ≤ 11 (range: 0-12) prior to randomization in the study.
6. Endoscopic subscore ≥ 2 (range: 0-3) on the Mayo score prior to randomization in the study.
7. Subjects are required to have a colonoscopy if not performed within 12 months of the Screening Visit.
8. Subjects must have had a therapeutic failure, been intolerant to, or have a contraindication to, at least one of the following: oral aminosalicylates (ie, 5-aminosalicylic acid [5-ASA] compounds or sulfasalazine [SSZ]), budesonide, systemic corticosteroids, or immunosuppressants (eg, 6-mercaptopurine [6-MP], azathioprine [AZA], or methotrexate [MTX]).
9. Subjects receiving oral corticosteroids may continue their use during the study, provided that the dose (prednisone ≤ 20 mg/day or equivalent, budesonide ≤ 9 mg/day) has been stable for 3 weeks prior to the Screening Visit. If oral corticosteroids were recently discontinued, discontinuation must have been completed at least 3 weeks prior to the Screening Visit. Corticosteroid doses should remain stable until the subject is eligible to start corticosteroids tapering, beginning at the Week 12 Visit.
10. Oral aminosalicylates are permitted during the study, provided that treatment started at least 6 weeks prior to screening with a stable dose of at least 14 days prior to the Screening Visit. The dose of oral aminosalicylates must remain stable through Week 52 or until Week 104 for subjects who participate in the Extension Phase.
11. Must meet the following laboratory criteria:
    - White blood cell count ≥ 3000/mm^3 (≥ 3.0 X 10^9/L) and < 14,000/mm^3 (< 14 X 10^9/L)
    - Platelet count ≥ 100,000/mm^3 (≥ 100 X 10^9/L)
    - Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 µmol/L)

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- AST (SGOT) and ALT (SGPT) ≤ 2 X upper limit of normal (ULN). If initial test shows ALT or AST > 2 times the ULN, one repeat test is allowed during the screening period
- Total bilirubin ≤ 2 mg/dL (≤ 34 µmol/L) or albumin > lower limit of normal (LLN). If initial test result is > 2 g/dL, one repeat test is allowed during the screening period
- Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L)

12. Females of childbearing potential (FCBP) must have a negative pregnancy test at Screening and the Baseline Visit. While on IP and for at least 28 days after taking the last dose of IP, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options[2] described below:

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

    OR

    Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]; PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide

13. Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (male latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on investigational product and for at least 28 days after the last dose of investigational product.

7.3. Exclusion Criteria

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

1. Diagnosis of Crohn's disease, indeterminate colitis, ischemic colitis, microscopic colitis, radiation colitis or diverticular disease-associated colitis.
2. Ulcerative colitis restricted to the distal 15 cm or less (eg, ulcerative proctitis).
3. Subjects who have had surgery as a treatment for UC or who, in the opinion of the Investigator, are likely to require surgery for UC during the study.
4. Clinical signs suggestive of fulminant colitis or toxic megacolon.
5. Evidence of pathogenic enteric infection.
6. History of colorectal cancer or colorectal dysplasia (with the exception of adenomatous colonic polyps that have been completely resected).
7. Prior use of any TNF inhibitor (or any biologic agent).

[2] The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

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8. Prior use of mycophenolic acid, tacrolimus, sirolimus, cyclosporine or thalidomide.
9. Use of IV corticosteroids within 2 weeks of the Screening Visit.
10. Use of immunosuppressants (AZA, 6-MP or MTX) within 8 weeks the Screening Visit.
11. Use of topical treatment with 5-ASA or corticosteroid enemas or suppositories within 2 weeks of the Screening Visit.
12. History of any clinically significant neurological, renal, hepatic, gastrointestinal, pulmonary, metabolic, cardiovascular, psychiatric, endocrine, hematological disorder or disease, or any other medical condition that, in the investigator's opinion, would preclude participation in the study.
13. Prior history of suicide attempt at any time in the subject's lifetime prior to randomization in the study or major psychiatric illness requiring hospitalization within 3 years of study randomization.
14. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she was to participate in the study or confounds the ability to interpret data from the study.
15. Pregnant or breast feeding.
16. History of any of the following cardiac conditions within 6 months of screening: myocardial infarction, acute coronary syndrome, unstable angina, new onset atrial fibrillation, new onset atrial flutter, second- or third-degree atrioventricular block, ventricular fibrillation, ventricular tachycardia, heart failure, cardiac surgery, interventional cardiac catheterization (with or without a stent placement), interventional electrophysiology procedure, or presence of implanted defibrillator.
17. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease and herpes zoster), human immunodeficiency virus (HIV), or any major episode of infection requiring hospitalization or treatment with intravenous (IV) or oral antibiotics within 4 weeks of screening.
18. Subjects with active hepatitis B infection, as described in Appendix E, are ineligible for the study. Subjects without current hepatitis B infection, as described in Appendix F, may participate in the study.
19. Subjects who are confirmed positive for hepatitis C are not eligible for the study.
20. History of congenital or acquired immunodeficiency (eg, Common Variable Immunodeficiency Disease).
21. History of malignancy, except for:
    a. Treated (ie, cured) basal cell or squamous cell in situ skin carcinomas
    b. Treated (ie, cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years
22. Any condition that could affect oral drug absorption, including gastric resections, gastroparesis or bariatric surgery, such as gastric bypass.

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23. Subject has received any investigational drug or device within 1 month or 5 elimination half-lives, whichever is longer, prior to the Screening Visit.
24. History of alcohol, drug, or chemical abuse within the 6 months prior to screening.
25. Known hypersensitivity to apremilast or any excipients in the formulation.

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8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

The chemical name of apremilast (CC-10004) is acetamide, N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl) ethyl]-2, 3-dihydro-1, 3-dioxo-1H-isoindol-4-yl].

Apremilast will be provided as 10-mg, 20-mg, or 30-mg tablets. Placebo will be provided as identically appearing 10-mg, 20-mg or 30-mg tablets. In addition, tablets (both, apremilast and placebo) required for dose titration cards will also be provided.

8.2. Treatment Administration and Schedule

Tablets will be taken by mouth twice daily, in the morning (AM) and in the evening (PM), approximately 12 hours apart, with no food restrictions. With the aim to mitigate potential dose-related side effects associated with apremilast such as headache and GI disturbances, apremilast-treated subjects will be dose-titrated in 10-mg/day increments over the first 8 days of treatment in the Double-blind Placebo-controlled Phase.

After 12 weeks of treatment, apremilast-treated subjects who do not achieve at least a 20% decrease from baseline in the TMS, will receive apremilast 40 mg BID. Placebo subjects, will be re-randomized to receive apremilast 30 mg BID or 40 mg BID, and will be dose-titrated prior to receiving active treatment (Table 5). However, in order to maintain the blind for the treatment assigned at baseline, all subjects will receive blister cards of identical appearance during both titration periods. In the absence of a 40-mg tablet, two 20-mg tablets or identically appearing placebo will be taken by those subjects randomized to the 40-mg BID apremilast dose group.

Subjects who complete 52 weeks of treatment and have a Mayo endoscopy score ≤ 1 will be eligible to participate in the 52-week Extension Phase and receive apremilast treatment. With the implementation of Amendment 4, subjects entering the Extension Phase from the Week 52 Visit will receive apremilast 30 mg BID. Subjects currently in the Extension Phase who are receiving apremilast 40 mg BID will be switched to 30 mg BID at the next scheduled visit.

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Table 5: Treatment Schema for Dose Titration

Treat-ment Group	Treatment Schema for Dose Titration[a]															
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8 + Thereafter	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
30 mg BID	10 mg A	10 mg P	10 mg A	10 mg A	10 mg A	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P				
	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg A	20 mg A	20 mg A	20 mg A	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P
	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P
	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg A	30 mg A	30 mg A	30 mg A	30 mg A	30 mg A	30 mg A
40 mg BID	10 mg A	10 mg P	10 mg A	10 mg A	10 mg A	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P				
	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg A	20 mg A	20 mg A	20 mg A	20 mg P	20 mg P	20 mg P	20 mg P	20 mg A	20 mg A	20 mg A
	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg A	20 mg A	20 mg A
	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg A	30 mg A	30 mg A	30 mg A	30 mg P	30 mg P	30 mg P
Placebo	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P	10 mg P				
	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P
	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P	20 mg P
	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P	30 mg P

A = Apremilast; BID = twice daily; P = Placebo.
Note: In the absence of a 40 mg tablet, subjects will take 2 x 20 mg apremilast tablets or placebo BID.
[a] Active apremilast subjects will be dose titrated during the first 8 days of the study (Week 0, Day 1); At the week 12 Visit, placebo subjects will be re-randomized to apremilast 30 mg or 40 mg BID and will be dose titrated for the first 8 days of treatment.

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8.3. Method of Treatment Assignment

After the informed consent is signed, subjects will be assigned a subject identification number using a centralized IVRS/IWRS. At the Baseline Visit, a centralized schema will be applied to assign subjects who meet the inclusion/exclusion criteria in a 1:1:1 ratio to receive either apremilast 30 mg PO BID or 40 mg PO BID, or placebo.

Subjects will be randomized by following two stratification parameters:

- Concomitant use of oral corticosteroids
- Previous exposure to immunosuppressants (eg, 6-MP, AZA, or MTX)

The number of subjects with previous exposure to immunosuppressants is targeted to comprise no more than 50% of the subjects enrolled, and no less than 30%.

Following 12 weeks of treatment, subjects will enter the Blinded Active-treatment Phase. At the Week 12 visit, subjects will be evaluated for clinical improvement based on the TMS. The endoscopy subscore assessed by the investigator will be used for the calculation of the Week 12 TMS.

Subjects who achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive the following IP between the Week 12 Visit and the Week 52 Visit:

- Subjects who were randomized to apremilast (30 mg BID or 40 mg BID) at baseline will continue to receive the treatment assigned at baseline.
- Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments over the first 8 days of treatment (Table 5).

Subjects who do not achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive the following IP until the Week 52 Visit:

- Subjects who were randomized to apremilast 30 mg BID at baseline will be re-assigned apremilast 40 mg BID, with no dose titration.
- Subjects who were randomized to apremilast 40 mg BID at baseline will continue to receive apremilast 40 mg BID.
- Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments over the first 8 days of treatment (Table 5).

Subjects who participate in the Extension Phase will receive apremilast 30 mg BID. With the implementation of Amendment 4, subjects currently in the Extension Phase who are receiving 40 mg BID will be switched to 30 mg BD at the next scheduled visit.

Designated study personnel at the investigational sites will be assigned password-protected, coded identification numbers that give them authorization to call into the IVRS/IWRS to randomize subjects. The system will present a menu of questions by which the study personnel will identify the subject and confirm eligibility. When all questions have been answered, the

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IVRS/IWRS will assign a randomization identification number. Confirmation of the randomization will be sent via fax to the investigational site, Celgene and/or its representative.

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

8.4. Packaging and Labeling

All IP, including placebo and apremilast tablets, will be supplied by Celgene to the principal investigator as blister cards for the duration of the study.

Apremilast will be provided in blister cards as 10-mg, 20-mg, or 30-mg tablets in the clinical image. Tablets will be taken by mouth twice daily, morning and evening, approximately 12 hours apart, with no food restrictions.

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.

8.5. 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 will be stored according to the storage conditions identified on the drug 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).

8.6. 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 Table 4, Table of Events. The subjects will be instructed to return the IP containers, including any unused medication, 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 Post-treatment Observational Follow-up Phase.

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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.

8.6.1. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the IP (apremilast), and on a per dose basis, is defined as ingestion of greater than 100 mg of apremilast (greater than two AM or PM sections in the blister card) in any 24-hour dosing period whether by accident or intentionally. Adverse Events associated with an overdose must be collected on the AE page of the eCRF (see Section 11.1) 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.

For subjects receiving open-label apremilast 30 mg BID in the Extension Phase, overdose on a per dose basis is defined as ingestion of 4 or more 30-mg apremilast tablets in any 24-hour period whether by accident or intentional. On a schedule or frequency basis, overdose is defined as dosing more than 4 times in any 24-hour period.

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

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9. CONCOMITANT MEDICATIONS AND PROCEDURES

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

9.1. Permitted Concomitant Medications and Procedures

The following medications are allowed during the study:

- Oral aminosalicylates (sulfasalazine [SSZ] or 5-ASA compounds) are allowed during the study, provided that treatment was initiated at least 6 weeks prior to screening, and has been given at a stable dose for at least 14 days prior to the Screening Visit. The dose of oral aminosalicylates must remain stable through the duration of the study or early termination from the study.
- Oral corticosteroids are allowed during the study, provided that the subject has been receiving therapy at a stable dose (prednisone ≤ 20 mg/day or equivalent mg/day) for at least 3 weeks prior to the Screening Visit. The subject must remain on a stable dose until the Week 12 Visit, after which time the dose may be tapered according to the following tapering schedule:
  - For prednisone doses > 10 mg (or equivalent) daily dose, 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.
  - Subjects who experience UC-related symptoms after the tapering regimen is completed are permitted to receive the same corticosteroid treatment taken prior to the initiation of the tapering schedule, provided that the dosage is the same as the dose taken prior to tapering.

  If oral corticosteroids were recently discontinued, discontinuation must have been completed at least 3 weeks prior to the Screening Visit.
- Acetaminophen and low-dose aspirin for cardiovascular prophylaxis are allowed.

Note: The dose of concomitant oral aminosalicylates cannot be increased above the baseline dose during the study. No new UC therapy can be prescribed once the subject has been randomized to the study.

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9.2. Prohibited Concomitant Medications and Procedures

The following concomitant medications are prohibited during all treatment portions of the study including the Double-blind Placebo-controlled Phase (Week 0 to Week 12), the Blinded Active-treatment Phase (Week 12 to Week 52); and for subjects who participate in the Extension Phase, from Week 52 to Week 104, or to the Early Termination Visit for subjects who discontinue prematurely from the study:

- Use of the CYP3A4 inducers, rifampin and carbamazepine, bosentan, efavirenz, etravirine, modafinil, nafcillin, St. John's wort
- Uses of any biologic agents, including TNF blockers
- Use of mycophenolic acid, tacrolimus, sirolimus, cyclosporine or thalidomide
- Use of topical treatment with 5-ASA or corticosteroid enemas or suppositories is prohibited during the study and must be discontinued 2 weeks prior to the Screening Visit
- Use of intravenous corticosteroids is prohibited during the study and must be discontinued 2 weeks prior to the Screening Visit
- Use of AZA, 6-MP, or MTX is prohibited during the study and must be discontinued 8 weeks prior to the Screening Visit
- Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs).

9.3. Required Concomitant Medications and Procedures

There are no required concomitant medications.

Required procedures include endoscopy (rectosigmoidoscopy or colonoscopy) CCI [redacted] as noted in Table 4.

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10. STATISTICAL ANALYSES

10.1. Overview

Key elements of the statistical analysis plan are outlined in this section. The comprehensive plan will be documented in a separate Statistical Analysis Plan (SAP).

Planned data analyses include: 1) an analysis at the completion of the 12-week Placebo-controlled Phase for all subjects (referred to as the Double-blind Placebo-controlled Phase analysis hereafter); 2) an analysis at the completion of the Active-treatment Phase for all subjects after 52 weeks of treatment; and 3) the final analysis at the completion of the entire study.

10.2. Study Population Definitions

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

The intent-to-treat (ITT) population will be the primary population for efficacy analyses. The ITT population will consist of all subjects who are randomized as specified in the protocol and receive at least one dose of IP. Subjects will be included in the treatment group to which they were randomized, irrespective of the treatment actually received, for the analyses using the ITT population.

The per-protocol (PP) population will consist of all subjects included in the ITT population who have at least one post-baseline efficacy evaluation and no protocol violations that may substantially affect the efficacy results. The final determination on these protocol violations, and thereby the composition of the PP population, will be made prior to the Placebo-controlled Phase analysis, and will be separately documented. Subjects will be included in the treatment group to which they were randomized, irrespective of the treatment actually received, for the analyses using the PP population.

10.3. Sample Size and Power Considerations

A 2-group chi-square test with a 0.1 two-sided significance level will have approximately 80% power to detect a true 20% absolute difference (30% versus 10%) between a dose of apremilast and placebo, for the proportion of subjects achieving a clinical remission at Week 12 when the sample size in each group is 49. Assuming a dropout rate of 10% prior to Week 12, approximately 165 subjects (approximately 55 subjects per group) are planned to be randomized in this study.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and other continuous demographic and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

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10.5. Subject Disposition

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

10.6. Efficacy Analysis

The ITT population (Section 10.2) will be the primary population for efficacy analyses. A supportive analysis using the PP population will also be performed for the primary efficacy endpoint.

The comparisons for the primary efficacy endpoint will be based on two-sided statistical tests at a significance level of 0.1. A hierarchical approach will be used to adjust for multiplicity. For the primary endpoint, the first test in the hierarchy will be the apremilast 40 mg BID treatment group compared to placebo, followed by the apremilast 30 mg BID treatment group compared to placebo. If any of the active treatment groups (apremilast 30 mg or 40 mg BID) is discontinued prior to the end of the study, the treatment comparison will be conducted for the retained treatment group vs. placebo based on a two-sided statistical test at the 0.1 level. Additional endpoints subsequent to the primary endpoint comparisons may be added to the hierarchy and specified in the SAP.

Summary of all efficacy endpoints over time will be provided using frequency and percent for categorical endpoints and descriptive statistics for continuous endpoints.

10.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is clinical remission, as defined as a TMS of ≤ 2 with no individual subscore > 1 at Week 12. The proportion of subjects who achieve a clinical remission at Week 12 between any apremilast (30 mg BID or 40 mg BID) group and the placebo group will be compared using the Cochran-Mantel-Haenszel (CMH) test controlling for the randomization stratification factors specified. Subjects who prematurely discontinue the study before Week 12 will be considered as nonresponders.

10.6.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints defined in Section 3.2.1 will be analyzed using the CMH test controlling for the randomization stratification factors as will be done for the primary efficacy endpoint.

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10.7. Safety Analysis

The safety analyses will be performed using the safety population (Section 10.2).

Treatment-emergent adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All AEs will be summarized by system organ class, preferred term, severity and relationship to IP. Adverse events leading to death or to discontinuation from treatment and SAEs 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 data will be summarized descriptively by visit. In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal ranges pretreatment versus post-treatment will be provided.

Vital sign measurements, including weight, will be summarized descriptively by visit.

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11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (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 11.3), 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 drug exposure eCRF page. (See Section 8.6.1 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

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; weight loss; diarrhea; 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 and 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 CRF 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.

11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all AEs as to:

11.2.1. 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);

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- Results in persistent or significant incapacity / disability (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect; and/or
- 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 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 starting of treatment on study) must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- 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 CRF and the SAE Report Form must be completed.

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

11.2.2. 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

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- 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.

11.2.3. Causality

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

Not Suspected:	Means 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:	Means 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, the name of the manufacturer when reporting the event will be provided.

11.2.4. Duration

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

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11.2.5. 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 reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. 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, recovered with sequelae, not recovered, or death (due to the SAE).

11.3. 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.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a 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 CRF. 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).

11.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

11.4.1. Females of Childbearing Potential

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

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

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

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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.

11.4.2. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. 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 CRF. 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. This instruction pertains to initial SAE reports as well as any follow-up reports.

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

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

Where required by local legislation, the investigator is responsible for informing the Institutional Review Board/ Ethics Committee (IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. 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.

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11.6. 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 apremilast 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, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the investigator of the following information:

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

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

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

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

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12. DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the IP and/or from the study:

- Adverse event(s)
- Lack of efficacy
- Withdrawal by subject
- Death
- Lost to follow up
- Protocol violation
- Study terminated by sponsor
- Pregnancy
- Unexplained weight loss ≥ 7.5% from baseline

The decision to discontinue a subject 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. The reason for discontinuation should be recorded in the eCRF and in the source documents.

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13. EMERGENCY PROCEDURES

13.1. 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/CRO 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.

13.2. Emergency Identification of Investigational Products

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

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, the investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The investigator should ensure that the code is broken only in accordance with the protocol. The investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the investigator in the subject's source documentation.

Emergency unblinding should only be performed by the investigator thorough the IVRS/IWRS by using an emergency unblinding personal identification number (PIN), and the investigator should call IVRS/IWRS for unblinded dose information.

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14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

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

14.2. Investigator Responsibilities

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

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

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

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

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14.3. 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 informed consent form 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 form, the informed consent form 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 informed consent form. The revised informed consent form 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.

14.4. 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 informed consent form it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

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

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

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

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

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

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

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

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

14.7. Ongoing Information for Institutional Review Board/Ethics Committee

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

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

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc.).

In addition, the investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

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

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15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

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

15.2. Data Management

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

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. 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 informed consent form for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;

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- 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/institution should take measures to prevent accidental or premature destruction of these documents.

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16. 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.

16.1. 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 investigator meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, 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, CRFs, 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 CRFs 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 CRFs 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.

16.2. Audits and Inspections

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

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

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17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for 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. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

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19. APPENDICES

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APPENDIX B. MAYO SCORING SYSTEM

Stool frequency subscore (SFS)*

0 = Normal number of stools for this patient

1 = 1 – 2 stools more than normal

2 = 3 – 4 stools more than normal

3 = 5 or more stools more than normal

* Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.

Rectal bleeding subscore (RBS)**

0 = No blood seen

1 = Streaks of blood with stool less than half the time

2 = Obvious blood with stool most of the time

3 = Blood alone passed

** The daily bleeding score represents the most severe bleeding of the day.

Endoscopy subscore: Findings of flexible sigmoidoscopy

0 = Normal or inactive disease

1 = Mild disease (erythema, decreased vascular pattern, mild friability)

2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)

3 = Severe disease (spontaneous bleeding, ulceration)

Physician's Global Assessment subscore (PGA)

0 = Normal

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Source: Schroeder, 1987.

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APPENDIX C. 12-ITEM SHORT FORM HEALTH SURVEY, VERSION 2

SF-12v2™ Health Survey

(SF-12 v2 Standard, US Version 2.0)

To be completed by the PATIENT

Identification Number

Event

Directions: *This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. If you need to change an answer, completely erase the incorrect mark and fill in the correct circle. If you are unsure about how to answer a question, please give the best answer you can.*

Today's Date (MM/DD/YY) / /

Shade circles like this: ● **Not like this:** ⊗ ✓

Mark only one answer for each question. Please do not mark outside the circles or make stray marks on the questionnaire.

	Excellent	Very Good	Good	Fair	Poor
01. In general, would you say your health is:	○	○	○	○	○
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
02. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○		
03. Climbing several flights of stairs	○	○	○		
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
04. Accomplished less than you would like	○	○	○	○	○
05. Were limited in the kind of work or other activities	○	○	○	○	○
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
06. Accomplished less than you would like	○	○	○	○	○
07. Did work or activities less carefully than usual	○	○	○	○	○
08. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely
	○	○	○	○	○
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...	All of the time	Most of the time	Some of the time	A little of the time	None of the time
09. Have you felt calm and peaceful	○	○	○	○	○
10. Did you have a lot of energy	○	○	○	○	○
11. Have you felt downhearted and depressed	○	○	○	○	○
12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	○	○	○	○	○

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Source: Ware, 1996.

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APPENDIX E. HEPATITIS B CRITERIA INDICATING CURRENT INFECTION OR RISK OF CURRENT INFECTION

	Result	Interpretation
HBsAg anti-HBc IgM anti-HBC anti-HBs	Positive Positive Positive Negative	Acutely infected
HBsAg anti-HBc IgM anti-HBC anti-HBs	Positive Positive Negative Negative	Chronically infected
HBsAg anti-HBc anti-HBs	Negative Positive Negative	Interpretation unclear; four possibilities: • Resolved infection (most common) • False-positive anti-HBc, thus susceptible • "Low level" chronic infection • Resolving acute infection

Abbreviations: HBsAg= hepatitis B surface antigen; anti- HBc= antibody to the hepatitis B core antigen; anti- HBs= antibody to hepatitis B surface antigen; IgM anti-HBC= IgM antibody to hepatitis B core antigen
(Source: Mast, 2005).

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APPENDIX F. HEPATITIS B CRITERIA INDICATING THE ABSENCE OF CURRENT INFECTION

	Result	Interpretation
HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible to hepatitis B infection
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to natural infection
HBsAg anti-HBc anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination

Abbreviations: HBsAg= hepatitis B surface antigen; anti-HBc= antibody to the hepatitis B core antigen; anti-HBs= antibody to the hepatitis B surface antigen (Source: Mast, 2005).

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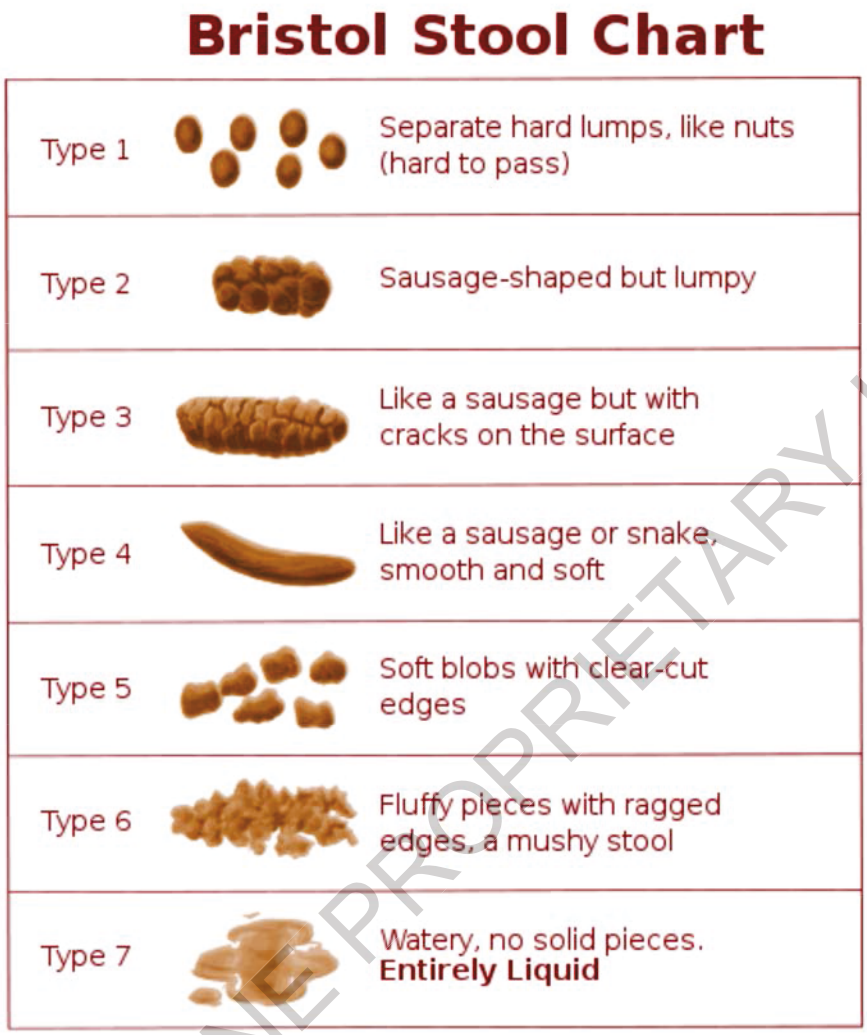
APPENDIX G. BRISTOL STOOL CHART



Source: Lewis, 1997.

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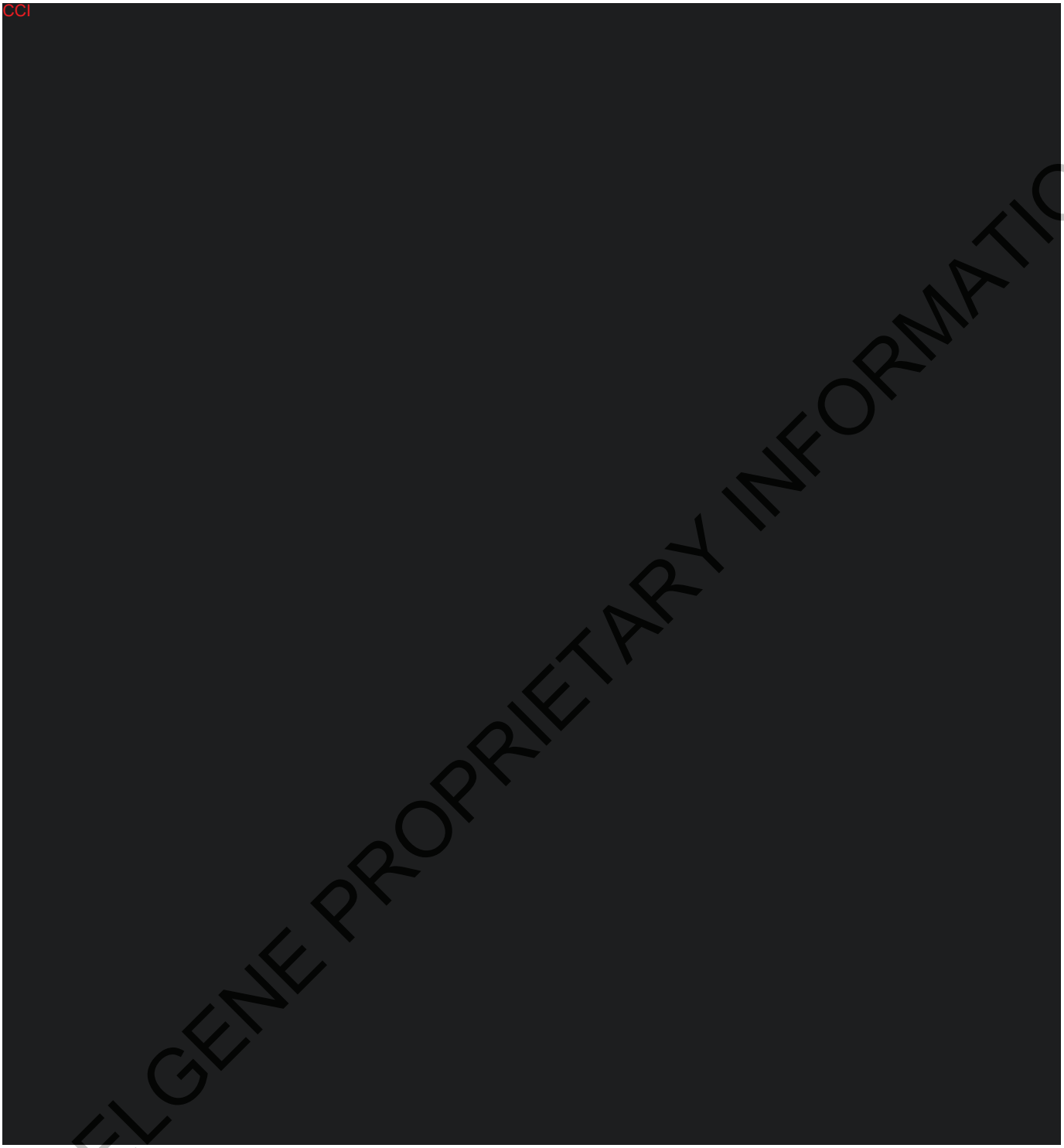

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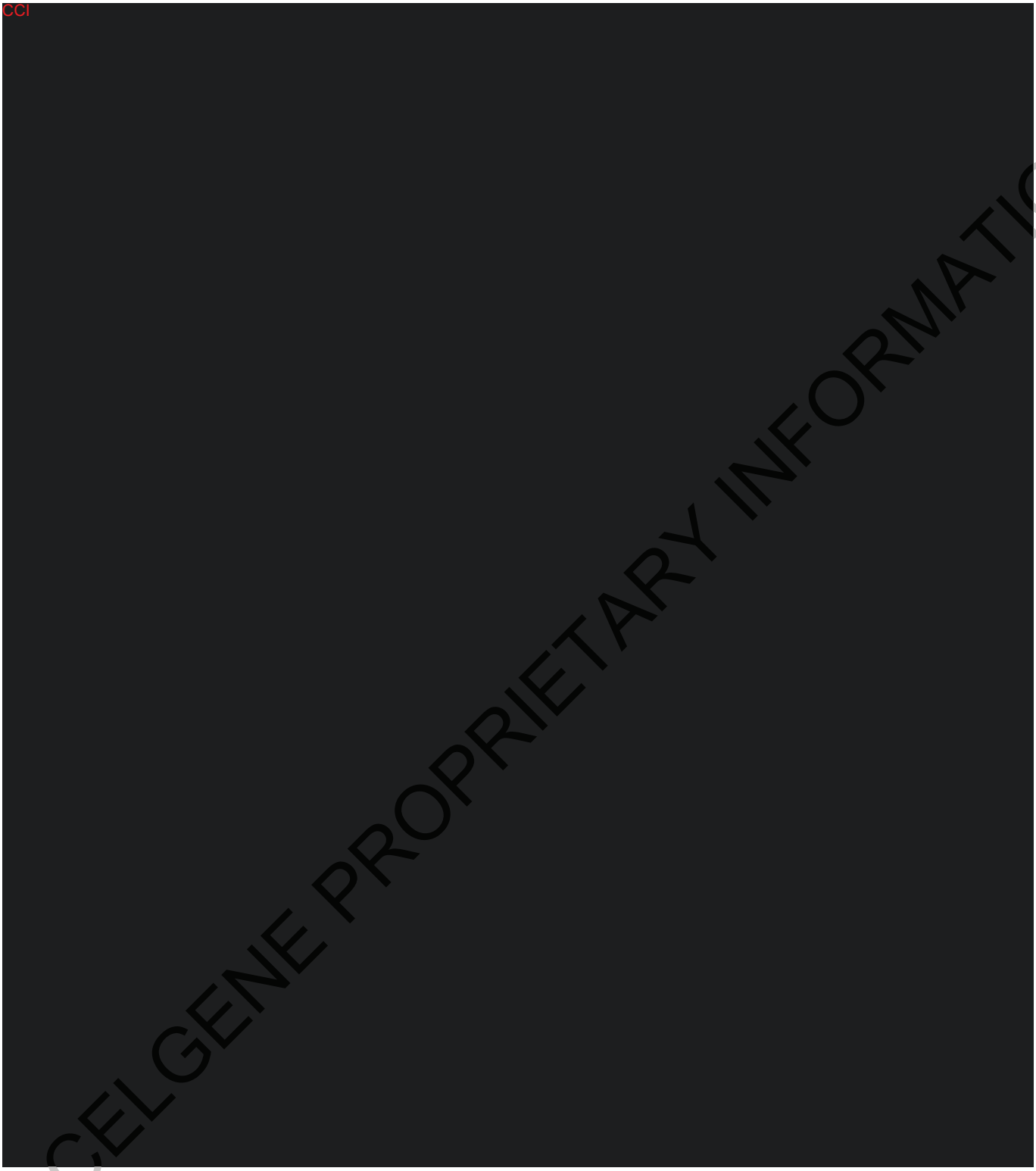

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UserName: PPD
Title: PPD
Date: Friday, 10 August 2018, 06:54 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Subject	Revised Section(s)	Change / Justification
Dose for Extension Phase	Protocol Summary, Dose Justification (Section 1.4.3), Study Design (Sections 4.1, 4.2 [Figure 1]), Table of Events [footnote b], Description of Study Treatments (Sections 8.2, 8.3, 8.4)	The primary purpose of this protocol amendment is to adjust the dose in the Extension Phase such that all patients receive apremilast 30 mg twice daily (BID). Based upon the similarity of the clinical, endoscopic CCI endpoints and the plateau of dose response observed in subjects treated with apremilast 30 mg and 40 mg BID after the first 12 weeks, as well as the extensive marketed safety experience with this dose, the 30 mg BID dose was determined to be the minimum dose that provides the maximum treatment response with an acceptable safety profile.
Overdose definition for Extension Phase	Overdose (Section 8.6.1)	For subjects receiving apremilast 30 mg BID in the Extension Phase, overdose for this period is now defined as 4 or more 30 mg tablets in any 24-hour period, or dosing more than 4 times in 24 hours. This is consistent with the overdose definition for other apremilast protocols using 30 mg BID.
Data Monitoring Committee (DMC) and Internal Data Safety Monitoring Board (iDSMB) Decommissioning	Internal Data Safety Monitoring Board During the Study (Section 4.1.2), External Safety and Efficacy Monitoring During Apremilast Program (Section 4.1.3)	With the implementation of Amendment 4, all subjects will be in the Extension Phase and will receive open-label apremilast 30 mg BID as of their next visit. Therefore, the iDSMB is no longer necessary to support CC-10004-UC-001. After all subjects completed the 12-week Placebo-controlled Phase, Celgene determined that the DMC was no longer necessary to support CC-10004-UC-001, as the safety profile of apremilast in ulcerative colitis (UC) is similar to that observed in the approved indications and no new safety signal emerged in CC-10004-UC-001. Celgene's Safety Management Team (SMT) will continue to review safety data for CC-10004-UC-001 on a regular basis.

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The amendment also includes several other minor clarifications and corrections:

Subject	Revised Section(s)	Change / Justification
Safety Update	Safety (Section 1.4.2)	Section was updated to reflect the most current information in Investigator Brochure (IB).
CCI [redacted]	[redacted]	[redacted]
Footnotes in Table of Events	Table of Events (Section 5, Table 4)	Minor clarifications were made to footnotes d and e.
Subject Diary	Subject Diary for Ulcerative Colitis Disease Activity (Section 6.7.1)	The reference to paper diaries was removed as diaries are completed via an electronic device. In addition, abdominal pain/cramps and general well-being were added to the bulleted list of items that are collected in the subject diary.
Corticosteroid Treatment and Tapering	Permitted Concomitant Medications and Procedures (Section 9.1)	This section now clarifies that subjects who experience UC-related symptoms after completing the corticosteroid tapering regimen are permitted to receive the same treatment taken prior to tapering, provided that the dose is the same.
Endoscopy time points	Required Concomitant Medications and Procedures (Section 9.3)	This section now references Table 4 (Table of Events) for the time points at which endoscopy is required.
Reasons for Discontinuation	Discontinuations (Section 12)	The reasons for discontinuation were updated to align with the Clinical Data Interchange Standard Consortium (CDISC).
ICH definition	Good Clinical Practice (Section 14.1)	ICH acronym was updated to reflect current name (International Council for Harmonisation).
Medical Monitor Contact	Medical Monitor/ Emergency Contact	Medical monitor title was updated to PPD [redacted].

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