A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY, FOLLOWED BY AN ACTIVE-TREATMENT PHASE TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN THE TREATMENT OF SUBJECTS WITH ACTIVE BEHÇET'S DISEASE

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PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Parallel Group Study, followed by an Active-Treatment Phase to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in the Treatment of Subjects with Active Behçet's Disease.

Indication

Behçet's disease (BD) is a chronic, relapsing, multisystemic inflammatory disorder characterized by recurrent oral and genital ulcers, which may be accompanied by cutaneous, ocular, articular, gastrointestinal, and/or central nervous system inflammatory lesions. In some cases, uncontrolled inflammation may lead to blindness, intestinal complications, stroke and even meningitis, which can be fatal. The main clinical feature of Behçet's disease is recurrent (exacerbations and remissions) painful oral ulcerations appearing either alone or in combination with painful ulcers of the genitals, as well as lesions of the skin and eyes, and involvement of joints and other organs. Oral ulcers are the most frequent sign at onset (Kone-Paut, 1998; Krause, 1999; Alpsoy, 2007; Kerkeni, 2010; Atmaca, 2011) being observed in nearly every patient (range, 90% to 100% of cases). Genital ulcerations are generally less frequent, occurring in about 80% of adults (range, 55% to 97% of cases).

In BD, the pro-inflammatory mediators that are upregulated include the T cell derived cytokines interferon (IFN)-γ, interleukin (IL)-2 and IL-17 (Sugi-Ikai, 1998; Frassanito, 1999; Ahmed, 2004, Hamzaoui, 2002, Hamzaoui, 2011), as well as IL-1β, IL-6, IL-8, IL-12 and tumor necrosis factor (TNF)-α (Hamzaoui, 1990; Ozoran 1995, Evereklioglu, 2002; Hamzaoui, 2002). Elevated IL-12 and IL-17 levels in patients with active BD appear to correlate with disease activity (Frassanito, 1999; Hamzaoui, 2002; Turan, 1997; Hamzaoui, 2011). Together, these data indicate that pro-inflammatory responses prevail in active BD, and that targeted inhibition of 1 or more of these mediators may be an effective treatment in BD.

Apremilast (CC-10004), an oral small-molecule inhibitor of phosphodiesterase (PDE) 4, works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. Phosphodiesterase 4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. Phosphodiesterase 4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17, and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. Apremilast has immunomodulatory activity and, therefore, has the potential to be effective in the treatment of BD.

Objectives

Primary Objective:

- To evaluate the efficacy of apremilast for the treatment of oral ulcers in active Behçet's disease

Secondary Objectives:

- To evaluate the efficacy of apremilast in subjects with active Behçet's disease

- To evaluate the effect of apremilast on Patient Reported Outcomes (PROs) in subjects with active Behçet's disease

Safety Objective:

- To evaluate the safety and tolerability of apremilast in subjects with active Behçet's disease

Exploratory [redacted] Objectives:

[redacted]

Exploratory [redacted] Objective:

[redacted]

Exploratory Objectives:

[redacted]

Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study, followed by an active-treatment phase to evaluate the efficacy and safety of apremilast (CC-10004) in the treatment of subjects with active BD. The study consists of a Screening Phase of up to 6 weeks; a 12-week Double-blind Placebo-controlled Treatment Phase; a 52-week Active Treatment Phase, an optional Open-label Extension Phase; and a 4-week Posttreatment Observational Follow-up Phase.

Subjects will have the opportunity to enter an optional Open-label Extension Phase after the 52-week Active Treatment Phase (Week 64 visit). Subjects may continue in the optional Open-label Extension Phase until apremilast is commercially available for BD or until the benefit/risk of apremilast is found not to be acceptable for BD, according to either the sponsor or health authority.

To estimate the treatment difference for the primary endpoint for the study, approximately 204 eligible subjects will be randomized; stratified by gender, history of uveitis and region (Japan and Other). Subjects will be randomized 1:1 to receive apremilast 30 mg twice daily (BID) (APR 30 BID), or identically-appearing placebo tablets BID for the 12-week Placebo-controlled Treatment Phase.

Upon completion of the Week 12 visit, subjects initially randomized to placebo will transition to APR 30 BID, while subjects initially randomized to APR 30 BID will continue on the same treatment during the 52-week Active Treatment Phase.

Subjects who complete Visit 14 of the 52-week Active Treatment Phase will have an opportunity to continue to receive APR 30 BID in an optional Open-label Extension Phase. Subjects who

choose to not enter the optional Open-label Extension Phase will complete the 4-week Posttreatment Observational Follow-up Phase.

Subjects who discontinue at any time from the study for any reason, are to enter the 4-week Posttreatment Observational Follow-up Phase.

Study Population

Male and female subjects ≥ 18 years old at the time of consent, who have BD, meeting the International Study Group (ISG) criteria, without major organ involvement, and who have at least 2 oral ulcers at Visit 1 (Screening Visit) AND at least 2 oral ulcers at Visit 2 (day of randomization), when Visit 2 occurs at least 14 days after Visit 1 OR at least 3 oral ulcers at Visit 2 (day of randomization), when Visit 2 occurs at any time between 1 day and 42 days after Visit 1.

Length of Study

The study will consist of the following phases:

- Screening Phase — up to 6 weeks
- Double-blind, Placebo-controlled Treatment Phase — 12 weeks
- Active Treatment Phase — 52 weeks
- Optional Open-label Extension Phase until apremilast is commercially available for BD or until the benefit/risk of apremilast is found not to be acceptable for BD, according to either the sponsor or health authority.
- Posttreatment Observational Follow-up Phase – 4 weeks after the last dose (if a subject early terminates or chooses not to enter the optional Open-label Extension 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

Double-blind, Placebo-controlled Treatment Phase:

- Following a 7-day dose titration, apremilast (30 mg) and identically-appearing placebo tablets will be provided and administered orally BID

Active Treatment Phase

- Apremilast (30 mg) tablets will be provided and administered orally BID

Optional Open-label Extension Phase:

- Apremilast (30 mg) tablets will be provided and administered orally BID

Overview of Efficacy Assessments

- Oral ulcer count using area under the time curve (AUC) through Week 12

- Visual analogue scale (VAS) to assess pain of oral and genital ulcers separately
- BD Quality of Life measure
- BD Current Activity Form
- Behçet's Syndrome Activity Score (BSAS)
- [redacted]
- Physician's Global Assessment (PGA) of skin lesions
- [redacted]
- BD-related inflammatory eye disease
- [redacted]

Overview of Safety Assessments

- Adverse events
- Vasculitis and psychiatric evaluations
- Chest radiographs
- Physical examinations
- Vital signs
- Weight measurements
- Clinical laboratory safety evaluations
- Manual 12-lead electrocardiograms (ECGs)
- Pregnancy test

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1. Behçet's Disease

Behçet's disease (BD) is a chronic, relapsing, multisystemic inflammatory disorder of unknown etiology characterized by four major symptoms (oral aphthous ulcers, genital ulcers, skin lesions, and ocular lesions) and occasionally by five minor symptoms (arthritis, gastrointestinal ulcers, epididymitis, vascular lesions, and central nervous system [CNS] symptoms) (Cho, 2012).

The main clinical feature of BD is recurrent (exacerbations and remissions), painful oral ulcerations appearing either alone or in combination with painful ulcers of the genitals, as well as lesions of the skin, and eyes, and involvement of joints and other organs. Oral ulcers are the most frequent sign at onset (Kone-Paut, 1998; Krause, 1999; Alpsoy, 2007; Kerkeni, 2010; Atmaca, 2011) being observed in nearly every patient (range, 90% to 100% of cases). These ulcers can be severe enough to interfere with normal diet and nutrition, leading to malnutrition and weight loss. Due to their severity and frequency of reoccurrence, oral ulcers are an important aspect of the chronically debilitating nature of BD (Bang 1995; Davatchi, 2010). Genital ulcerations generally occur less frequently (approximately 80% of adults, range, 55% to 97% of cases). Skin involvement, eg, nodosum-like lesions, papulopustular lesions, pathergy reaction and erythema multiforme ranges from 39% to 93% of cases in adults. Ocular and joint involvement typically affects approximately 50% of patients (54.2% and 53.8% of cases, respectively), but there was significant variability between studies (Davatchi, 2010). Inflammatory disease of the eye manifesting as uveitis remains one of the leading causes of blindness in some parts of the world (Cho, 2012). Classification criteria for the diagnosis of BD were established by the International Study Group (ISG) (ISGBD, 1990). The diagnosis of BD is based on a manifestation of recurrent oral ulcerations plus 2 of the following criteria: recurrent genital ulceration, eye lesions, skin lesions, or positive pathergy test.

In BD, the pro-inflammatory mediators that are upregulated include the T cell derived cytokines interferon (IFN)-γ, interleukin (IL)-2 and IL-17 (Sugi-Ikai, 1998; Frassanito, 1999; Ahmed, 2004; Hamzaoui, 2002; Hamzaoui, 2011), as well as IL-1β, IL-6, IL-8, IL-12 and tumor necrosis factor (TNF)-α (Hamzaoui, 1990; Ozoran 1995, Evereklioglu, 2002; Hamzaoui, 2002). Elevated IL-12 and IL-17 levels in patients with active BD appear to correlate with disease activity (Frassanito, 1999; Hamzaoui, 2002; Turan, 1997; Hamzaoui, 2011), and BD is also associated with an imbalance in numbers of Th17 and regulatory T cells (Tregs) (Direskeneli, 2011). Together, these data indicate that pro-inflammatory responses prevail in active BD, and that targeted inhibition of one or more of these mediators may be an effective treatment in BD.

Treatment

The treatment of BD is generally empirical and the drug of choice is based on specific clinical manifestations in each patient (Fresko, 2008; Hatemi, 2008; Davatchi, 2010; Yazici 2010). The aim of treatment is to control symptoms, suppress inflammation and prevent end-organ damage. It is also important to avoid exacerbations of mucocutaneous and joint involvement, which may affect quality of life (Hatemi, 2008). To achieve these aims, the European League Against Rheumatism (EULAR) recommendations for the management of BD were developed by a multidisciplinary expert committee (Hatemi, 2008). These recommendations focus on the

treatment of Behçet-related eye disease, major vessel involvement, gastrointestinal involvement, arthritis, central nervous system involvement and mucocutaneous ulceration.

For isolated oral and genital ulcers, the most prevalent manifestations of BD, topical corticosteroids are the first line treatment of choice based on the EULAR guidelines (Hatemi, 2008). Corticosteroids have a significant side effect profile, especially when used for a long period of time. The most common side effects of oral mucosal application of topical corticosteroids include oral candidiasis, dry mouth, mouth burning, hypogeusia, sore throat, gingival atropy, halitosis and nausea (Thongprasom, 2008; Gonzalez-Moles, 2010). In addition to topical corticosteroids, supportive care including lidocaine gel and/or chlorhexidine are also used for oral ulcers, and sucralfate for genital lesions (Fresko, 2008; Hatemi, 2008). The most that these topical treatments offer is short-term symptomatic relief. Although oral and genital ulcers do not cause organ damage, it is important to avoid their exacerbations and recurrence, since they affect the patients' quality of life (Fresko, 2008; Hatemi, 2008). Systemic therapy may be required in a substantial number of cases with more severe manifestations. Colchicine has been widely used, however, there is no definitive evidence to show that it is beneficial for all mucocutaneous lesions (Aktulga, 1980, Yurdakul, 2001). Side effects associated with colchicine use include nausea, vomiting, diarrhea and abdominal pain, neuropathy, as well as bone marrow suppression, which has been reported with long-term usage (Colchicine SmPC). Other rare adverse events (AEs) include peripheral neuritis, myopathy, purpura, dermatosis, alopecia and reversible azospermia. Other oral systemic treatments, such as azathioprine, and biologic parenteral therapies such as IFN-α and TNF-α antagonists have been used off-label for the more recalcitrant manifestations of BD (Fresko, 2008; Hatemi, 2008). TNF-α antagonists include anti-TNF monoclonal antibodies (infliximab and adalimumab) and the soluble TNF receptor blocker (etanercept). The level of evidence regarding the effectiveness of these oral and biologic systemic treatments for the treatment of BD is limited, and their use is associated with hepatic, renal, metabolic, endocrinologic, and hematologic adverse events. Increased susceptibility to infections and development of malignancies are also known to occur (Hatemi, 2008). As such, there is an unmet medical need for a medication with a more acceptable safety profile in BD.

1.2. Apremilast

Apremilast (CC-10004), an oral small-molecule inhibitor of phosphodiesterase (PDE) 4, works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. Apremilast has immunomodulatory activity and, therefore, has the potential to be effective in the treatment of BD.

The pharmacologic profile of apremilast suggests a potential therapeutic benefit in the treatment of BD by a mechanism that involves restraining pro-inflammatory cytokine levels that occurs in active BD, through modulation of TNF-α, IL-2, IL-8, IL-12, IL-17 and IFN-γ production.

1.2.1. Clinical Safety

As of the clinical cutoff date of 10 May 2014, apremilast had been administered at daily doses ranging from 10 to 100 mg/day to approximately 5200 subjects in Celgene-sponsored studies, Phase 1 to 3 studies, including 4180 subjects who received apremilast in Phase 2 or Phase 3 studies in psoriasis, psoriatic arthritis (PsA), or rheumatoid arthritis (RA).

In total, 26 clinical studies have been completed, including 18 Phase 1 studies (14 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) and 8 Phase 2 studies (4 studies in subjects with psoriasis, 1 study in subjects with PsA, 1 study in subjects with RA, 1 study in subjects with BD, and 1 study in subjects with asthma). More than 4500 subjects have been enrolled in 2 ongoing Phase 2 studies (both in subjects with psoriasis) and in 9 ongoing Phase 3 studies (5 in subjects with PsA, 3 in subjects with psoriasis, and 1 in subjects with AS). 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 reported AEs were mild or moderate in severity and resolved while subjects continued apremilast treatment.

Based on the pooled data from the ongoing Phase 3 PsA studies, as of the data cutoff date of 01 Mar 2013, the incidence of withdrawal from investigational product (IP) due to these common AEs was low (≤ 2.1% for the individual AE). The most frequently reported AEs that led to IP withdrawal were diarrhea (0.4%, 1.2%, and 2.1%, for the placebo, apremilast 20 mg BID, and apremilast 30 mg BID treatment groups, respectively), nausea (0.4%, 1.0%, and 2.0%, for the placebo, apremilast 20 mg BID, and apremilast 30 mg BID treatment groups, respectively), and headache (0.3%, 0.5%, and 1.4%, for the placebo, apremilast 20 mg BID, and apremilast 30 mg BID treatment groups, respectively).

Based on the pooled data from the ongoing Phase 3 psoriasis studies, as of the data cutoff date of 11 Jan 2013, the incidence of withdrawal from IP due to these common AEs was low (≤ 1.4% for the individual AE). The most frequently reported AEs that led to IP withdrawal were nausea (0.2% and 1.4%, for the placebo and apremilast 30 mg BID treatment groups, respectively), diarrhea (0.2% and 0.9%, for the placebo and apremilast 30 mg BID treatment groups, respectively), and psoriasis (1.0% and 0.9%, for the placebo and apremilast 30 mg BID treatment groups, respectively).

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.

Ten deaths have been reported as of 10 May 2014, including two deaths in completed Celgene-sponsored studies, seven deaths in ongoing Celgene-sponsored studies, and one death in an ongoing investigator-initiated study. Among nine deaths in Celgene-sponsored studies, four subjects were taking apremilast 30 mg BID, two subjects were taking apremilast 20 mg BID, and three were taking placebo at the time of death. One subject whose death was reported in an investigator-initiated study died 20 months after the last dose of apremilast.

Detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of apremilast can be found in the Investigator's Brochure.

1.3. Efficacy and Safety of Apremilast in Behçet's Disease

Apremilast has been studied for the treatment of BD in one completed Phase 2 study.

Study CC-10004-BCT-001 was a Phase 2, multicenter, randomized, placebo-controlled, double-blind, parallel-group study that assessed the safety and efficacy of apremilast in the treatment of Behçet's disease. The study consisted of 4 phases: a 12-week Screening Phase; a 12-week, Placebo-controlled Treatment Phase; a 12-week Dose Blinded Extension Phase; and a 4-week Posttreatment Observational Follow-up Phase.

A total of 111 subjects were randomized and treated with placebo or apremilast 30 mg twice daily (BID) (APR 30 BID) for 84 days. A total of 100 subjects completed the Double-blind Phase and opted to continue to the 12-week period of active treatment with APR 30 BID.

In the BCT-001 study, apremilast demonstrated a treatment benefit in subjects with BD with the achievement of the primary endpoint as subjects randomized to the APR 30 BID group had statistically significantly fewer oral ulcers on Day 85 compared with the placebo group. The mean oral ulcer counts at baseline were 2.7 and 2.9 in the APR 30 BID and placebo groups, respectively. On Day 85, the least squares (LS) mean oral ulcer counts were 0.4 and 2.0 in the APR 30 BID and placebo groups, respectively, yielding an LS mean difference (2-sided 95% confidence interval [CI]) of -1.6 (-2.4, -0.9) ($p < 0.0001$).

The analyses of the secondary endpoints supported the results of the primary analysis. A significantly greater proportion of subjects in the APR 30 BID group achieved complete (oral ulcer-free) response at Day 85 compared with the placebo group (70.9% APR 30 BID; 28.6% placebo; $p < 0.0001$). Similarly, a significantly greater proportion of subjects in the APR 30 BID group achieved partial ($\geq$ 50% reduction in oral ulcer number [including oral ulcer-free]) response at Day 85 compared with the placebo group (89.1% APR 30 BID group; 50.0% placebo group; $p < 0.0001$). The area under the curve at Day 85 (AUC_{85}) for oral ulcer count, average daily AUC_{85}, and average number of ulcers from Day 1 to Day 85 were more than 2-fold lower in the APR 30 BID group compared with the placebo group.

The mean oral ulcer counts in subjects randomized to the APR 30 BID group decreased sharply, reaching maximum reduction on Day 15 (first postbaseline assessment), and remained reduced for up to 24 weeks on treatment. In subjects randomized to the placebo group, the mean oral ulcer counts were consistently higher than in subjects randomized to the APR 30 BID group during the Treatment Phase. When the placebo subjects were transitioned to APR 30 BID in the Extension Phase, a reduction in mean oral ulcer counts was observed that was similar to those in the APR 30 BID-treated subjects. The oral ulcer counts increased in both treatment groups during the Observational Follow-up Phase when apremilast treatment was stopped.

Oral ulcer pain visual analog scale (VAS) scores in APR 30 BID- and placebo-treated subjects showed a pattern of change over time that was similar to that of oral ulcer counts. At Day 85, there was a more than 2-fold greater improvement (indicating decreased pain) in VAS scores from baseline in the APR 30 BID group compared with the placebo group (nominal $p < 0.0001$). When the placebo subjects were transitioned to APR 30 BID in the Extension Phase, an improvement in oral ulcer pain VAS scores was observed that was similar to the APR 30 BID-

treated subjects. During the Observational Follow-up Phase, recurrence of pain was noted when apremilast treatment was stopped.

A small number of subjects had genital ulcers at baseline. Therefore, formal statistical comparisons between the APR 30 BID and placebo treatment groups were not done. However, a complete genital ulcer response (genital ulcer-free at Day 85) was achieved by all 10 (100%) subjects with baseline lesions in the APR 30 BID group versus 3 (50.0%) subjects with baseline lesions in the placebo group. Further, only 1 subject in the APR 30 BID group who did not have genital ulcers at baseline developed a single, new genital ulcer at Day 85, compared with 6 subjects in the placebo group.

In addition to demonstrating efficacy in the treatment of mucocutaneous ulcers associated with BD, the use of APR 30 BID also significantly reduced overall disease activity compared to placebo as measured by the BD Current Activity Form (BDCAF) and Behçet's Syndrome Activity Score (BSAS). Aside from mucocutaneous ulcers, these validated instruments also take into account the involvement of other organ systems, such as the skin, joints, gastrointestinal tract, vascular, and nervous systems. Significantly greater reductions (improvements) in the BDCAF from baseline were observed at Day 85 in the APR 30 BID group compared with the placebo group with an LS mean change of -1.2 and -0.1, respectively (nominal $p = 0.0007$). Similarly, BSAS mean scores were significantly reduced (improved) from baseline at Day 85 in the APR 30 BID group compared with the placebo group ($p < 0.0001$).

Significant improvements in physical function and quality of life (QoL) measured by the SF-36v2 Physical Component Score (PCS) and the BD QoL questionnaires, were also observed with APR 30 BID treatment compared to placebo. At Day 85, the SF-36v2 PCS mean scores were significantly higher relative to baseline (improved physical functioning) in the APR 30 BID group compared with the placebo group (LS mean APR 30 BID, 4.12; placebo, -1.10; $p = 0.0011$). The improvement observed in the APR 30 BID treatment group at Day 85 exceeded the minimal clinically important difference (MCID) of a 2.5-point increase from baseline. Similarly, at Day 85, the BD QoL mean scores were significantly reduced (improved) from baseline in the APR 30 BID group compared with the placebo group (LS mean APR 30 BID group, -4.3; placebo group, -1.8; $p = 0.0397$).

Overall, the improvements seen at Week 12 were maintained through Week 24 for subjects who remained on apremilast treatment during the Treatment and Extension Phases, thus demonstrating persistence of response.

During the Placebo-controlled Phase, the majority of subjects reported at least 1 TEAE, 89.3% of subjects in the placebo group and 89.1% of subjects in the APR 30 BID group. Severe TEAEs were reported in less than 10% of subjects, 8.9% of subjects in the placebo group and 9.1% of subjects in the APR 30 BID group. Serious TEAEs were reported in 3 subjects in the placebo group and 2 subjects in the APR 30 BID group. None of the serious TEAEs in the APR 30 BID group were considered related to investigational product (IP). One subject in the APR 30 BID group had IP interrupted due to a TEAE. Less than 10% of subjects had IP withdrawn due to TEAEs, ie, 8.9% of subjects in the placebo group and 7.3% of subjects in the APR 30 BID group. The proportion of subjects with TEAEs, drug-related TEAEs, severe TEAEs, serious TEAEs and TEAEs leading to IP interruption or withdrawal was similar in the placebo and APR 30 BID groups. No deaths were reported in this study.

The most common TEAEs in the APR 30 BID group, in decreasing order of frequency, were headache, nausea, Behçet's syndrome/flare, and diarrhea. The most common TEAEs in the Placebo group, in decreasing order of frequency, were Behçet's syndrome/flare, headache, nausea, and abdominal pain.

The design of the Study CC-10004-BCT-002 is guided by the design of, and results from CC-10004-BCT-001.

1.4. Rationale for Dose Chosen

Apremilast

Based on the safety and efficacy results of 3 completed Phase 2 studies in psoriasis and PsA, the dose of APR 30 BID was chosen for the BCT-001 study (Section 1.3), to minimize the number of subjects required to evaluate this rare disorder and to maximize the opportunity to demonstrate efficacy. Since apremilast is known to be associated with gastrointestinal side effects and headaches, the dose was escalated gradually to 30 mg BID over the first week of treatment, and subjects who could not tolerate the full dose of IP were allowed to reduce their dose to 20 mg BID. During the placebo-controlled period, 2 subjects in the APR 30 BID group dose-reduced. During the apremilast-exposure period, 2 subjects in the APR 30 BID/APR 30 BID group dose-reduced; thus although dose reduction was allowed, it was infrequent.

Data from the BCT-001 study indicated that APR 30 BID effectively reduced the number of oral and genital ulcers, decreased oral and genital ulcer pain, and improved physical function and quality of life in subjects with BD. Apremilast exhibited a safety profile in BD that was consistent with those observed in other inflammatory diseases in which apremilast was evaluated (eg, psoriasis and psoriatic arthritis). Taken together, these data demonstrate that APR 30 BID has an acceptable benefit/risk ratio profile in subjects with BD.

Based on this rationale, APR 30 BID will be investigated in this BD study.

2. STUDY OBJECTIVES

2.1. Primary Objective

- The primary objective of the study is to evaluate the efficacy of apremilast in the treatment of oral ulcers in active Behçet's disease.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of apremilast in subjects with active Behçet's disease
- To evaluate the effect of apremilast on Patient Reported Outcomes (PROs) in subjects with active Behçet's disease

2.3. Safety Objective

- To evaluate the safety and tolerability of apremilast in subjects with active Behçet's disease

2.4. Exploratory [redacted] Objectives

The exploratory [redacted] objectives of the study are:

[redacted]

2.5. Exploratory [redacted] Objective

[redacted]

2.6. Exploratory Objective

The exploratory objective of the study is:

[redacted]

Data from exploratory objectives will be included in the Clinical Study Report or a separate report.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- Area under the curve (AUC) for the number of oral ulcers from baseline through Week 12

3.2. Secondary Endpoints

- Complete response rate for oral ulcers at Week 12
  - A complete response is defined as the proportion of subjects who are oral ulcer-free.
- Change from baseline in the pain of oral ulcers as measured by VAS at Week 12
- Complete response rate for genital ulcers at Week 12 for subjects who had genital ulcers at Baseline
  - A complete response is defined as the proportion of subjects who are genital ulcer-free.
- Change from baseline in the pain of genital ulcers, as measured by VAS at Week 12 in subjects who had genital ulcers at baseline
- Change from baseline in disease activity as measured by Behçet's Disease Current Activity scores (BD Current Activity Form) at Week 12
- Change from baseline in the BD QoL score at Week 12
- Change from Baseline in Behçet's Syndrome Activity Score (BSAS) at Week 12
- Time to oral ulcer resolution (complete response), ie, the first instance when a subject has a complete response, during the Placebo-controlled Treatment Phase
- Proportion of subjects with no oral ulcers following complete response, ie, the first time when a subject has a complete response, during the Placebo-controlled Treatment Phase
- Number of oral ulcers following loss of complete response, ie, the first instance when a subject has a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase
- Time to recurrence of oral ulcers following loss of complete response, ie, the first instance when a subject has a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase
- Change from baseline in the total score of the Static Physician's Global Assessment (PGA) of skin lesions (acne-like lesions, folliculitis and erythema nodosum) of BD at Week 12 in subjects who had BD skin lesions at baseline
- Proportion of subjects achieving an oral ulcer complete response (oral ulcer-free) by Week 6, after start of dosing, and who remain oral ulcer free for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase

3.3. Safety Endpoints

Safety and tolerability as defined by the following:

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

3.4. Exploratory [redacted] Endpoints

[redacted]

3.5. Exploratory [redacted] Endpoint

[redacted]

3.6. Exploratory Endpoint(s)

[redacted]

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study, followed by an active-treatment phase to evaluate the efficacy and safety of apremilast (CC-10004) in the treatment of subjects with active BD.

Approximately 204 eligible subjects will be randomized 1:1 (102 subjects per group) to receive apremilast (APR 30 BID) or identically-appearing placebo tablets BID for the 12-week Placebo-controlled Treatment Phase. Subjects will be stratified by gender, history of uveitis and region (Japan and Other).

Upon completion of the Week 12 visit, subjects initially randomized to placebo will transition to APR 30 BID, while subjects initially randomized to APR 30 BID will continue on the same treatment during the 52-week Active Treatment Phase.

Subjects who complete Visit 14 of the 52-week Active Treatment Phase will have an opportunity to continue to receive APR 30 BID in an optional Open-label Extension Phase. Subjects who choose to not enter the optional Open-label Extension Phase will complete the 4-week Posttreatment Observational Follow-up Phase.

Subjects who discontinue at any time from the study for any reason, are to enter the 4-week Posttreatment Observational Follow-up Phase.

The study will include the following (Figure 1):

- Screening Phase: up to 6 weeks
- Double-blind, Placebo-controlled Treatment Phase: 12 weeks
  - APR 30 BID
  - Placebo
- Active Treatment Phase: 52 weeks
  - APR 30 BID
- Optional Open-label Extension Phase until apremilast is commercially available for BD or until the benefit/risk of apremilast is found not to be acceptable for BD, according to either the sponsor or health authority.
  - APR 30 BID
- Posttreatment Observational Follow-up Phase – 4 weeks after the last dose (if a subject early terminates or chooses not to enter the optional Open-label Extension Phase)

4.1.1. Internal Celgene Safety Monitoring During the Apremilast Program: Role of the Safety Management Team

In addition to daily safety monitoring conducted by Investigators and individual study personnel, cumulative and interval blinded AEs, serious adverse events (SAEs), discontinuations, and laboratory findings are reviewed internally by a Safety Management Team (SMT) at Celgene. 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. The scope, conduct, processes, and accountabilities of the SMT are specified in the SMT charter.

4.1.2. External Safety and Efficacy Monitoring During Apremilast Program: Role of the Independent Data Monitoring Committee

Monitoring is also performed by an independent, external Data Monitoring Committee (DMC) that will assess both safety and efficacy, as outlined in the DMC charter (available upon request). The DMC will review data in a blinded manner, but reserves the right to unblind data for safety or efficacy reasons. The DMC is comprised of three independent external trialists and an independent external statistician for whom there is no identified conflict of interest. The DMC is convened approximately every 12 months, or ad hoc, at the request of the SMT. The DMC's scope, conduct, processes, and accountabilities are specified in its charter. Recommendations of the DMC, based on the overall benefit/risk evaluation, may include proceeding with the study according to the protocol, proceeding with the study with modification, or study suspension.

4.2. Study Design Rationale

The design of this study was guided by the results from a Phase 2 study in Behçet's disease (Section 1.3).

The safety profile of apremilast in Behçet's disease was consistent with its known safety profile as demonstrated in the overall development program.

The primary purpose of the CC-10004-BCT-002 study is to evaluate the efficacy of apremilast in the treatment of mucocutaneous manifestations in subjects with Behçet's disease. The primary endpoint will be the AUC for the number of oral ulcers from Day 1 through Week 12. Oral ulcers have spontaneous flares and remissions; thus, using an AUC for the number of oral ulcers from baseline through Week 12 provides a better representation of the effect of apremilast on the number of oral ulcers the subject experiences during the Placebo-controlled Treatment Phase rather than at one point in time, such as Day 85, the primary endpoint, in the CC-10004-BCT-001 study.

Active Treatment Phase

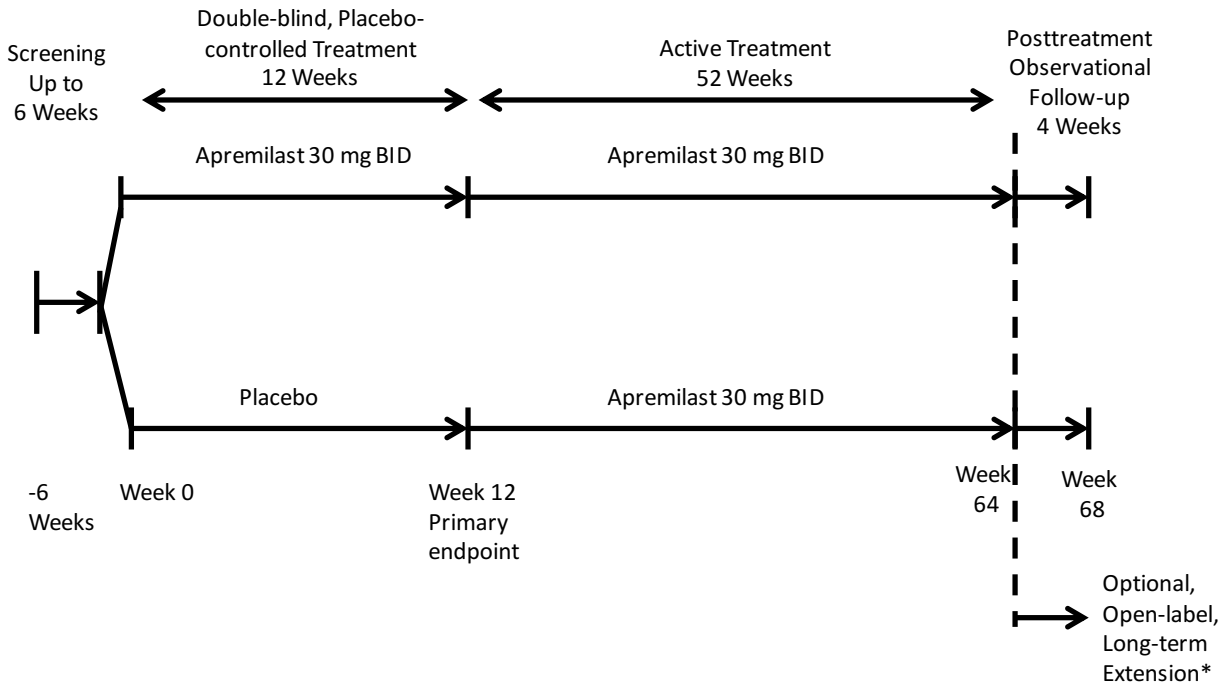
Establishing the long-term safety and tolerability benefit/risk profile of any new therapy, especially one with a new and novel mechanism of action, is a critical aspect of drug development. The 52-week active treatment, wherein all subjects including those initially randomized to placebo receive apremilast, will support the assessment of the long term safety profile of apremilast.

Optional Open-label Extension Phase

Subjects who complete Visit 14 of the 52-week Active Treatment Phase will have an opportunity to continue to receive APR 30 BID in an optional Open-label Extension Phase.

Further to and consistent with the principles of the Declaration of Helsinki, study subjects should also share in any benefit arising from the study, which may include access to treatments identified as being beneficial. For these reasons, a longer active treatment phase and optional Extension Phase, compared to the CC-10004-BCT-001 study, has been included.

Figure 1: Overall Study Design



* Subjects will have an opportunity to enter an Optional Open-label Extension Phase until apremilast is commercially available for BD or until the benefit/risk of apremilast is found not to be acceptable for BD, according to either the sponsor or health authority.

4.3. Study Duration

The study will consist of the following phases:

- Screening Phase – up to 6 weeks
- Double-blind, Placebo-controlled Treatment Phase – 12 weeks
- Active Treatment Phase – 52 weeks
- Optional Open-label Extension Phase until apremilast is commercially available for BD or until the benefit/risk of apremilast is found not to be acceptable for BD, according to either the sponsor or health authority.
- Posttreatment Observational Follow-up Phase – 4 weeks after the last dose (if a subject early terminates or chooses not to enter the optional Open-label Extension Phase)

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 pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

5. TABLE OF EVENTS

Table 1: Table of Events (up to Week 64)

Phases	Screening Phase	Double-blind, Placebo-controlled Treatment Phase (12 weeks)								Active Treatment Phase (52 weeks)					Post-treatment Observational FU Visit (4 weeks after last dose of IP) [a]	Early Termination (ET)[b]
Visit Number	**1**	**2** Randomization	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Week	**-6 to 0**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**28**	**40**	**52**	**64**	**68**	
Day	**-42 to 0**	**1**	**8± 1**	**15 ±1**	**29 ±3**	**43 ±3**	**57 ±3**	**71 ±3**	**85 ±3**	**113 ±7**	**197 ±7**	**281 ±7**	**365 ±7**	**449 ±7**	**476 ±7**	
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demography	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History including BD history[c]	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior/Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vasculitis and Psychiatric Evaluations[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination[g]	X	-	-	-	-	-	-	-	X	-	-	-	-	X	-	X
Limited Physical Examination[h]	-	X	-	-	X	-	X	-	-	X	X	X	X	-	X	-
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[i]	X	X	-	-	X	-	-	-	X	X	-	X	X	X	X	X
Serum Chemistry[j]	X	X	-	-	X	-	-	-	X	X	-	X	X	X	X	X
Urinalysis[k]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pregnancy Testing[l]	X	X	-	-	-	-	-	-	X	-	-	-	-	X	X	X
Contraception Education[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Table of Events (Continued)

Phases	Screening Phase	Double-blind, Placebo-Controlled Treatment Phase (12 weeks)								Active Treatment Phase (52 weeks)					Post-treatment Observational FU Visit (4 weeks after last dose of IP) [a] [a]	Early Termination (ET)[b]
Visit Number	**1**	**2** Randomization	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Week	**-6 to 0**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**28**	**40**	**52**	**64**	**68**	
Day	**-42 to 0**	**1**	**8 ±1**	**15 ±1**	**29 ±3**	**43 ±3**	**57 ±3**	**71 ±3**	**85 ±3**	**113 ±7**	**197 ±7**	**281 ±7**	**365 ±7**	**449 ±7**	**476 ±7**	
Chest Radiograph[n]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12-lead ECG[o]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Efficacy Assessments																
Number of Oral Ulcers	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Number of Genital Ulcers	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pain VAS for Oral Ulcers	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pain VAS for Genital Ulcers	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BD Current Activity Form	-	X	-	-	-	-	-	-	X	-	-	-	-	X	X	X
BD Quality of Life Measure	-	X	-	-	-	-	-	-	X	-	-	-	-	X	X	X
BSAS	-	X	-	-	-	-	-	-	X	-	-	-	-	X	X	X
[redacted]																
Physician's Global Assessment of Skin Lesions[p]	-	X	X	X	X	-	X	-	X	X	X	X	X	X	X	X
[redacted]																
Assessment of BD-related Inflammatory Eye Disease[r]	X	-	-	-	-	-	-	-	X	-	-	-	-	X	-	X
[redacted]																

Table 1: Table of Events (Continued)

Phases	Screening Phase	Double-blind, Placebo-Controlled Treatment Phase (12 weeks)								Active Treatment Phase (52 weeks)					Post-treatment Observational FU Visit (4 weeks after last dose of IP)[a]	Early Termination (ET)[b]
Visit Number	1	2 Randomization	3	4	5	6	7	8	9	10	11	12	13	14	15	
Week	-6 to 0	0	1	2	4	6	8	10	12	16	28	40	52	64	68	
Day	-42 to 0	1	8 ±1	15 ±1	29 ±3	43 ±3	57 ±3	71 ±3	85 ±3	113 ±7	197 ±7	281 ±7	365 ±7	449 ±7	476 ±7	
[redacted]																
Investigational Product[w]																
Dispense IP	-	X	-	-	X	-	X	-	X	X	X	X	X	X[x]	-	-
IP Accountability	-	-	X	X	X	-	X	-	X	X	X	X	X	X	-	X

BD = Behçet's disease; BSAS = Behçet's Syndrome Activity Score; ECG = electrocardiogram; FU = follow-up; IP = investigational product; [redacted] VAS = visual analog scale.

[a] Observational Follow-up Visit - Subjects who discontinue at any time from the study for any reason and subjects who do choose to not enter the optional Open-label Extension Phase are to enter the 4-week Posttreatment Observational Follow-up Phase.

[b] ET assessments are to be completed when a subject withdraws from any of the treatment phases.

[c] Medical history and BD-related history (as listed in Appendix A) will be captured.

[d] See Section 6.5 for details.

[e] A vasculitis assessment (Section 6.6.5) and psychiatric evaluation (Section 6.6.6) are to be assessed as appropriate. Evaluate the need for referral to a psychiatrist and other actions, including discontinuation, as required in Section 6.6.6. Please answer the question in the eCRF as Yes/No for whether the subject was sent for a psychiatric evaluation.

[f] Vital signs include temperature, pulse, respiratory rate, and seated blood pressure.

[g] Complete physical examinations include height (Visit 1), weight (street clothes; no shoes), skin, nasal cavities, eyes, ears, lymph nodes, genitalia, and respiratory, cardiovascular, gastrointestinal, neurological and musculoskeletal systems evaluations.

[h] Limited physical examinations will include evaluations to assess the subject's BD. If a subject presents with symptoms other than BD, the Investigator should determine whether a complete physical examination should be performed.

[i] See Section 6.6.7.1 for details.

[j] See Sections 6.6.7.2 and 6.6.7.4 for details.

[k] See Section 6.6.7.3 for details.

[l] Urine pregnancy testing (females of childbearing potential [FCBP]) will be performed at Visit 2 (Baseline Visit; prior to randomization). At all other time points indicated in Section 5, a serum pregnancy test will be performed. A urine pregnancy test(s) should be administered if the FCBP subject misses a menstrual period.

[m] Contraception education is for males and FCBP. The Investigator will educate all FCBP and males about the different options of contraceptive methods and their correct use at Visits 1 and 2. The subject will be reeducated every time their contraceptive measures/methods or their ability to become pregnant changes.

[n] A chest radiograph (posteroanterior [PA] and lateral views) should be taken prior to randomization at Visit 2 (Baseline Visit), when most of the eligibility criteria are met, so that results are available prior to randomization. A PA view is required. An additional lateral view is strongly recommended but not required. Alternatively, PA or PA/lateral radiographs that were taken within the 12 weeks prior to Visit 1 will be accepted.
Additional chest radiographs should be performed as indicated by local treatment guidelines or, if guidelines are not available/applicable, chest radiographs should be performed when clinically indicated (see Section 6.6.10).

[o] A 12-lead ECG will be performed after the subject has been supine for 3 minutes. Results must be within normal limits or not clinically significant.

[p] See Appendix G for details.

[redacted]

[r] An ophthalmological exam should be completed during the Screening Phase, once the subject has met most of the eligibility criteria, after the chest radiograph and ECG, but prior to randomization at Visit 2 (Baseline Visit). A complete evaluation of the eyes, including a slit lamp examination, must be performed by an ophthalmologist during the Screening Phase and at Visits 9, 14, ET, and at any time when the subject is suspected of new onset/worsening of Behçet's disease-related inflammatory eye disease, including uveitis, retinitis, ophthalmitis and iritis. If a subject has a report from his/her ophthalmologist, dated within 12 weeks of Visit 2 (Baseline Visit; day of randomization), stating that the subject does not have BD-related ophthalmological symptoms, then the subject will not be required to have an ophthalmological exam during Screening Phase unless there is an eye-related complaint during the Screening Phase.

[redacted]

[w] See Sections 6.8, 8.3, and 8.6 for details.

[x] Subjects who complete Visit 14 and choose to continue in the optional Open-label Extension Phase will be dispensed IP at Visit 14.

Table 2: Table of Events (Years 2 to 4)

	Optional Open-label Extension Phase												Observational FU Visit (4 weeks ±7 days after last dose) [a]	Early Termination (ET) [b]
Year	**Year 2**				**Year 3**				**Year 4[c]**					
Visit Number	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**		
Week	**76**	**88**	**100**	**112**	**124**	**136**	**148**	**160**	**172**	**184**	**196**	**208**		
Day	**533 ±7**	**617 ±7**	**701 ±7**	**785 ±7**	**869 ±7**	**953 ±7**	**1037 ±7**	**1121 ±7**	**1205 ±7**	**1289 ±7**	**1373 ±7**	**1457 ±7**		
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments														
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limited Physical Examination[e]	-	X	-	-	-	X	-	-	-	X	-	-	-	-
Complete Physical Examination[f]	-	-	-	X	-	-	-	X	-	-	-	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[g]	-	X	-	X	-	X	-	X	-	X	-	X	X	X
Serum Chemistry[h]	-	X	-	X	-	X	-	X	-	X	-	X	X	X
Pregnancy Testing[i]	-	-	-	-	-	-	-	-	-	-	-	X	X	X
Investigational Product														
Dispense IP	X	X	X	X	X	X	X	X	X	X	X	-	-	-
IP Accountability	X	X	X	X	X	X	X	X	X	X	X	X	-	-

BD = Behçet's disease; ET = Early Termination; FCBP = female of child-bearing potential; FU = follow-up; IP = investigational product.

[a] Observational Follow-up Visit - Subjects who discontinue at any time from the study for any reason and subjects who do not choose to enter the optional Open-label Extension Phase are to enter the 4-week Posttreatment Observational Follow-up Phase.

[b] ET assessments are to be completed when a subject withdraws at any time from the Extension study.

[c] After Year 4 – if apremilast is not commercially available the visits will repeat starting at Visit 16 until apremilast is commercially available for BD or until the benefit/risk of apremilast is found not to be acceptable for BD, according to either the sponsor or health authority.

[d] Vital signs include temperature, pulse, respiratory rate, and seated blood pressure.
[e] Limited physical examinations will include evaluations to assess the subject's BD. If a subject presents with symptoms other than BD, the Investigator should determine whether a complete physical examination should be performed.
[f] Complete physical examinations will include weight (street clothes; no shoes), skin, nasal cavities, eyes, ears, lymph nodes, genitalia, and respiratory, cardiovascular, gastrointestinal, neurological and musculoskeletal systems evaluations.
[g] See Section 6.6.7.1 for details.
[h] See Sections 6.6.7.2 and 6.6.7.4 for details.
[i] A urine pregnancy test(s) should be administered if the FCBP subject misses a menstrual period. If a FCBP terminates the study early, a serum pregnancy test will be completed after the last dose of IP.

6. PROCEDURES

Assessments, as detailed in the following sections, will be done at the intervals specified in the Table of Events, Section 5.

6.1. Informed Consent

An Informed Consent Document must be signed before any study related assessments are performed.

6.2. Demographic Data

The demographic data will include (but not be limited to) the subject's initials (as allowed per local regulations), date of birth (as allowed per local regulations), age, gender, and race/ethnic origin. The demographic profile will be recorded in the source documents and electronic case report form (eCRF).

6.3. Complete Medical History

Relevant medical history should be recorded, including previous relevant surgeries. History of BD will be reported in the eCRF including diagnosis date and a detailed history of BD manifestations, as listed in Appendix A, and BD treatment history.

6.4. Inclusion/Exclusion Criteria

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). The subject's source documents must support his/her qualifications for the study (eg, if a female subject does not require pregnancy testing and birth control because of a hysterectomy, the date of the hysterectomy must be included in the medical history).

6.5. Prior and Concomitant Medications

All medications and therapies (including systemic and topical medications, prescription, and non-prescription, including herbal supplements) taken by the subject up to 30 days prior to Visit 1 should be recorded, including the stop dates for medications prohibited in the study, at the time of consent.

Previous biologic use should be recorded, including start and stop dates regardless of when it was administered.

All medications and therapies being taken by the subjects, at any time during the study, must also be recorded.

6.6. Safety Assessments

The following safety assessments will be performed as outlined in Section 5.

6.6.1. Adverse Events

The time frames for recording all AEs are indicated in Section 5. It should be noted that during the first 64 weeks of the study worsening of a subject's BD should be considered as worsening of the disease under study, and should not be captured as an AE. Worsening of disease will be captured on a separate BD activity page in the eCRF that lists each of the BD manifestations.

Worsening of a subject's BD will be captured on the AE eCRF for subjects who continue in the optional Open-label Extension Phase after Week 64.

6.6.1.1. Adverse Events of Special Interest

The PDE4 inhibitors, including apremilast, have been associated with AE reports of diarrhea. Diarrhea has not been well characterized in previous apremilast studies.

Diarrhea is the passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual (World Health Organization [WHO], 2013). Following the definition of diarrhea by the WHO and taking a more conservative approach, the AE of diarrhea in this protocol is defined as having two or more watery/liquid stools in a day.

In order to better characterize diarrhea and to distinguish similar events coding to the Medical Dictionary of Regulatory Activities (MedDRA) preferred term of diarrhea, subjects reporting diarrhea or similar events (eg, frequent bowel movements, loose bowels, etc.) will be asked whether they have had two or more watery/liquid stools in a day. Subjects who respond "yes" to this question will be further asked how often, on average, since their last visit have they experienced two or more watery/liquid stools in a day. Subjects who respond "no" to the question will not be asked any further questions.

6.6.2. Vital Signs, Height and Weight

Weight (to be measured in street clothes, no shoes) and vital signs, including temperature, pulse, respiratory rate, and seated blood pressure, will be taken during the visits indicated in Section 5.

Height will be recorded at Visit 1 only.

Vital signs will be obtained after the subject has been in a comfortable position for at least 5 minutes.

If body temperature is measured orally, since drinking hot or cold beverages (including water) has a significant impact on recorded oral body temperature, no beverages should be ingested within 15 minutes of the measurement. Investigators are to report any clinically significant abnormal findings as AEs.

6.6.3. Complete Physical Examinations

Complete physical examinations, including height (Visit 1 only), skin, nasal cavities, eyes, ears, lymph nodes, genitalia, and respiratory, cardiovascular, gastrointestinal, neurological, and musculoskeletal systems evaluations will be performed as indicated in Section 5.

6.6.4. Limited Physical Examinations

Limited physical examinations will include evaluations to assess the subject's BD. If a subject presents with symptoms other than BD, the Investigator should determine whether a complete physical examination should be performed.

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 subject 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. If vasculitis is assessed as being BD-related, then the vasculitis should be reported on the BD activity pages in the eCRF.

6.6.6. Psychiatric Evaluation

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 Posttreatment Observational Follow-up Phase Visit.

At any time during the study (post randomization), the Investigator (and/or appropriate site staff) should evaluate any subject who reports thoughts of suicide to determine if the subject truly has suicide ideation. In such a 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 Posttreatment Observational Follow-up Phase Visit.

A copy of the psychiatric evaluation report must be in the subject's source document, especially if the subject is confirmed not to be at risk for suicide and is continuing in the study.

A Yes/No question should be completed in the eCRF as to whether the subject was sent for a psychiatric evaluation.

6.6.7. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed as indicated in Section 5.

A central laboratory will be used for this study. The Principal Investigator (PI) or medically-qualified designee will review and assess all clinical laboratory results for each subject participating at their sites, and indicate whether the results are clinically significant. The laboratory reports should be initialed and dated by the PI or medically-qualified designee to indicate that they have been reviewed. Abnormal laboratory results may be repeated to rule out laboratory errors. Any clinically significant abnormal laboratory result that is not part of a

clinical diagnosis AE should be reported as a separate AE and should be followed to resolution (ie, stabilizes, returns to baseline, or improves and considered as no longer clinically significant).

Additional clinical safety laboratory evaluations should be performed if judged clinically appropriate by the PI or by a medically-qualified designee, or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is warranted.

6.6.7.1. Hematology

As indicated in Section 5, hematology laboratory evaluations will include complete blood count (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell (WBC) count (absolute and differential), and platelet count.

6.6.7.2. Serum Chemistry

During Visits 1 and 2, serum chemistry laboratory evaluations will include sodium, potassium, chloride, bicarbonate, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), and alanine aminotransferase/serum glutamate pyruvic transaminase (ALT/SGPT).

At subsequent visits, as indicated in Section 5, serum chemistry laboratory evaluations will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, alkaline phosphatase, bilirubin (total and direct), AST/SGOT, and ALT/SGPT.

6.6.7.3. Urinalysis

Urinalysis will be done at Visit 1 (Screening Visit) and as clinically necessary; dipstick urinalysis (specific gravity, pH, glucose, protein, ketones, bilirubin, and hemoglobin/blood) will be performed. A microscopic urinalysis (epithelial cells, casts, RBCs, and WBCs) will be performed in the event of a positive dipstick result.

6.6.7.4. Hepatitis Testing

Screening tests for hepatitis B and C antigen or antibodies for study inclusion/exclusion purposes will not be performed. A complete medical history must be taken and must include a query to rule out whether a subject has known active current or history of recurrent infections including hepatitis B and C (see Exclusion #13). Subjects must be asymptomatic and their liver function test (ie, ALT/SGPT, AST/SGOT, and alkaline phosphatase) levels must be ≤ 1.5 x upper limit of normal (ULN) at baseline.

At any time post randomization, a subject's liver function tests should be repeated when ALT/SGPT, AST/SGOT, or alkaline phosphatase levels are ≥ 2.0 x ULN. A viral hepatitis panel should be performed together with the repeat liver function tests. A viral hepatitis panel includes total hepatitis A virus antibody (HAV Ab), qualitative hepatitis B surface antibody (HBsAb) and hepatitis B surface antigen (HBsAg) with reflex confirmation, hepatitis B core antibody (HBcAb), and hepatitis C virus antibody (HCV Ab).

6.6.8. Contraception Education

The risks to a fetus or to a nursing child from apremilast are not known at this time. Results of the animal and in vitro studies can be found in the Investigator's Brochure.

Contraception education is for males and females of childbearing potential (FCBP)[1]. The Investigator will educate all FCBP and males about the different options of contraceptive methods and their correct use at Visits 1 and 2. All males and FCBP must use one of the approved contraceptive options as described in Section 7.2, while on IP and for at least 28 days after administration of the last dose of the IP.

When a female subject's childbearing potential changes due to a change in contraceptive measures or her ability to become pregnant changes at the time of study entry, or at any time during the study, the Investigator will educate the subject regarding options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

6.6.9. Pregnancy Tests for Females of Childbearing Potential

For all FCBP,[1] pregnancy testing will be performed during the study as indicated in Section 5. A serum pregnancy test with a sensitivity of ≤ 25 mIU/mL will be required at Visit 1, Visit 9, after the last dose of IP (eg, the ET Visit), and at the Observational Follow-up Visit, (4 weeks after the last dose of IP). In addition, a local urine pregnancy test kit will be provided by the central laboratory and the test performed on all FCBP subjects at Visit 2 (Baseline Visit; day of randomization) at the site, prior to randomization. A urine pregnancy test(s) should be administered if the FCBP subject misses a menstrual period.

6.6.10. Chest Radiograph

Subjects must have an essentially normal chest radiograph. Results must be within normal limits or not clinically significant in order to allow a subject to enroll in the study.

A chest radiograph (posteroanterior [PA] and lateral views) should be taken prior to Visit 2, when most of the eligibility criteria are met, so that results are available prior to randomization. A PA view is required. An additional lateral view is strongly recommended, but not required. Alternatively, PA or PA/lateral radiographs that were taken within the 12 weeks prior to Visit 1 will be accepted for evaluation for participation in the study.

Additional chest radiographs should be performed as indicated by local treatment guidelines or, if guidelines are not available/applicable, chest radiographs should be performed when clinically indicated.

6.6.11. 12-lead ECG

A 12-lead ECG will be performed during the Screening Phase.

[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).

An ECG will be performed after the subject has been supine for approximately 3 minutes. Sites are to use their own, local ECG machines for the study and the ECG readings will be interpreted by the Investigator by clinically correlating with the subject's condition.

The Investigator's interpretation will be recorded in the ECG eCRF as: normal; abnormal, not clinically significant; or abnormal, clinically significant.

Results must be within normal limits or not clinically significant in order to allow a subject to continue in the study.

6.7. Efficacy Assessments

The following efficacy assessments will be performed as indicated in Section 5.

6.7.1. Number of Oral and Genital Ulcers

The number of oral and genital ulcers will be counted. For females, both vulvar and vaginal ulcers will be counted for genital ulcers.

6.7.2. Pain VAS for Oral and Genital Ulcers

Pain VAS scales (100 mm) for oral and genital ulcers (Appendix B) will be evaluated separately. These will be completed by the subject on a secure, validated hand-held device. Subjects will be asked to click on a the VAS line at the point that represents the severity of their pain during the previous week, with zero (the left-hand end of the scale) representing no pain and 100 mm (the right-hand end of the scale) representing the worst possible pain.

6.7.3. BD Current Activity Form

The BD Current Activity Form (BDCAF) was developed for the International Scientific Committee on Behçet's disease for routine monitoring of subjects, as well as for clinical studies (Lawton, 2004; Appendix C). The questionnaire is administered to the subject by the Investigator (Investigator will complete the form on a secure, validated hand-held device), and disease manifestations over the previous 4 weeks are quantified on a 12-point scale, with a higher score indicating higher level of activity. As a validated instrument, the BDCAF was found to be a reliable instrument for the classic mucocutaneous and articular manifestations of BD, as well as, for general complaints and non-mucocutaneous manifestations of BD.

6.7.4. Behçet's Disease Quality of Life Measure

The BD QoL questionnaire was developed to measure the influence of BD on a subject's life (Gilworth, 2004; Appendix D). It consists of 30 self-completed items that measure disease-related restrictions on the subject's activities and the subject's emotional response to these restrictions. The BD QoL Measure will be completed by the subject on a secure, validated hand-held device.

6.7.5. Behçet's Syndrome Activity Score

The Behçet's Syndrome Activity Score (BSAS) (Forbess, 2008; Appendix E) contains 10 questions, including ones that assess the number of new oral and genital ulcers and skin lesions; assess gastrointestinal (GI), CNS, vascular, and ocular involvement; and evaluates the subject's

current level of discomfort. The item scores are totaled to create a score ranging from 0 to 100. The BSAS will be completed by the subject on a secure, validated hand-held device.

[redacted]

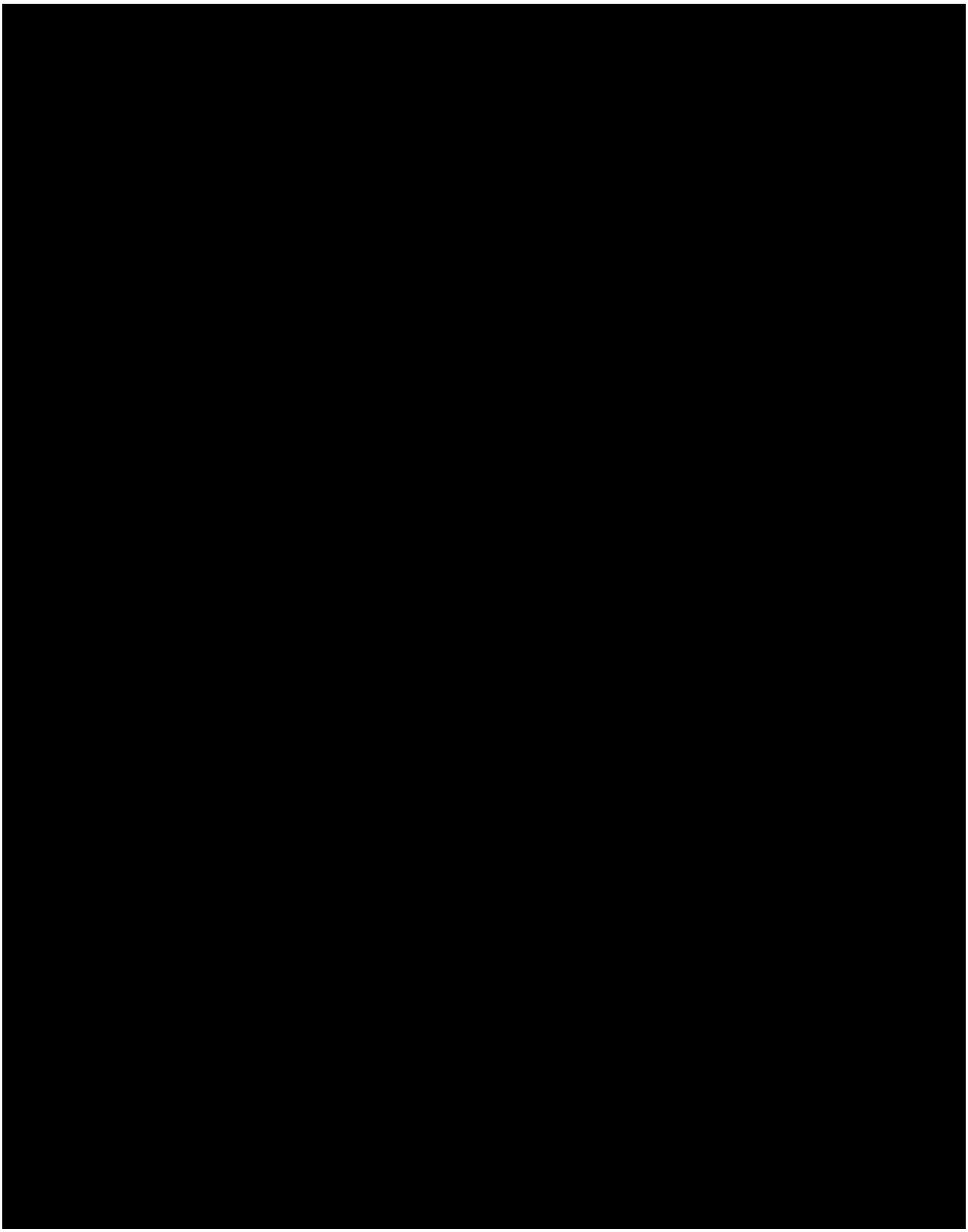
6.7.7. Physician's Global Assessment of Skin Lesions

Physician's global assessment (PGA) of BD related skin lesions (on skin lesions except oral/genital ulcers) will be completed by the Investigators as described in Appendix G.

[redacted]

6.7.9. Assessment of Behçet's Disease-related Inflammatory Eye Disease

An ophthalmological examination should be completed during the Screening Phase, once the subject has met most of the eligibility criteria, after the chest radiograph and ECG but prior to randomization at Visit 2, to determine whether the subject has BD-related uveitis. If a subject has BD-related uveitis and only requires corticosteroid eye drops to manage the uveitis, then the subject will be allowed to enroll into the study. A complete evaluation of the eyes, including a slit lamp examination, should be performed by an ophthalmologist as indicated in Section 5 and at any time when the subject is suspected of new onset or worsening of BD-related inflammatory eye disease, such as uveitis, retinitis, ophthalmitis and iritis. If a subject has a report from an ophthalmologist, dated within 12 weeks of Visit 2, stating that the subject does not have BD-related ophthalmological symptoms, then the subject will not be required to have an ophthalmological examination during Screening Phase unless there is an eye-related complaint during the Screening Phase.



6.8. Investigational Product

6.8.1. Study Medication Dispensing and Counting

After the subject has satisfied all eligibility criteria, IP will be dispensed as specified by the interactive response technology (IRT). The tear-off label from each blister card should be pasted into the drug accountability document. Subjects must be instructed to return all previously issued empty blister cards and/or unused IP at the time of their next visit at the site. A detailed record of tablets issued and returned at each visit must be maintained in the subject's record.

6.8.2. Site Instructions for Dosing the Subject

At each visit that new IP is dispensed, 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.

6.9. Investigational Product Discontinuation

Investigational product discontinuation is defined as the date when the subject took his/her last dose of IP prior to withdrawal or early discontinuation from the study (prior to Week 64).

The date of IP discontinuation should be entered into the IRT as the end of dosing. Sites are requested to make every effort to determine and record the last day of dosing.

When IP is discontinued early, an Early Termination Visit (see Section 6.10) should be scheduled as soon as possible. The Observational Follow-up Visit (see Section 6.11) should also be scheduled 4 weeks (± 7 days) after the subject's last dose of IP, regardless of the reason for IP discontinuation.

6.10. Early Termination Visit

The Early Termination Visit is based on the subject's withdrawal from any time during the study. 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. Please see the Table of Events, Section 5, for the assessments to be performed at the Early Termination Visit. The Observational Follow-up Visit (see Section 6.11) should also be scheduled 4 weeks (± 7 days) after the subject's last dose of IP, regardless of the reason for IP discontinuation.

6.10.1. Observational Follow-up Visit

The Observational Follow-up Visit should occur 4 weeks after the last dose of IP for subjects who Early Terminate or for those subjects who decide to not continue in the optional Open-label Extension phase. Subjects who complete the optional Open-label Extension phase do not need to complete the Observational Follow-up Visit.

6.10.2. Lost to Follow-up

Subjects will be considered lost to follow-up when they fail to attend study visits without stating an intention to withdraw from the study. The investigator should show due diligence by documenting in the source documents the steps taken to contact the subject through 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.

6.11. Study Completion

Study completion for an individual subject who decides to not continue in the optional Open-label Extension phase is defined as reaching Visit 15 (Observational Follow-up Visit), following the completion of active treatment phase.

Study completion for an individual subject who enters the optional Open-label Extension phase, is defined as completion of the optional Open-label Extension Phase.

Subjects who do not meet these definitions are considered under Section 6.10, Early Terminations. All subjects who early terminate the study are to enter the Posttreatment Observational Follow-up Phase (Visit 15) approximately 4 weeks after the last dose of IP was taken.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Approximately 204 subjects with BD will be enrolled with 1:1 randomization for approximately 102 subjects in the APR 30 BID treatment group and 102 subjects in the placebo treatment group. Approximately 45 sites will be included in this study. This study will include sites in different regions including North America, Europe and Asia.

7.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

General Patient Population:

1. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted.
1. Male and female subjects ≥18 years of age at the time of signing the informed consent document.
2. Able to adhere to the study visit schedule and other protocol requirements.

Disease Specific Parameters:

3. Diagnosed with Behçet's disease meeting the International Study Group (ISG) criteria (Appendix K).
4. Oral ulcers that occurred at least 3 times in the previous 12-month period, including oral ulcers at the Screening Visit.
5. Subjects must have at least 2 oral ulcers at Visit 1 (Screening Visit), and:
    a) at least 2 oral ulcers at Visit 2 (day of randomization), when Visit 2 occurs at least 14 days after Visit 1,

    OR

    b) at least 3 oral ulcers at Visit 2 (day of randomization), when Visit 2 occurs at any time between 1 day and 42 days after Visit 1.
6. Have prior treatment with at least 1 non-biologic BD therapy, such as, but not limited to, topical corticosteroids, or systemic treatment.
7. Candidate for systemic therapy, for the treatment of oral ulcers.
    a. A candidate for systemic therapy is a subject judged by the study Investigator as someone whose mucocutaneous ulcers are considered inappropriate for topical therapy based on the severity of disease and extent of the affected area, or whose oral ulcers cannot be adequately controlled by topical therapy.
8. Laboratory Measures: Must meet the following laboratory measures:
    - Hemoglobin > 9 g/dL

- White blood cell (WBC) count ≥ 3000 /μL (≥ 3.0 X 10^9/L) and ≤ 14,000/μL (≤ 14 X 10^9/L)
- Platelet count ≥ 100,000 /μL (≥ 100 X 10^9/L)
- Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L)
- Total bilirubin ≤ 2.0 mg/dL
- Aspartate transaminase (AST [serum glutamic oxaloacetic transaminase, SGOT]) and alanine transaminase (ALT [serum glutamate pyruvic transaminase, SGPT]) < 1.5 X ULN. Subjects who fail screening due to ≥ 1.5 X ULN AST/SGOT and/or ALT/SGPT will be allowed to repeat AST/SGOT and/or ALT/SGPT tests within the Screening Phase. Repeat test results should be ≤ ULN (within reference range) to be eligible.

Laboratory tests will be allowed to be repeated 1 time if, in the Investigator's clinical judgment, there is a reasonable possibility of the repeat tests not meeting the exclusion values, and with concurrence from the Medical Monitor.

9. Contraception Requirements:

   All FCBP[2] must use one of the approved contraceptive options as described below while taking apremilast and for at least 28 days after administration of the last dose of the apremilast.

   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 the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

   All FCBP must have a negative pregnancy test at Visits 1 and 2. All FCBP subjects who engage in activity in which conception is possible must use one of the approved contraceptive options described below:

   Option 1: Any one of the following highly effective methods: hormonal contraception (oral, 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 non-latex 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.

   Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (latex or non-latex condoms

[2] 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).

NOT made out of natural [animal] membrane [for example, polyurethane]) while on IP and for at least 28 days after the last dose of IP.

7.3. Exclusion Criteria

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

Disease Specific Exclusions:

1. Behçet's disease-related active major organ involvement – pulmonary (eg, pulmonary artery aneurysm), vascular (eg, thrombophlebitis), gastrointestinal (eg, ulcers along the gastrointestinal tract), and central nervous systems (eg, meningoencephalitis) manifestations, and ocular lesions (eg, uveitis) requiring immunosuppressive therapy; however:
    - Previous major organ involvement is allowed if it occurred at least 1 year prior to Visit 1 (Screening Visit) and is not active at time of enrollment.
    - Subjects with mild BD-related ocular lesions not requiring systemic immunosuppressive therapy are allowed.
    - Subjects with BD-related arthritis and BD-skin manifestations are also allowed.

Previous and Current Medications:

2. Previous exposure to biologic therapies for the treatment of BD oral ulcers
    - Previous biologic therapy exposure is allowed for other indications, including other manifestations of BD
3. Prior use of apremilast.
4. Use of any investigational medication within 4 weeks prior to Visit 2 or 5 pharmacokinetic/pharmacodynamic half-lives (whichever is longer).
5. Current use of strong cytochrome P450 enzyme inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin)
6. Having received concomitant immune modulating therapy (except oral or topical corticosteroids) within:
    - Seven days prior to Visit 2 (Baseline Visit; day of randomization) for colchicine
    - Ten days prior to Visit 2 (Baseline Visit; day of randomization) for azathioprine and mycophenolate mofetil
    - Four weeks (28 days) prior to Visit 2 (Baseline Visit; day of randomization) for cyclosporine, methotrexate, cyclophosphamide, thalidomide, and dapsone

        Note: Oral and topical corticosteroids must have been tapered as appropriate and discontinued prior to the day of Visit 2 (day of randomization).
    - At least 5 terminal half-lives for all biologics, including, but not limited to, those listed below; within:
        - Four weeks prior to Visit 2 (Baseline Visit; day of randomization) for etanercept

- Eight weeks prior to Visit 2 (Baseline Visit; day of randomization) for infliximab
- Ten weeks prior to Visit 2 (Baseline Visit; day of randomization) for adalimumab, golimumab, certolizumab, abatacept, and tocilizumab
- Six months prior to Visit 2 (Baseline Visit; day of randomization) for secukinumab

7. Having received intra-articular or parenteral corticosteroids within 6 weeks (42 days) prior to Visit 2 (Baseline Visit; day of randomization).

General Health:

8. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
9. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
10. Inability to provide voluntary consent.
11. Pregnant women or breast feeding mothers.
12. Systemic or opportunistic fungal infection.
13. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, hepatitis B and C and herpes zoster, histoplasmosis, coccidiomycosis, but excluding onychomycosis) or any major episode of infection requiring hospitalization or treatment with IV or oral antibiotics within 4 weeks of the Screening Phase.
14. Clinically significant abnormality on chest radiograph.
15. Clinically significant abnormality on 12-lead ECG.
16. History of positive test for, or any clinical suspicion of, human immunodeficiency virus (HIV), or congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease).
17. Malignancy or history of malignancy, except for:
    - treated (ie, cured) basal cell or squamous cell in situ skin carcinomas;
    - treated (ie, cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years of Visit 1.
18. Any condition that confounds the ability to interpret data from the study.
19. Scheduled surgery or other interventions that would interrupt the subject's participation in the study.
20. Prior history of suicide attempt at any time in the subject's lifetime prior to Visit 2 (Baseline Visit; day of randomization) or major psychiatric illness requiring hospitalization within 3 years prior to Visit 2 (Baseline Visit; day of randomization).

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product

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

Apremilast is supplied for oral administration in tablets containing 10, 20, and 30 mg active ingredient.

8.2. Description of Placebo

Placebo tablets will be provided as identically appearing apremilast 10, 20, or 30 mg tablets.

8.3. Treatment Administration and Schedule

Beginning at Visit 2 (Baseline Visit; ie, at randomization day), APR 30 BID or placebo BID will be taken orally, approximately 12 hours apart, without respect to food or drink. To mitigate potential GI side effects dose titration will be implemented in the first week of this study (Table 4). For dose titration, 10 mg, 20 mg and 30 mg apremilast tablets, or identically-appearing placebo tablets, will be dispensed in dose titration cards at Week 0. IP will be dispensed as indicated in Section 5.

- Weeks 0 to 12: Double-blind, Placebo-controlled Treatment Phase: APR 30 BID or placebo BID
    - Week 0 to 1: subjects will be dose titrated as described above
- Weeks 12 to 64: Active Treatment Phase: APR 30 BID
- After Week 64: Optional Open-label Extension Phase: APR 30 BID

During Weeks 12 to 64, the IP will remain blinded, to prevent study personnel and subjects from knowing the IP assignment in the Placebo-controlled Treatment Phase. To maintain the blind regarding the initial treatment assignment, all subjects will receive dose titration cards at Visit 9 (Table 5). Although only subjects initially randomized to placebo will be dose titrated during their first week of the Active Treatment Phase, all subjects entering the active treatment phase will receive identically-appearing titration/treatment cards.

Any dose modifications outside of those described above are not permissible in this study.

Table 4: Treatment Schema for Dose Titration at Visit 2

	Week 0											
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6-7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
APR 30 BID	10mg A 20mg P 30mg P	10mg P 20mg P 30mg P	10mg A 20mg P 30mg P	10mg A 20mg P 30mg P	10mg A 20mg P 30mg P	10mg P 20mg A 30mg P	20mg A 30mg P	20mg A 30mg P	20mg A 30mg P	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A
Placebo	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	10mg P 20mg P 30mg P	20mg P 30mg P	20mg P 30mg P	20mg P 30mg P	20mg P 30mg P	20mg P 30mg P	20mg P 30mg P

A=Apremilast; BID= twice daily; P= Placebo.

Table 5: Treatment Schema for Dose Titration at Visit 9

	Week 12											
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6-7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
APR 30 BID	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	10mg P 20mg P 30mg A	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A
Placebo to APR 30 BID	10mg A 20mg P 30mg P	10mg P 20mg P 30mg P	10mg A 20mg P 30mg P	10mg A 20mg P 30mg P	10mg A 20mg P 30mg P	10mg P 20mg A 30mg P	20mg A 30mg P	20mg A 30mg P	20mg A 30mg P	20mg P 30mg A	20mg P 30mg A	20mg P 30mg A

A=Apremilast; BID= twice daily; P= Placebo.

8.3.1. Dose Modification or Interruption

Dose interruptions are not permitted except for safety reasons. If a subject misses 4 or more consecutive days of dosing, Celgene should be contacted for further instructions.

8.3.2. Overdose

Overdose for this protocol, on a per dose basis, is defined as ingestion of 4 or more APR 30 BID (or matching placebo) tablets in any 24 hour period whether by accident or intentionally. On a schedule or frequency basis, an overdose is defined as complete dosing more than 4 times during any 24 hour period.

Adverse events associated with an overdose must be collected on the AE page of the eCRF for all overdosed subjects, but the overdose itself is not considered an AE. Other required or optional non-study drugs intended for prophylaxis of certain side effects, etc, are excluded from this definition.

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

8.4. Method of Treatment Assignment

8.4.1. Placebo-controlled Treatment Phase (12 Weeks)

At Visit 2, subjects who meet entry criteria will be randomized using a permuted block randomization in parallel 1:1 to receive either APR 30 BID or placebo, using a centralized IRT. Eligible subjects will be stratified according to gender, history of uveitis, and region (Japan and Other). The detailed information is documented in the IRT (IVRS) System Requirements document.

Designated research personnel at the investigational sites will be assigned password protected, coded identification numbers, which give them authorization to enter the IRT to randomize subjects. The system will present a menu of questions by which the research center personnel will identify the subject and confirm eligibility. When all questions have been answered, the IRT will assign a randomization identification number. Confirmation of the randomization will be sent 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 IRT.

8.4.2. Active Treatment Phase (52 Weeks)

All subjects who complete the Placebo-controlled Treatment Phase will be eligible to enter the Active Treatment Phase.

8.4.3. Optional Open-label Extension Phase

All subjects who complete Visit 14 will be eligible to enter the optional Open-label Extension Phase.

8.5. Packaging and Labeling

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.

8.6. Investigational Product Accountability and Disposal

8.6.1. Investigational Product Accountability

The Investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study.

The Investigator(s) or designee(s) is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying IP accountability form. The Investigator(s) or designee(s) 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.

At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access.

The IP should be stored as directed on the package label.

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).

8.6.2. Record of Administration

Accurate recording of all IP administration (including dispensing and dosing) will be made in the appropriate section of the subject's eCRF and source documents.

8.7. Investigational Product Compliance

Study personnel will review the instructions printed on the package with the study subjects prior to dispensing the IP. New IP will be dispensed as indicated in Section 5. The subjects will be instructed to return the IP blister cards, including any unused IP, to the study site at each visit for pill 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. 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. This definition of compliance is only for the purpose of study analysis, not study conduct.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

The following medications will be permitted:

- Corticosteroid eye drops for BD-related or other ocular diseases are allowed at any time during this study.
- Oral/topical analgesics (lidocaine gel), chlorhexidine, used according to product prescribing information, will be allowed throughout the study except for 24 hours prior to clinic visits to avoid interference with the pain assessments of oral or genital ulcers.
- Use of topical corticosteroids for ulcers and skin disease will be allowed until the day of randomization AND/OR **after the Week 12 visit (Visit 9)** and assessments for any non-responders
  - Non-responders: subjects who fail to achieve at least a partial response (≥ 50% improvement [reduction] in the number of oral ulcers from baseline).
- Use of colchicine will be allowed at any time **after the Week 12 visit (Visit 9)** and assessments for any non-responders (subjects who fail to achieve at least a partial response in the number of oral ulcers) or for any subjects who experience a worsening of BD (eg, arthritis, skin disease, uveitis, etc).
- Chronic medication should be dosed on a stable regimen. For medications restricted by the protocol, see Section 7.3. For details about prohibited medications, see Section 9.2.
- Subjects may take any medication that is not restricted by the protocol or that does not confound the efficacy and safety assessments in the study. All medications (prescription and non-prescription), treatments, and therapies taken from Visit 1 through the last visit, including the Posttreatment Observational Follow-up Phase Visit, must be recorded on the appropriate page of the eCRF. The dose, unit, frequency, route, indication, the date the medication was started, and the date the medication was stopped (if not ongoing) must be recorded.

9.2. Prohibited Concomitant Medications and Procedures

The following medications are prohibited.

- Topical corticosteroids will be prohibited for ulcers and skin disease during the first 12 week Placebo-controlled Treatment Phase of the study (through Visit 9).
- Use of colchicine will be prohibited during the 12-week Placebo-controlled Treatment Phase of the trial (through Visit 9).
- Systemic therapy, other than colchicine, including, but not limited to, systemic corticosteroids (including low doses), cyclosporine, methotrexate, cyclophosphamide, hydroxychloroquine, thalidomide, dapsone, azathioprine, and mycophenolate mofetil are prohibited for the Treatment Phases of the study.

- Biologic agents, including, but not limited to, adalimumab, infliximab, etanercept, and rituximab are prohibited for the Treatment Phases of the study.

9.3. Required Concomitant Medications and Procedures

Subjects must agree to maintain the same stable dose of background medication (or lack of medication) prior to Visit 2 (day of randomization) as described in the background medication inclusion criterion (see Section 7.2), except for a safety reason (eg, AEs).

All required procedures for this study are described in Section 6.

10. STATISTICAL ANALYSES

10.1. Overview

This is a 12-week placebo-controlled study, followed by a 52-week Active Treatment Phase and optional Open-label Extension Phase, to evaluate the efficacy and safety of apremilast (CC-10004) in the treatment of Behçet's disease. The primary efficacy endpoint, AUC from baseline through Week 12 for the number of oral ulcers, will be assessed and the APR 30 BID group will be compared to the placebo group.

A Statistical Analysis Plan (SAP), which includes detailed list of analyses, will be written based on this Statistical Analyses section.

10.2. Study Population Definitions

The safety population will include all randomized subjects who received at least one dose of IP. The analysis of safety data in this study will be based on the safety population and subjects will be included in the treatment group they actually received.

The intent-to-treat (ITT) population will be defined as all randomized subjects who received at least one dose of IP. This ITT population will be used for the primary efficacy analysis. Subjects will be included in the treatment group to which they are randomized.

The per protocol (PP) population will include all randomized subjects who received at least one dose of IP, have a baseline and at least one postbaseline oral ulcer evaluation, and have no important protocol violations during the 12-week Placebo-controlled Treatment Phase. The final determination of important protocol violation criteria will be made prior to the unblinding of the database and will be documented separately.

10.3. Sample Size and Power Considerations

The sample size estimation is based on the consideration from the results of the Phase 2 study CC-10004-BCT-001. A two-sided t-test at a 0.05 significance level will have 90% power to detect a treatment difference of 66 in the AUC of oral ulcer counts from Day 1 through Week 12 (AUC of placebo – drug = 66), the primary efficacy endpoint, when the sample size in each group is 102, assuming a common standard deviation of 144.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, 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.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percentage for placebo-controlled, active treatment and follow-up phases. Subject disposition for the optional Open-

label Extension Phase will be reported separately. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

All efficacy analyses will be performed using the ITT population. In addition, analysis using the PP population will be provided for the primary efficacy endpoint.

Efficacy results will be considered statistically significant after consideration of the control of multiplicity, as specified in Section 10.6.1.1. All statistical tests will be conducted at the $\alpha = 0.05$ (2-sided) level, and 2-sided p-values and CIs will be reported.

10.6.1. Efficacy Evaluation for the Double-blind, Placebo-controlled Treatment Phase

10.6.1.1. Multiplicity

Statistical tests for comparing the APR 30 BID and placebo groups will be conducted for the primary endpoint and other efficacy endpoints as listed in Section 3.

The multiplicity of the analyses of the primary and other efficacy endpoints will be adjusted using a Gate-Keeping Procedure. This procedure will preserve the Family Wise Error Rate of the multiple analyses. The analyses will be performed in sequence until one of the analyses has failed to show the significant difference or all analyses have been completed at a significance level of 0.05. The sequence of the analyses for the other efficacy endpoints will be specified in the statistical analysis plan (SAP).

10.6.1.2. Primary Analysis for Primary Efficacy Endpoint

The primary efficacy endpoint is the AUC for the number of oral ulcers from Day 1 through Week 12. It will be compared between the placebo and APR 30 BID groups using an analysis of covariance (ANCOVA) model with the AUC as the response variable, the treatment, gender and region as factors, and the number of oral ulcers at baseline as a covariate. Multiple imputation method will be used to impute missing oral ulcer counts when the AUC is derived.

Sensitivity analyses including missing data imputations conducted for the primary efficacy endpoint to assess the robustness of the primary analysis will be detailed in the SAP.

10.6.1.3. Analysis for Secondary Efficacy and Exploratory Endpoints

Secondary efficacy endpoints and exploratory endpoints will be summarized and analyzed similarly to that described for the primary efficacy endpoint. For continuous endpoints, such as change from baseline in the pain VAS, descriptive statistics (N, mean, median, standard deviation, quartiles, minimum and maximum) will be provided by treatment group at specified visits per study phase. The endpoints at Week 12 will also be compared between the placebo and APR 30 BID groups using a similar ANCOVA model as described in Section 10.6.1.2.

Frequency count and percentage will be provided for categorical variables such as ulcer responders. The proportions of subjects who achieve a response at Week 12 between the APR 30 BID and placebo groups will be compared using the Cochran-Mantel-Haenszel (CMH) test at the 0.05 level, controlling for stratification factors as specified in the SAP, using the ITT population.

Subjects who have discontinued early prior to Week 12, or who do not have data at Week 12, will be regarded as non-responders at Week 12.

10.6.2. Efficacy Evaluation for the Active Treatment Phase

For continuous endpoints, descriptive statistics (N, mean, median, standard deviation, quartiles, minimum and maximum) will be provided by treatment group at specified visits per study phase. Frequency count and percentage will be provided for categorical variables.

The detailed analysis methods for each efficacy endpoint will be specified in the SAP.

10.7. Safety Analysis

The safety analyses will be performed using the Safety population as defined in Section 10.2. Safety will be assessed by clinical review of all relevant parameters including AEs, AEs of special interest (ie, diarrhea), laboratory tests, and vital signs; no inferential testing for statistical significance will be performed.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All TEAEs will be summarized by system organ class, preferred term, severity and relationship to IP. 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 by visit descriptively. In addition, shift tables showing the number of subjects with values low, normal, high compared to the normal ranges pretreatment versus posttreatment, together with the number determined to be clinically significant, will be provided.

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

To account for the different exposure to the IP, AEs or marked laboratory abnormalities will also be summarized using the exposure adjusted incidence rate.

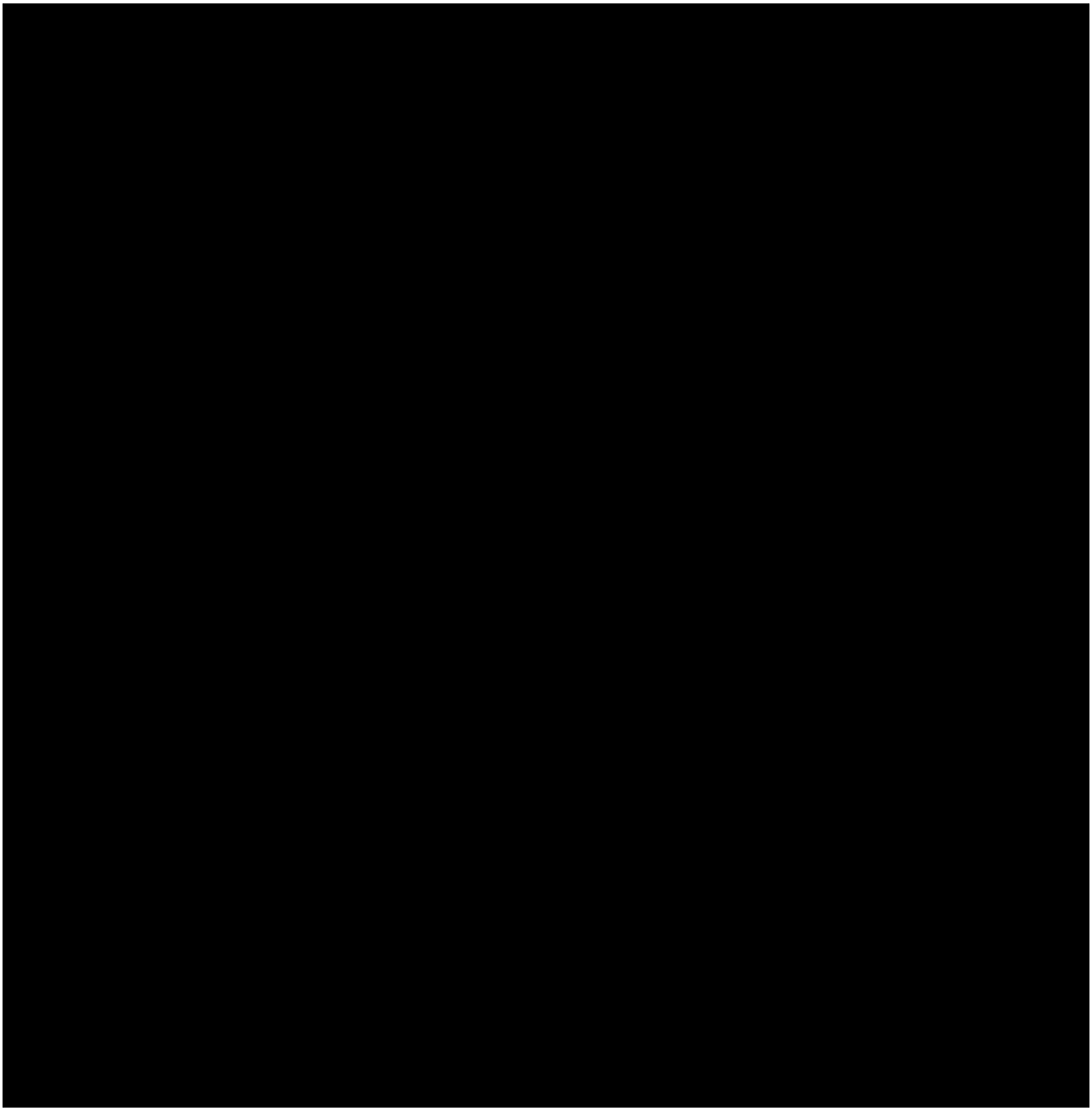
Safety data collected during the optional Open-Label Extension Phase will be listed.

The detailed safety analyses will be specified in the SAP.

10.8. Interim Analysis

None is planned.

10.9. Other Topics



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.

Worsening of a subject's BD (any manifestation) should be considered as worsening of disease under study, and should not be captured as an AE, unless the event meets the definition of an SAE. Worsening of disease will be reported on the BD activity pages that lists each of the BD manifestations in the eCRF, and not captured in the AE eCRF. See [redacted] for more details.

Worsening of a subject's BD will be captured on the AE eCRF for subjects who continue in the optional Open-label Extension Phase after Week 64. Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF (see Section 8.3.2 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and in the eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for apremilast overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

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

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. All AEs 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.

11.1.1. Monitoring, Recording and Reporting AEs of Diarrhea

The PDE4 inhibitors, including apremilast, have been associated with AE reports of diarrhea. To better characterize and understand all reported AEs of diarrhea, further information will be

collected on a separate eCRF page. Please refer to Section 6.6.1.1 for further details on how to record such AEs.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

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

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

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

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to 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, the AE screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to 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. The following grading scale should be used to evaluate severity/intensity.

Mild

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

Moderate

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

Severe (could be non-serious or serious)

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention
- Interference with ADL 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 adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

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

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

11.2.4. Duration

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

The AE of diarrhea can be continuous or intermittent. For intermittent diarrhea, please capture the start and stop date for each episode of intermittent diarrhea in the eCRF.

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 (returned to baseline), recovered with sequelae, 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 serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the 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 and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

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

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

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

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

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 any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the Informed Consent Form) 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.

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 Investigator's Brochure.

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

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned 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 (In Japan, Celgene KK shall notify the Heads of the Institutes in addition to the Investigators):

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR).
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- In Japan, measures taken in foreign countries to ensure subject safety, study reports that indicate potential risk of cancer, etc., or annual SAE reports according to the local regulations.

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, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

12. DISCONTINUATIONS

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

- Adverse event
- Lack of efficacy
- Non-compliance with IP
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Other

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

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.

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 the 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 the title page).This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/Contract Research Organization Medical Monitor, who will then contact you promptly.

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

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 discontinued if, in the opinion of the investigator, continuing IP can negatively affect the outcome of the subject's treatment. The subject must be withdrawn from the study once the treatment code for the subject has been unblinded.

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

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

Emergency unblinding should only be performed by the investigator through the IRT by using an emergency unblinding personal identification number (PIN), and the investigator should call the IRT for unblinding for the treatment group: APR 30 BID or placebo.

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 Conference on Harmonization (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.

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 document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document 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 document. The revised informed consent document 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 document, 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 document, 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 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 document 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.

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 CRFs or CD-ROM.

15.2. Data Management

Data will be collected via eCRF, and a secure, validated hand-held device at the site, and entered into the clinical database. 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 documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

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

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

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

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, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, site's secure, validated hand-held device, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

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

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 standard operating procedures (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, US Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

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

Appendix A: List of Behçet's Disease Clinical Features

Behçet Syndrome Diagnostic Criteria
Recurrent oral aphthous ulceration
Skin Lesions
Erythema nodosum
Subcutaneous thrombophlebitis
Papulopustular lesions
Pseudofolliculitis
Acneiform nodules
Positive pathergy test
Cutaneous hypersensitivity
Eye Lesions
Anterior uveitis, Iridocyclitis
Posterior uveitis
Chorioretinitis, retino-vasculitis
Definite history of chorioretinitis or retino-vasculitis
Genital Ulcers
Arthritis without deformity and ankylosis
Gastrointestinal lesions characterized by ileocecal ulcers
Epididymitis
Vascular lesions
Central nervous system symptoms

Appendix B: Visual Analog Scales (VAS) for Pain of Oral and Genital Ulcers

Visual Analog Scale of Pain

On average, how much pain have you had because of your oral ulcers in the past week?

Please use a vertical stroke

no pain **worst possible pain**

0 mm 100 mm

Visual Analog Scale of Pain

On average, how much pain have you had because of your genital ulcers in the past week?

Please use a vertical stroke

no pain **worst possible pain**

0 mm 100 mm

Appendix C: Behçet's Disease Current Activity Form

ISBD
International Society for Behcet's Disease

BEHÇET'S DISEASE CURRENT ACTIVITY FORM 2006

Date: Name: Sex: M/F
Centre: Telephone Date of birth:
Country:
Clinician: Address:

All scoring depends on the symptoms present over the **4 weeks** prior to assessment.
Only clinical features that the **clinician feels are due to Behçet's Disease** should be scored.

PATIENT'S PERCEPTION OF DISEASE ACTIVITY
(Ask the patient the following question:)

"Thinking about your Behçet's disease only, which of these faces expresses how you have been feeling over the last four weeks? "(Tick one face)

HEADACHE, MOUTH ULCERS, GENITAL ULCERS, SKIN LESIONS, JOINT INVOLVEMENT AND GASTROINTESTINAL SYMPTOMS

Ask the patient the following questions and fill in the related boxes **"Over the past 4 weeks have you had?"**

(please tick one box per line)

	not at all	Present for up to 4 weeks
Headache		
Mouth Ulceration		
Genital Ulceration		
Erythema		
Skin Pustules		
Joints - Arthralgia		
Joints - Arthritis		
Nausea/vomiting/abdominal pain		
Diarrhoea+altered/frank blood per rectum		

EYE INVOLVEMENT
(Ask questions below)

		(please circle) Right Eye		Left Eye	
"Over the last 4 weeks have you had?"	a red eye	No	Yes	No	Yes
	a painful eye	No	Yes	No	Yes
	blurred or reduced vision	No	Yes	No	Yes

If any of the above is present: "Is this new"? No Yes
(circle the correct answer)

Appendix C: Behçet's Disease Current Activity Form (Continued)

NERVOUS SYSTEM INVOLVEMENT (include intracranial vascular disease)

New Symptoms in nervous system and major vessel involvement are defined as those not previously documented or reported by the patient
(Ask questions below)

Over the last 4 weeks have you had any of the following?	*please circle*		tick if new
blackouts	No	Yes	
difficulty with speech	No	Yes	
difficulty with hearing	No	Yes	
blurring of/double vision	No	Yes	
weakness/loss of feeling of face	No	Yes	
weakness/loss of feeling of arm	No	Yes	
weakness/loss of feeling of leg	No	Yes	
memory loss	No	Yes	
loss of balance	No	Yes	

Is there any evidence of new active nervous system involvement? No Yes

MAJOR VESSEL INVOLVEMENT(exclude intracranial vascular disease)
(Ask question below)

"Over the last 4 weeks have you had any of the following?"	*please circle*		tick if new
had chest pain	No	Yes	
had breathlessness	No	Yes	
coughed up blood	No	Yes	
had pain/swelling/discolouration of the face	No	Yes	
had pain/swelling/discolouration of the arm	No	Yes	
had pain/swelling/discolouration of the leg	No	Yes	

Is there evidence of new active major vessel inflammation? No Yes

CLINICIAN'S OVERALL PERCEPTION OF DISEASE ACTIVITY

Tick one face that expresses how you feel the patient's disease has been over the last 4 weeks.

BEHÇET'S DISEASE ACTIVITY INDEX

Add up all the scores which are highlighted in blue (front page items, one tick = score of 1 on index, all other items score 'yes' = 1. You should now have a score out of 12 which is the patient's Behçet's Disease Activity Index Score.

SCORE

Patients index score	0	1	2	3	4	5	6	7	8	9	10	11	12
Transformed index score on interval scale	0	3	5	7	8	9	10	11	12	13	15	17	20

Appendix C: Behçet's Disease Current Activity Form (Continued)

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Explanation to doctor completing the form;

1. Use your clinical judgment recording only those features you believe are due to Behcet's disease.
2. Please explain to the patient the meaning of the words used, if necessary.
3. If there is pain in a joint (whether or not there is swelling etc) score 'arthralgia'.
4. If there is swelling or inflammation of a joint score 'arthritis'. Thus you can score 'arthralgia' and 'arthritis'.
5. The form concerns the impairments relating to Disease Activity. It is produced by Rasch analysis and is psychometrically robust. It is not measuring the impact of the disease activity.

Appendix D: Behçet's Disease Quality of Life Measure

BD-QoL

Date:

Name:_____ Age:_____Sex: _____

On the following pages you will find some statements which have been made by people who have Behçet'sDisease

Instructions: This questionnaire consists of 30 statements. Please read each statement carefully, and then choose **True** if the statement applies to you and choose **Not True** if it does not apply to you at the moment. Circle the appropriate number.

1. My life revolves around hospital visits
   1 True
   0 Not True

2. Nothing interests me
   1 True
   0 Not True

3. It's too much effort to go out and see people
   1 True
   0 Not True

4. Walking is painful
   1 True
   0 Not True

5. It takes me longer to do things
   1 True
   0 Not True

6. I cannot stand for long
   1 True
   0 Not True

7. My condition interferes with my life
   1 True
   0 Not True

8. It is difficult to get out of bed
   1 True
   0 Not True

9. I feel terrible about the way I look
   1 True
   0 Not True

10. Talking is stressful
    1 True
    0 Not True

11. I feel dependent on others
    1 True
    0 Not True

12. I feel older than my years
    1 True
    0 Not True

13. It limits the places I can go
    1 True
    0 Not True

14. I find it difficult to take care of the people I am close to
    1 True 0 Not True

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Continue on Back

Appendix D: Behçet's Disease Quality of Life Measure (Continued)

15. I cannot rely on how I will be tomorrow
    1 True
    0 Not True

16. My condition is drastically affecting my life
    1 True
    0 Not True

17. I often get frustrated
    1 True
    0 Not True

18. I feel like a prisoner in my own home
    1 True
    0 Not True

19. My condition affects important decisions in my life
    1 True
    0 Not True

20. I don't like being touched
    1 True
    0 Not True

21. I cannot speak properly
    1 True
    0 Not True

22. It puts a strain on my personal relationships
    1 True
    0 Not True

23. I feel useless
    1 True
    0 Not True

24. I worry that I hold others back
    1 True
    0 Not True

25. People close to me have lost out because of my condition
    1 True
    0 Not True

26. I feel unable to cope with my condition
    1 True
    0 Not True

27. I have lost contact with people
    1 True
    0 Not True

28. I worry about the effects on others
    1 True
    0 Not True

29. Everything is getting to me today
    1 True
    0 Not True

30. I feel lonely
    1 True
    0 Not True

Appendix E: Behçet's Syndrome Activity Score (BSAS)

Behçet's Syndrome Activity Scale (BSAS)

Your name:_____ **Date of Birth:** _____ **Today's Date:**_____

Your: **SEX:** ☐ Female ☐ Male **ETHNIC** ☐ Asian ☐ Hispanic ☐ Other _____
GROUP: ☐ Black ☐ White

1. How much have **ulcers in your mouth** bothered you over the last 4 weeks? Please indicate below

NO ULCERS ○○○○○○○○○○○○○○○○○○○○ **ULCERS WERE A MAJOR PROBLEM**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

2. How many **ulcers (new or old)** did you have in your **mouth** over the last 4 weeks?
   0 ☐
   1-3 ☐
   More than 3 ☐

3. How much has **ulcers in genital area** bothered you over the last 4 weeks? Please indicate below

NO ULCERS ○○○○○○○○○○○○○○○○○○○○ **ULCERS WERE A MAJOR PROBLEM**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

4. How many **ulcers (new or old)** did you have in your **genital area** over the last 4 weeks?
   0 ☐
   1-3 ☐
   More than 3 ☐

5. How much has **acne or acne like skin lesions (new or old)** bothered you over the last 4 weeks? Please indicate below

NO SKIN LESIONS ○○○○○○○○○○○○○○○○○○○○ **SKIN LESIONS WERE A MAJOR PROBLEM**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

6. How many **acne or acne like skin lesions (new or old)** did you have over the last 4 weeks?
   0 ☐
   1-5 ☐
   More than 5 ☐

7. Have you had **abdominal pain and diarrhea** lasting most of the day for most days of the week over the last 4 weeks?
   ☐**No** ☐ **Yes**

8. Did you have **painful or red eyes and/or blurred or reduced vision** over the last 4 weeks?
   ☐**No** ☐ **Yes**

9. Did you have any **swelling/discoloration of your lower extremities, or a blood clot** over the last 4 weeks?
   ☐**No** ☐ **Yes**

10. In terms of your **Behcet's activity, (oral ulcers, genital ulcers, skin problems, joint pains, eye, neurologic problems)**, how active would you say your condition has been over the last 4 weeks?

NOT ACTIVE AT ALL ○○○○○○○○○○○○○○○○○○○○ **EXTREMELY ACTIVE**
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

Appendix E: Behçet's Syndrome Activity Score (BSAS) (Continued)

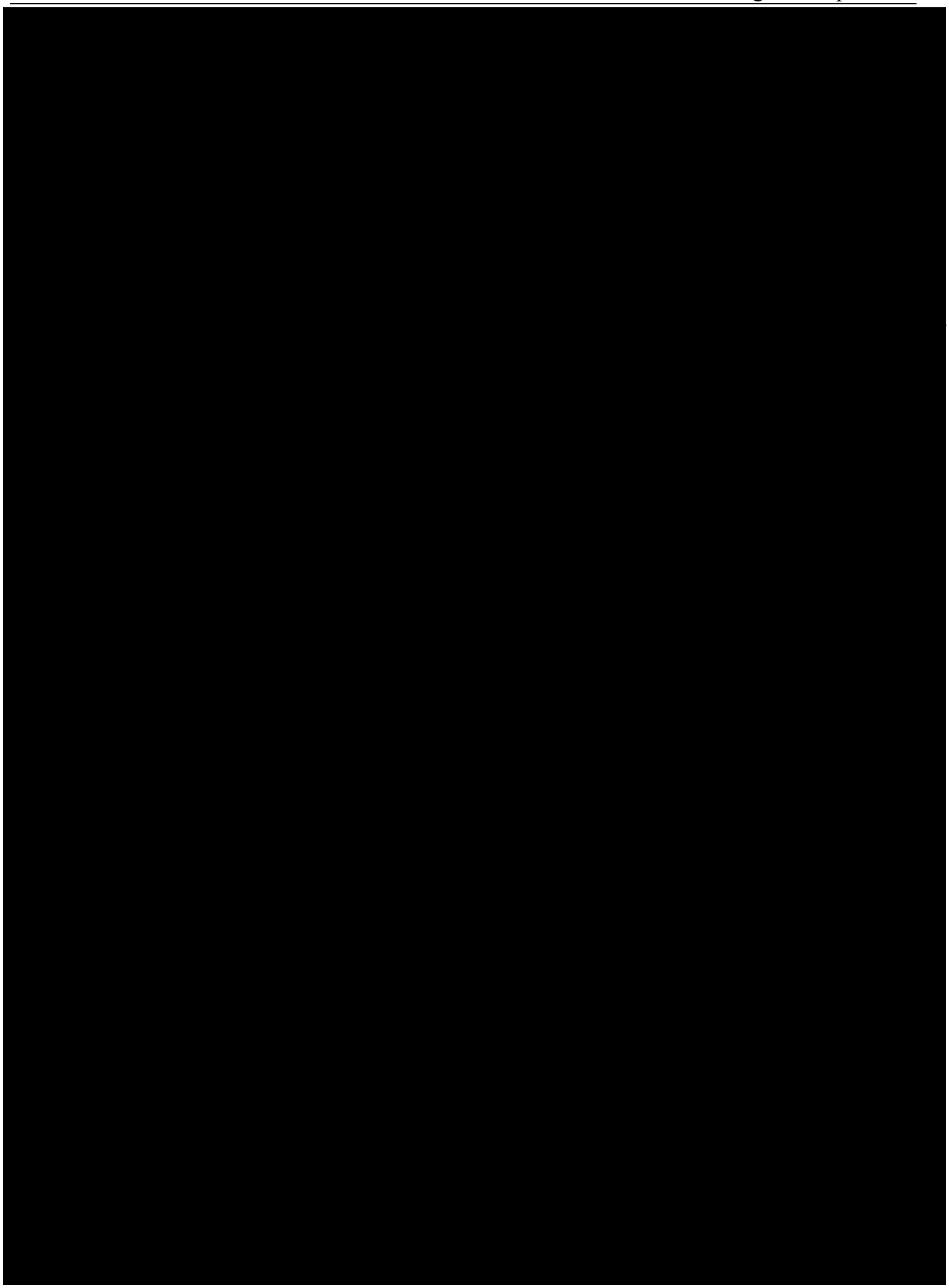
Scoring:

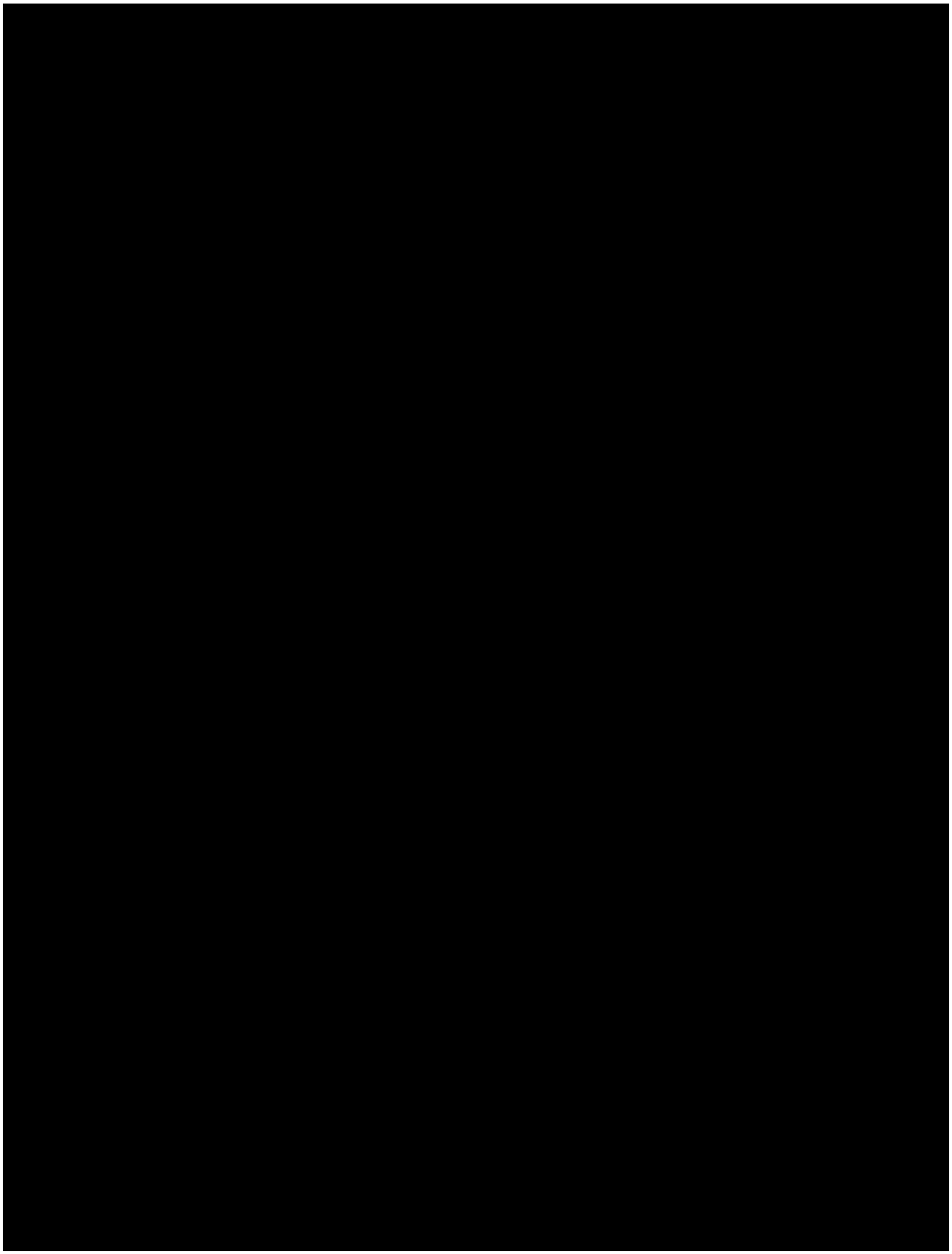
Questions 1, 3, 5, and 10 are scored 0-10

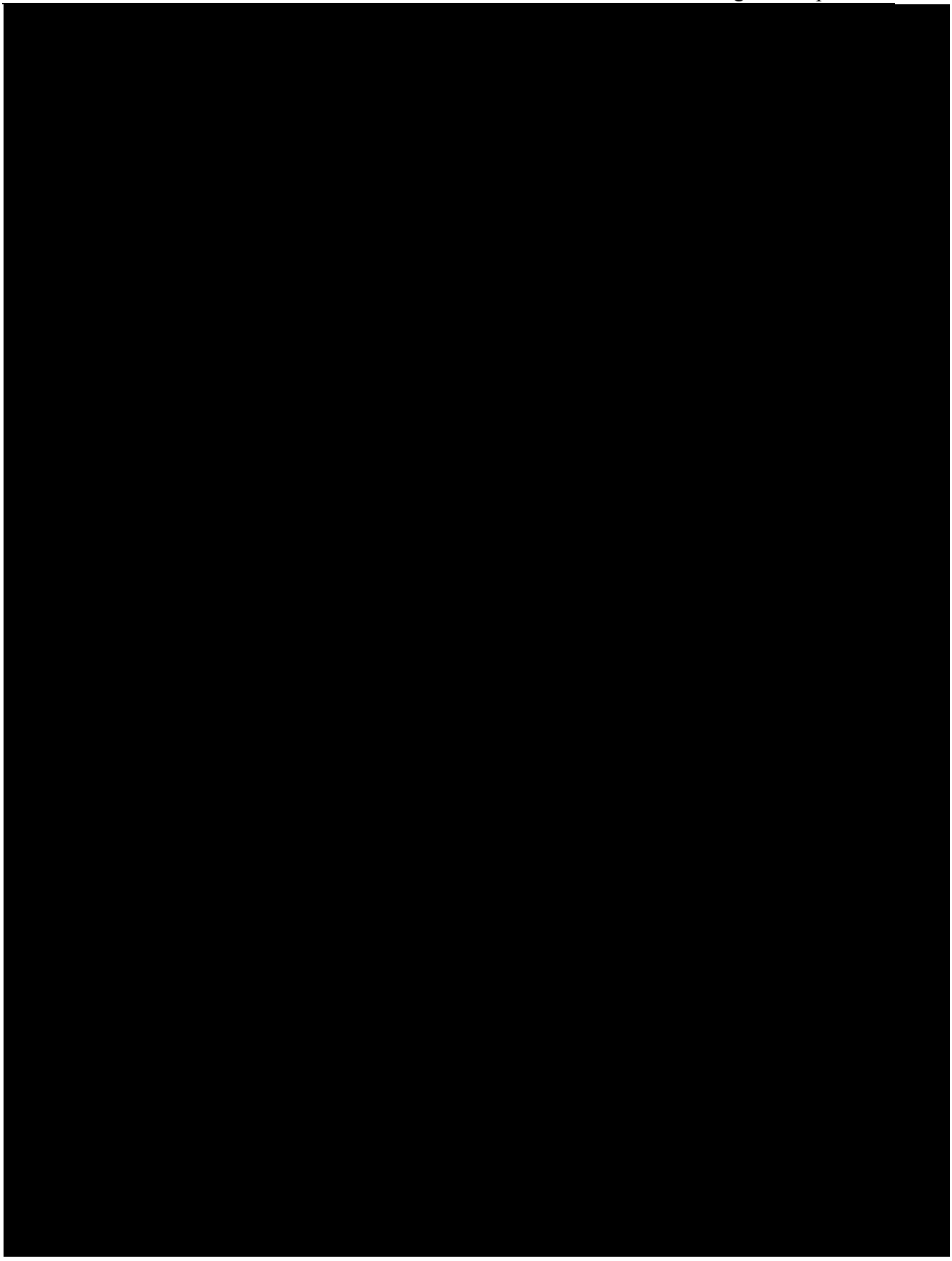
Questions 2, 4, 6, are scored 0, 5 or 10 depending on which of the 3 are checked

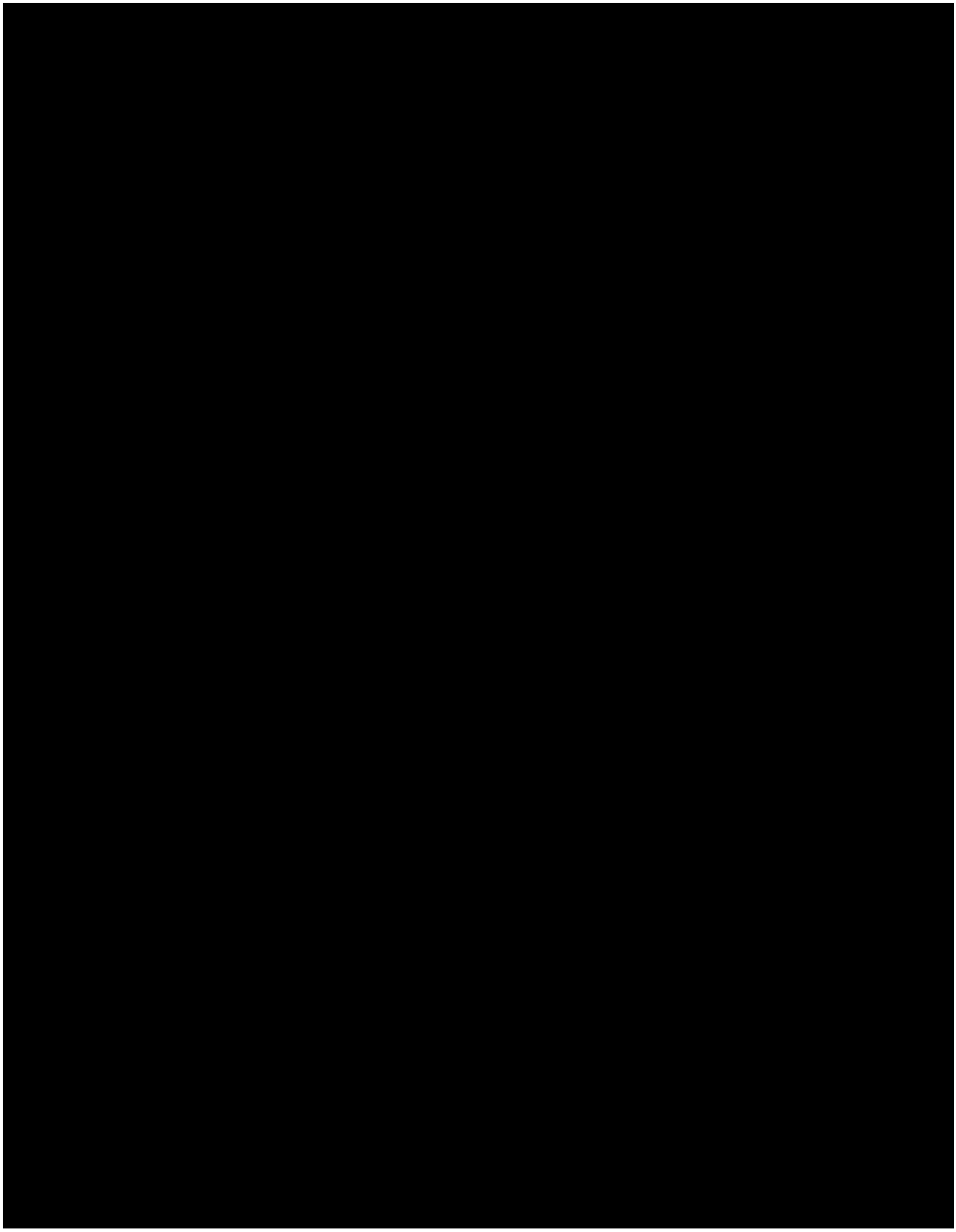
Questions 7, 8, 9 are scored 0 or 10

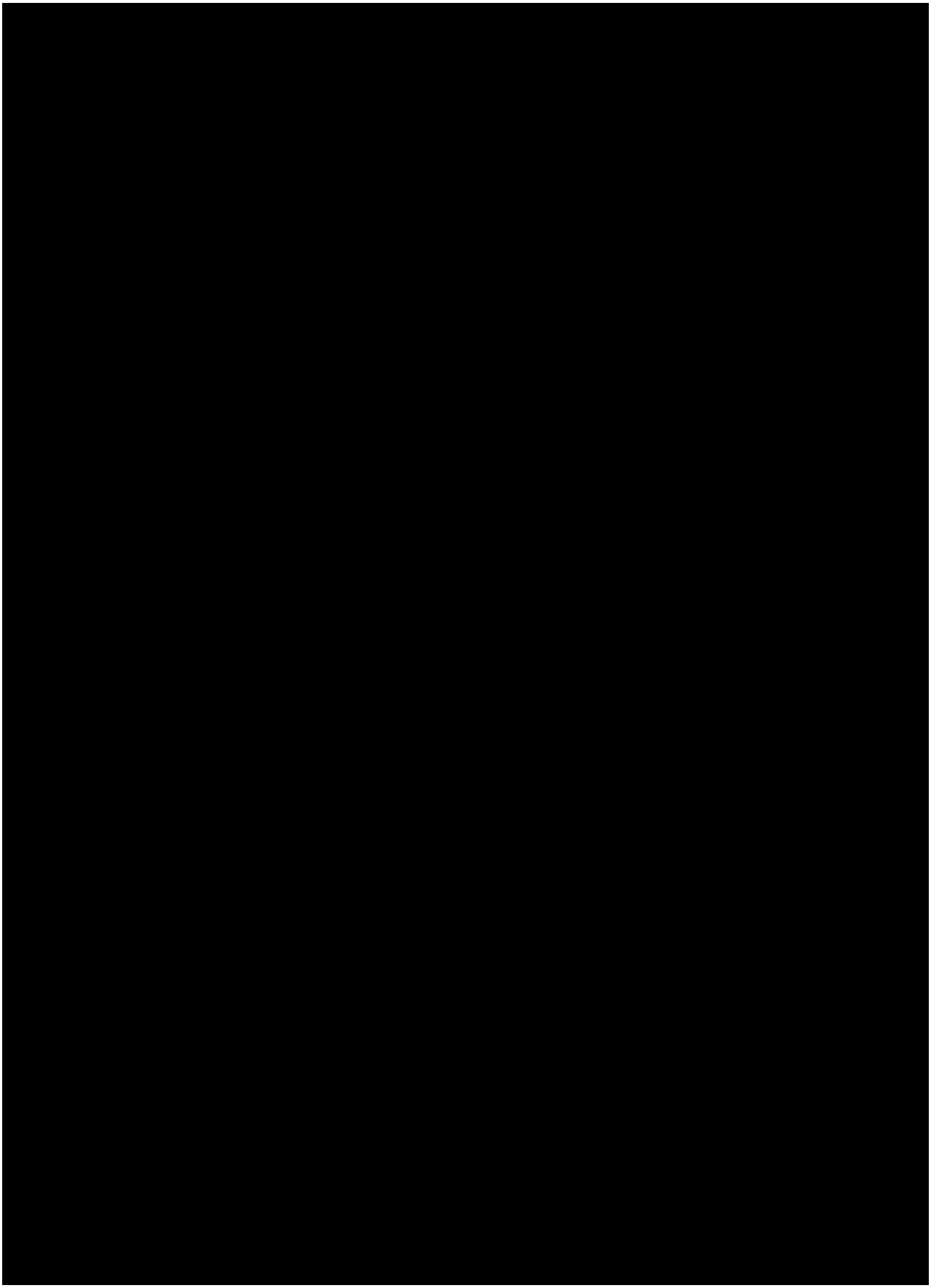
For a total score of 100











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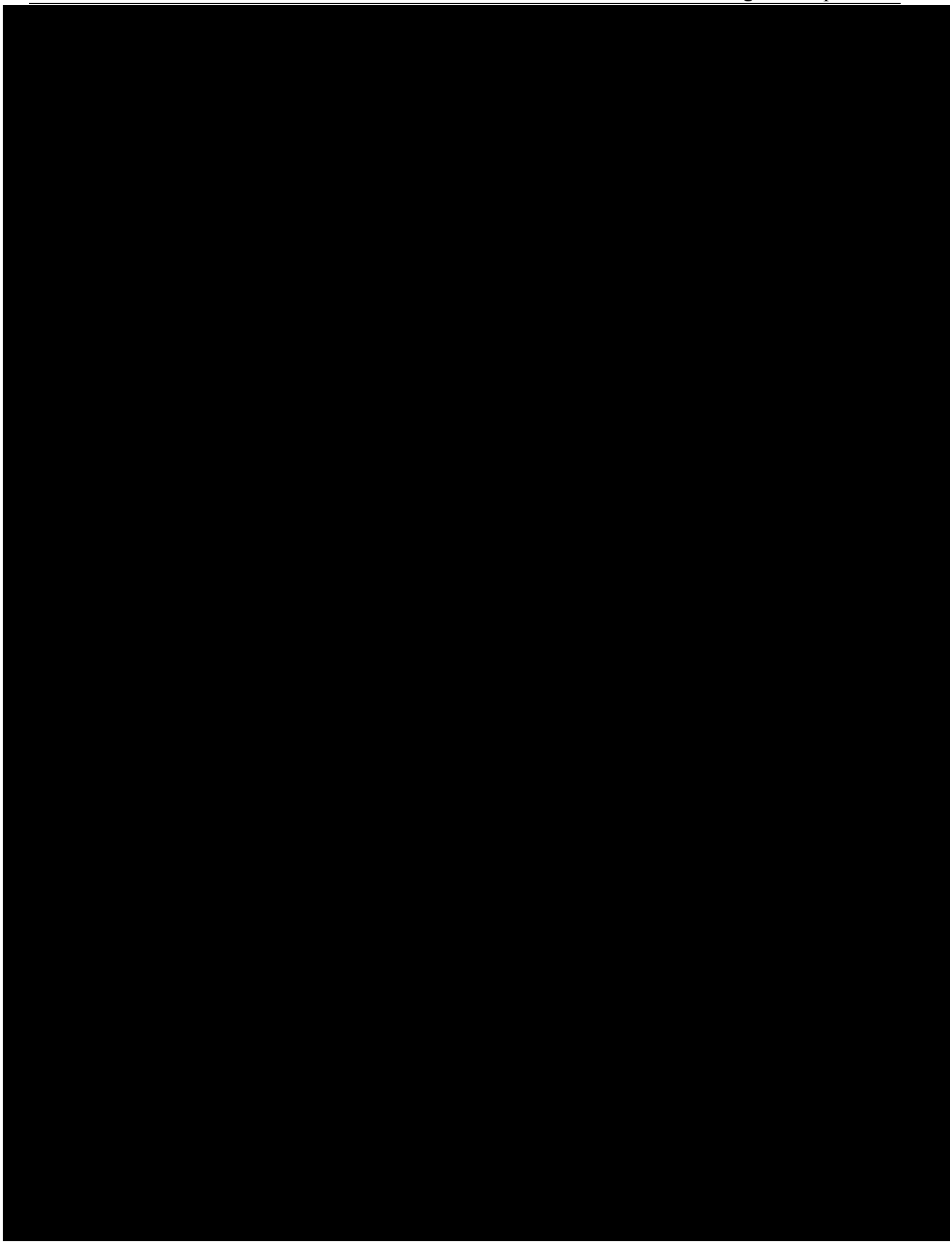


Appendix G: Static Physician's Global Assessment of Skin Lesions

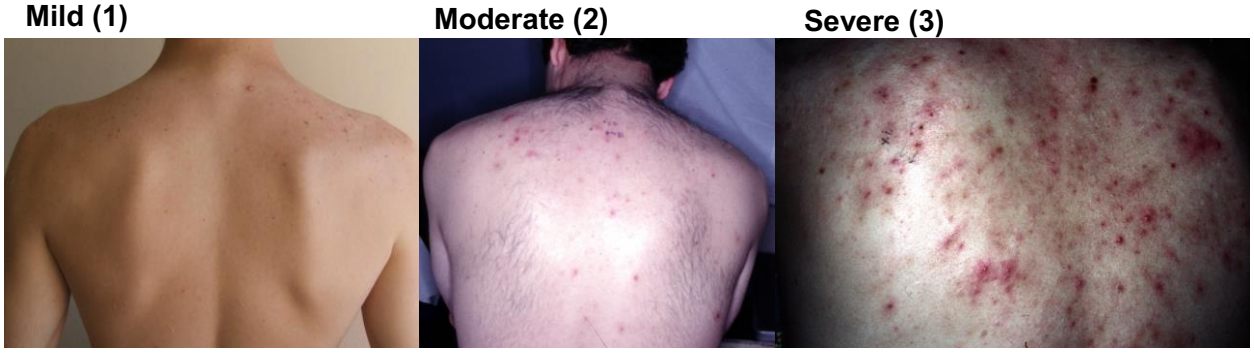
For uniform assessment of BD skin lesions, investigators will use and follow the scoring system in the Physician's Global Assessment of Behçet's disease-related skin lesions described below. These skin lesions include erythema nodosum, pseudofolliculitis, papulopustular or acneiform lesions on the face, back, chest, shoulders, arms, femoral regions, pubis and buttocks.

Acne-like lesions

Two types of acne-like lesions are observed in BD: inflammatory (papules, pustules and cysts) and non inflammatory (comedones).

Acne like lesions will be rated as described in the table below, on the face, upper back, chest and shoulders based on the Investigator's judgment.

Examples are presented for the mild (score of 1), moderate (score of 2), and severe (score of 3) acne-like lesions in the images below:



Scoring for Acne-like lesions:

Score	Severity	Description
0	Clear	Clear skin
1	Mild	Presence of 1 to 10 lesions (papules, pustules, cysts) at any anatomical site
2	Moderate	Presence of 11 to 20 lesions (papules, pustules, cysts) at any anatomical site
3	Severe	Presence of > 20 lesions (papules, pustules, cysts) at any anatomical site

Appendix G: Static Physician's Global Assessment of Skin Lesions (Continued)

Folliculitis

Folliculitis is localized at the face, chest, back, genital area, arms, buttocks, and legs, and is characterized by the following:

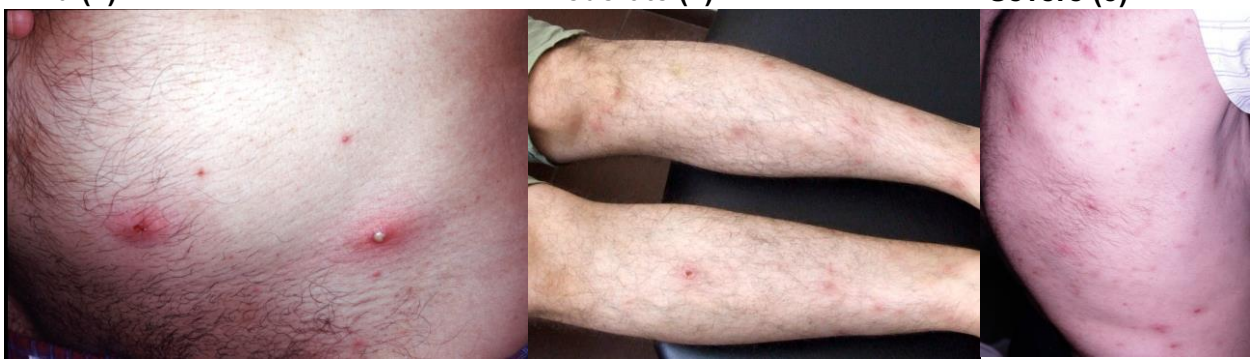
- Pustules, more commonly form in the follicular lesions, and are surrounded by an erythematous halo.
- Lesions typically heal within 2 to 3 days.
- During the healing phase, pustules may rupture and a crust presents at the pustule site and erythema fades.
- Healed lesions occasionally show pigmentation at the lesion site.
- It is more common among males for pustules to occur at the hairy sites.

Non follicular pustules are rare in BD subjects.

Evaluations of folliculitis will be rated as described in the table below, based on the Investigator's judgment.

Examples are presented for mild (score of 1), moderate (score of 2), and severe (score of 3) follicular lesions in the images below:

Mild (1) **Moderate (2)** **Severe (3)**



Scoring for Folliculitis:

Score	Severity	Description
0	Clear	Clear skin
1	Mild	Presence of 1 to 10 lesions (intact and/or ruptured lesions) at any anatomical site
2	Moderate	Presence of 11 to 20 lesions (intact and/or ruptured lesions) at any anatomical site
3	Severe	Presence of > 20 lesions (intact and/or ruptured lesions) at any anatomical site

Appendix G: Static Physician's Global Assessment of Skin Lesions (Continued)

Erythema nodosum

Erythem nodosum is usually localized to the front of the legs beneath the knees; it may also be found on the arms. Erythema nodosum is characterized by the following:

- Begins as red nodules on the shins and may be painful
- After about a week, lesions may appear purple or blue in color and then fade to yellow; appearing like a bruise
- Nodules may appear on the buttocks, thighs, arms, trunk, and ankles
- Nodules or lumps may vary in dimension from 1 cm to 5 cm

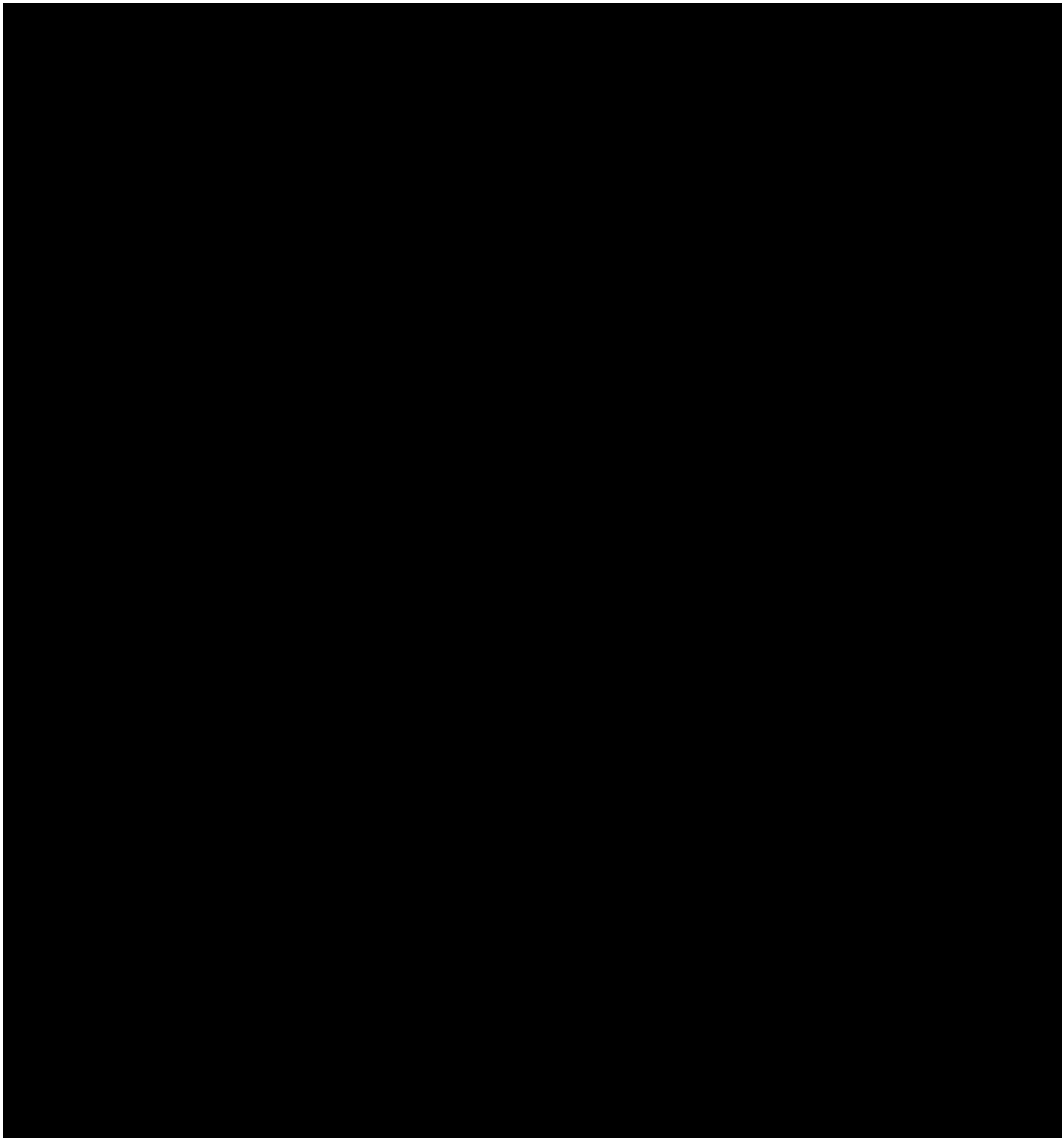
Scoring for Erythema nodosum:

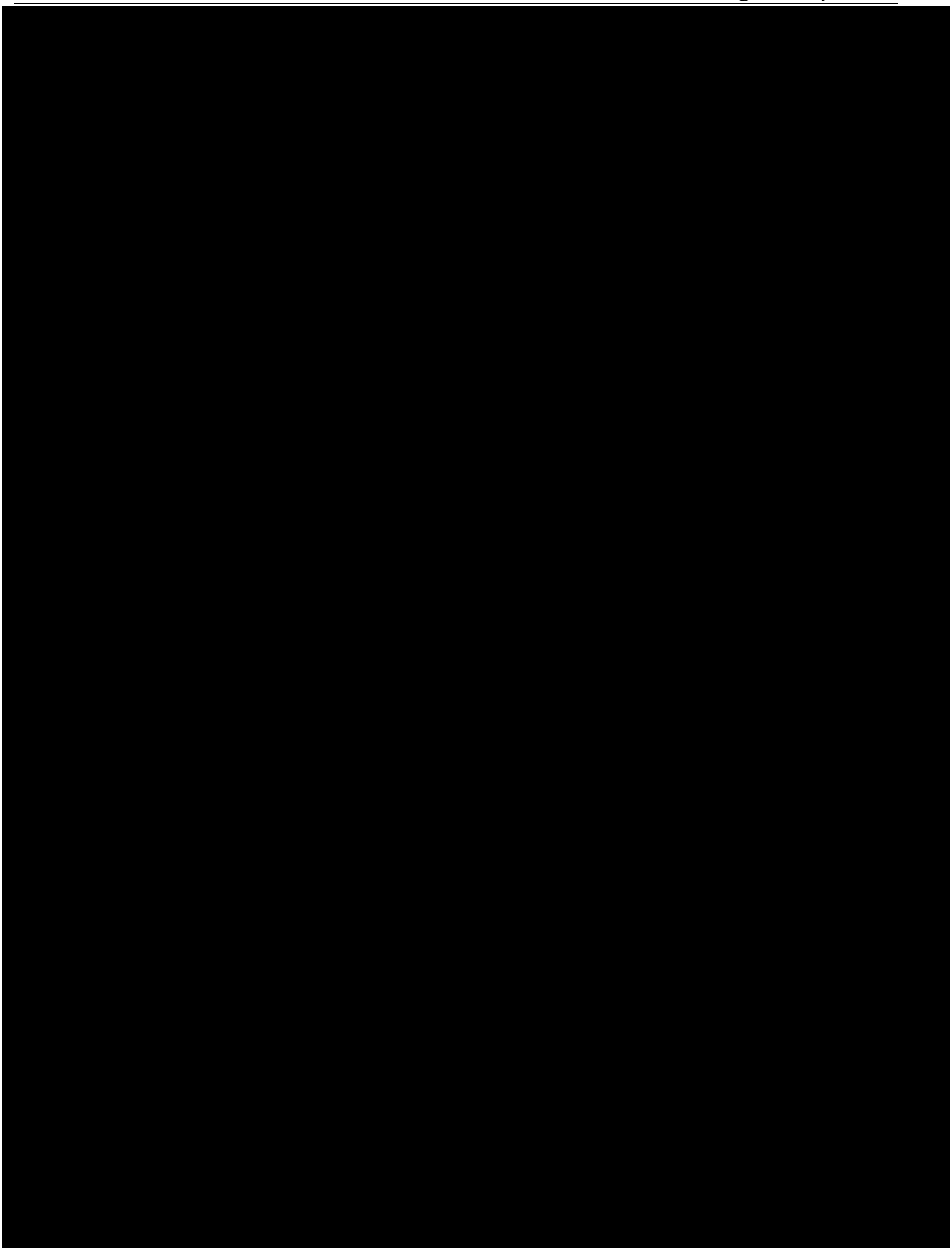
Score	Severity	Description
0	Clear	Clear skin
1	Mild	Presence of 1 to 10 nodules/lesions at any anatomical site
2	Moderate	Presence of 11 to 20 nodules/lesions at any anatomical site
3	Severe	Presence of > 20 nodules/lesions at any anatomical site

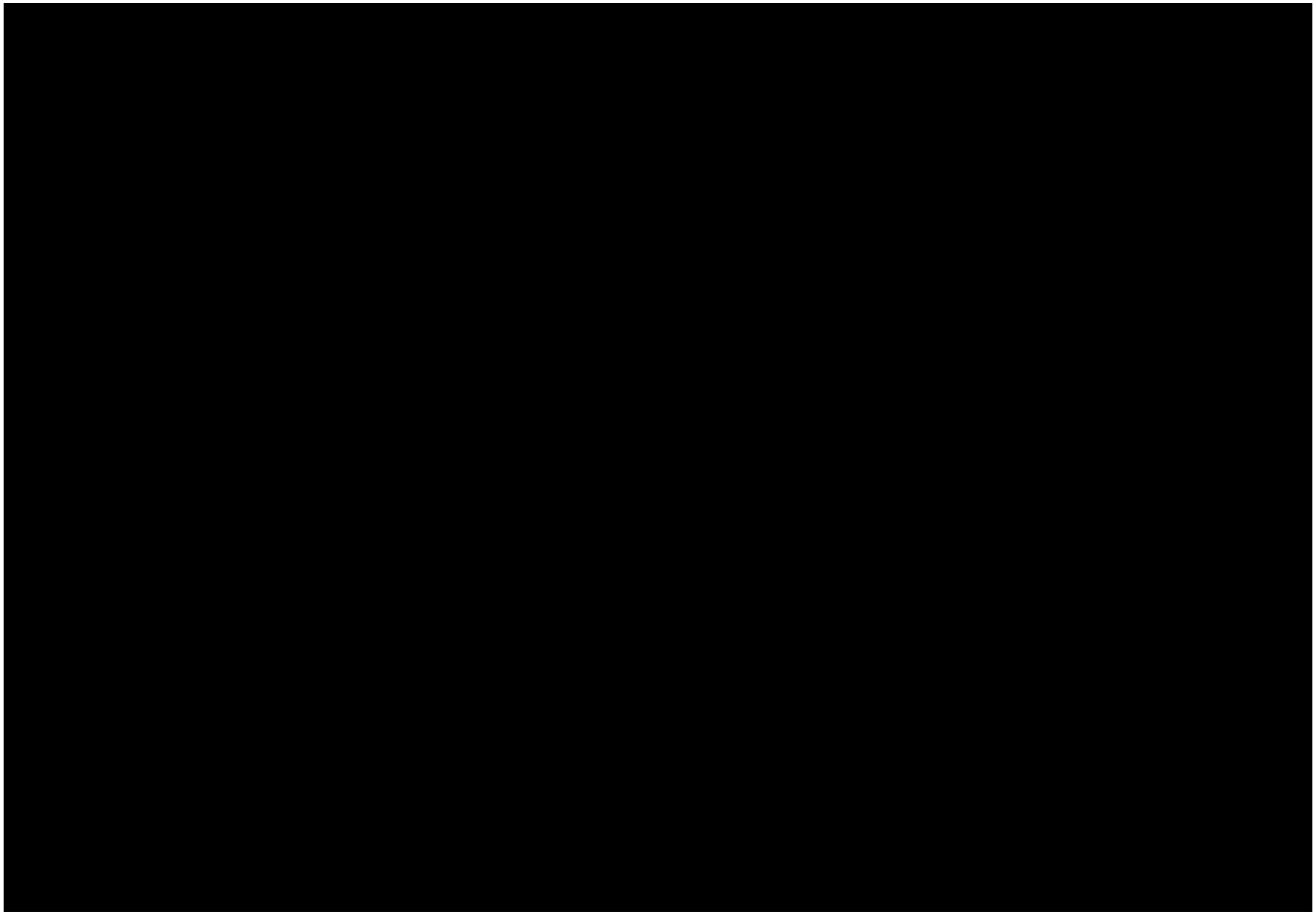
Total Score

The total score is calculated as:

Score for acne-like lesions + Score for follicultits + Score for erythema nodosum = Total Score







Appendix K: International Study Group Criteria For The Diagnosis Of Behçet's Disease (1990)

In the absence of other clinical explanations, subjects must have**:**

Recurrent Oral Ulceration (aphthous or herpetiform) observed by the physician or subject recurring at least three times in one 12-month period.

Plus at least two of the following criteria:

Recurrent Genital Ulceration:

Aphthous ulceration or scarring observed by physician or subject.

Eye Lesions:

Anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination;

or:

Retinal vasculitis observed by ophthalmologist.

Skin Lesions:

Erythema nodosum, pseudofolliculitis, or papulopustular lesions;

or:

Acneiform nodules in postadolescent subjects not on corticosteroid treatment.

Positive Result on Pathergy Testing:

Read by a physician at 24 to 48 hr.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Addition of an optional Open-label Extension Phase

This amendment will allow subjects the opportunity to enter an optional Open-label Extension Phase after the 52-week Active Treatment Phase (Week 64 visit). Subjects may continue in the optional Open-label Extension Phase until apremilast is commercially available for BD or until the benefit/risk of apremilast is found not to be acceptable for BD, according to either the sponsor or health authority.

Revised sections:

- Protocol Summary
- Section 4.1 – Study Design
- Section 4.2 – Study Design Rationale (including Figure 1)
- Section 4.3 – Study Duration
- Section 5 – Table of Events (Table 2)
- Section 6.6.1 – Adverse Events
- Section 6.6.9 – Pregnancy Tests for Females of Childbearing Potential
- [redacted]
- Section 6.10 – Early Termination Visit
- Section 6.10.1 – Observational Follow-up Visit
- Section 6.11 – Study Completion
- Section 8.3 – Treatment Administration and Schedule
- Section 8.4.3 – Optional Open-label, Extension Phase
- Section 10.1 – Statistical Analysis Overview
- Section 10.2 – Study Population Definitions
- Section 10.5 – Subject Disposition
- Section 10.7 – Safety Analysis
- Section 11.1 – Monitoring, Recording and Reporting of Adverse Events

Minor changes in this amendment are summarized below:

- Minor editorial and administrative changes

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. **Extending eligibility to patients previously exposed to biologic therapy (Sections 6.5, 7.3)**

The amendment will allow inclusion of potential subjects who have been previously exposed to biologic therapies for indications other than oral ulcers, including other manifestations of Behçet's Disease. The last dose for biologic therapies must correspond to at least 5 terminal half-lives of the individual drugs.

The greater availability of biologic therapies globally and the practice of prescribing them for specific indications in Behçet's Disease (BD) have become more common. While oral ulcers in BD are not typically treated with biologics, major organ manifestations such as gastrointestinal and CNS involvement and severe uveitis or retinal vasculitis may require treatment with biologics [eg, tumor necrosis factor (TNF)α antagonists and interferon (IFN)α]. Excluding BD patients who have had treatment with biologics regardless of the indications or the timing when treatment occurred has become unrealistic in terms of recruiting patients for the BCT002 study. The amendment will help improve recruitment while retaining the intent of enrolling a population with active BD who have 2 or 3 oral ulcers and no major organ involvement within one year of the screening visit (see number 3 below).

2. **Modifications related to previous and current medications (Sections 7.3, 9.1)**

   a. **Colchicine (Section 7.3 only)**

      The amendment will allow patients to continue taking colchicine until 7 days prior to randomization.

In a consultation meeting with PMDA held on 23 July 2014 on the design and conduct of the BCT002 Study of apremilast in Behçet's disease, the PMDA recommended to enroll patients using colchicine after establishing an appropriate washout period, and to not allow colchicine as a concurrent medication until completion of the double blind period. Celgene accepted this recommendation and subsequently implemented it in the protocol (Section 7.3, Exclusion #6, 3rd bullet). Patients on colchicine were allowed to enter the study provided it had been at least four weeks (28 days) since the last dose of colchicine was taken prior to randomization.

In the same meeting, Celgene recognized the clinical reality that in Japan colchicine has been used as a treatment for BD for many years. Celgene understood that prohibiting use of colchicine for an extended period of time may not be ethically acceptable.

For more than 14 months to date, the BCT002 study has been actively recruiting BD patients to participate in this clinical trial. Enrollment has been challenging. One of the reasons for the slow enrollment has been due to the reluctance of patients to discontinue taking colchicine from at least 4 weeks prior to randomization. The patients taking colchicine are not necessarily oral ulcer-free, but nonetheless feel that colchicine is having some positive impact on their disease. Patients feel that waiting for 4 weeks prior to randomization without colchicine would not be tolerable, and therefore would rather not participate in the BCT002 study.

Celgene considers that amending the protocol in terms of the required washout period of colchicine prior to randomization will benefit patients who would consider enrolling in the study if colchicine is discontinued closer to randomization. The maximal anti-inflammatory effects of colchicine develop over 24 to 48 hours, based on intraleukocyte accumulation where it reaches much higher concentrations compared to plasma (Slobodnick, 2015). Colchicine has been used in BD and has shown to improve oral ulcers, skin lesions, and arthralgia (Yardakul, 2001; Davatchi, 2009; Aktulga, 1980). Although the anti-inflammatory effects persist while taking colchicine, many BD patients continue to have oral ulcers. The proposed modification to the protocol is to allow the use of colchicine until at least 7 days prior to randomization, based on 5 elimination half lives of colchicine (t½ ~32 hours). Celgene considers this amendment reasonable because the amendment will only allow subjects who continue to have oral ulcers (required by the protocol) despite recent use of colchicine. The 7 day washout period will still be sufficient to ensure that colchicine will not confound efficacy assessments of apremilast in this study.

b. Oral and topical corticosteroids

The amendment will allow for tapering of topical and oral corticosteroids and subsequent discontinuation close to the day of randomization.

The modification to allow tapering of oral and topical corticosteroids with subsequent discontinuation close to randomization is not expected to confound assessments secondary to the potential carry over effects of corticosteroids on oral ulcers. The amendment will only allow subjects who continue to have oral ulcers (required by the protocol), despite continued use of oral and topical corticosteroids, until the day of randomization.

3. Clarification for the required number of oral ulcers (Protocol Summary, Section 7.2)

The required number of oral ulcers at screening AND at baseline are clarified to eliminate misinterpretation. All subjects must have at least 2 oral ulcers at Visit 1. Once 3 oral ulcers are observed, regardless of the time interval from the screening visit (ie, the interval of 2 weeks is not required) a subject is qualified to be randomized provided all other eligibility criteria are met. If only 2 oral ulcers are present at Visit 2, then at least 14 days must have passed since Visit 1 before the subject may be randomized.

4. Clarification on the Static Physician's Global Assessment of Skin Lesions (Appendix G)

The wording on scoring of severity of skin lesions as described in Appendix G, Static Physician's Global Assessment of Skin Lesions is revised. The protocol describes the scoring of the severity of skin lesions by the number of nodules/lesions present at one anatomical site. Since lesions can occur at different anatomical sites during the course of the study, it is more feasible to assess and score the lesions all together. As such, scoring of the number of nodules/lesions will be based NOT on one anatomical site at a time but at any anatomical site with respect to the whole body.

5. Hepatitis Testing (Section 6.6.7.4)

Revised to allow the decision to perform laboratory screening and clinical interpretation of tests for hepatitis B and C antigen or antibodies for study inclusion/exclusion purposes, to be left to the Investigator's discretion.

Minor changes in this amendment are summarized below:

- Change in Therapeutic Area Head (page 3, deleted [redacted] and added [redacted])
- Section 14.2, updated investigator responsibilities and confidentiality requirements
- Section 11.2.6, updated to ensure all serious adverse events (SAEs) will be followed until resolution or until the AE is no longer serious
- Minor editorial and administrative changes (including changing *document* to *form*, and punctuation edits)

References:

Aktulga E, Altaç M, Müftuoglu A, Özyazgan Y, Pazarli H, Tüzün Y, et al. A double blind study of colchicine in Behçet's disease. Haematologica 1980;65(3):399–402.

Davatchi F, Sadeghi Abdollahi B, Tehrani Banihashemi A, Shahram F, Nadji A, Shams H, et al. Colchicine versus placebo in Behçet's disease: randomized, double blind, controlled crossover trial. Mod Rheumatol 2009;19(5):542-549.

Slobodnick A, Shah B, Pillinger MH, Krasnokutsky S. Colchicine: old and new. Am J Med 2015;128:461-470.

Yurdakul S, Mat C, Tüzün Y, Özyazgan Y, Hamuryudan V, Uysal Ö, et al. A double-blind trial of colchicine in Behçet's syndrome. Arthritis Rheum 2001;44(11):2686-92.

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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- The Medical Monitor / Emergency Contact Information has been changed for Japan.
- The following sections were updated to meet local regulatory requirements: Title Page, Protocol Summary, 7.2, 11.6, 14, 14.6, 14.8, 15.1, 15.3, and 16.2.

In addition, minor editorial changes have been made.