2. STUDY SYNOPSIS

Name of Sponsor/Company: Biogen Idec Inc./Biogen Idec Ltd.	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: BG00012	**Name of Active Ingredient:** Dimethyl fumarate (DMF)	**Study Indication:** Rheumatoid Arthritis

Title of Study:

A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of BG00012 When Given with Methotrexate to Subjects with Active Rheumatoid Arthritis who have had an Inadequate Response to Conventional Disease-Modifying Anti-rheumatic Drug Therapy

Principal Investigator/Coordinating Investigator:

[redacted] Poland.

Study Period:	**Phase of Development:** 2a
Date of first treatment: 29 December 2008 End of Study Date: 17 March 2010	

Study Objective(s):

Primary objective(s):

The primary objective of this study was to evaluate the clinical efficacy of BG00012 with methotrexate (MTX) in subjects with active rheumatoid arthritis (RA) who have had an inadequate response to disease-modifying anti rheumatic drug (DMARD) therapy.

Secondary objective(s):

The secondary objective of this study was to determine the safety and tolerability of BG00012 with MTX in this population.

Additional/Exploratory objective(s):

- To assess the pharmacodynamic (PD) profile of biomarkers of drug mechanism of action and anti-inflammatory effect.
- To assess the pharmacokinetic (PK) profile of BG00012 and its relationship to selected PD parameters.
- To assess the effects of genetic and genomic determinants on BG00012 PK, PD, and efficacy parameters.

Study Design:

This was a randomized, double-blind, placebo-controlled, multicenter study of BG00012 administered orally with MTX for 12 weeks in subjects with RA. Approximately 150 subjects were to be randomized into 1 of 3 treatment groups: placebo by mouth (PO) 3 times daily (TID), BG00012 480 mg/day (240 mg PO twice daily [BID]), or BG00012 720 mg/day [240 mg PO TID]). All subjects were to initially receive half the active BG00012 dose for 1 week prior to receiving the full BG00012 dose for a further 11 weeks, and were to participate in the study for a maximum of 16 weeks.

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Number of Subjects (Planned and Analyzed):

Planned: Approximately 150 subjects

Randomized: 153 subjects

Dosed: 152 subjects

Analyzed: 152 subjects

Study Population:

Main inclusion criteria:

- Aged 18 to 75 years old, inclusive, at the time of randomization.
- Must have had a diagnosis of adult onset RA according to the 1987 Revised American Rheumatism Association Criteria for the Classification of Rheumatoid Arthritis and be Functional Class I – III for at least 6 months prior to Day 0.
- Must have been treated with, and have been tolerating, MTX (≥7.5 mg/week to ≤25 mg/week) for at least 3 months immediately prior to Day 0. The dose of MTX must have been stable for at least 4 weeks prior to Day 0.
- Must have had an inadequate response to at least 1 conventional DMARD therapy (e.g., MTX, leflunomide, sulfasalazine, etc.) due to inadequate efficacy or toxicity.
- Must have had a swollen joint count (SJC) ≥6 and a Tender Joint Count (TJC) ≥6 (66/68 joint count at Screening).
- Must have had elevated high sensitivity C-reactive protein (hsCRP) ≥1.5 times the upper limit of normal (ULN) or erythrocyte sedimentation rate (ESR) ≥28 mm/hr at Screening. The ULN for hsCRP for this study was 1.0 mg/dL.

Main exclusion criteria:

Medical History

- Subjects with a history of malignant disease, including solid tumors and hematologic malignancies (except basal cell and squamous cell carcinomas of the skin that have been completely excised and are considered cured).
- History of severe allergic or anaphylactic reactions or known drug hypersensitivity.
- Known active bacterial, viral, fungal, mycobacterial, opportunistic infection or other infection (including atypical mycobacterial disease, but excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with intravenous (IV) antibiotics within 4 weeks of Day 0.

Laboratory Tests

- Clinically significant laboratory tests at Screening.
- Serum creatinine >1.2×ULN established by the central laboratory.

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- Any of the following abnormal urine tests at the Screening visit confirmed by a second urinalysis 2 weeks later: proteinuria (1+ or greater), hematuria without known etiology (e.g., urinary tract infection, menses), or glycosuria without known etiology (e.g., recent steroid use, elevated serum glucose).
- Positive for hepatitis C antibody or current hepatitis B infection at the Screening visit.
- Known to be positive for human immunodeficiency virus (HIV) at the Screening visit.

Study Treatment, Dose, Mode of Administration, Batch Number(s):

BG00012 is a drug product formulated as enteric coated microtablets in gelatin capsules (blue and white) for oral administration. Each capsule contains 120 mg DMF. Subjects were to receive 2 capsules (240 mg) either twice daily (BID) or 3 times daily (TID) orally for 12 weeks. Capsules for BG00012 used in this study were from the following lot numbers:

BG00012: [redacted]

Comparator Therapy/Therapies, Dose, Mode of Administration, Batch Number(s):

The matched placebo for this study was supplied as enteric-coated microtablets in gelatin capsules (blue and white) for oral administration. DMF was replaced by lactose monohydrate in the placebo to maintain the total weight. Subjects were to receive 2 placebo capsules TID or once daily in the BID group for 12 weeks. Placebo capsules used in this study were from the following lot numbers:

Placebo: [redacted]

Duration of Treatment and Follow-Up:

Treatment period: 12 weeks

Follow-up period: 4 weeks

Criteria for Evaluation:

Efficacy:

- American College of Rheumatology (ACR) Core Data Set measurements (SJC, TJC, subject's and Investigator's Global Assessments, health assessment questionnaire-disability index [HAQ-DI], pain visual analog scale [VAS], hsCRP, and erythrocyte sedimentation rate [ESR])
- Quality of Life questionnaires (Short Form 36 and Functional Assessment of Chronic Illness Therapy Fatigue)

Pharmacokinetics:

- A subset of the participating investigational sites was to be selected by Biogen Idec to participate in a PK/PD sub-study of BG00012. Plasma concentrations of BG00012 were to be evaluated on Day 0 and at predefined timepoints over a 24-hour period starting on Day 7 in up to 30 subjects who consented to participate.

Pharmacodynamics:

- Markers of drug mechanism of action (MOA): markers of Nrf-2 pathway activation, including, but not limited to HO-1 and NQO-1, were to be examined to determine if change in these markers correlates with drug efficacy.

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- The effect of BG00012 on NFκB pathway signaling was to be assessed indirectly through its effects on select cytokines.
- Markers of anti-inflammatory effect: A panel of cytokines, chemokines, matrix metalloproteases, and growth factors was to be examined to determine if treatment with BG00012 reduces inflammatory signaling and if this correlates with clinical efficacy.
- Flow cytometry: populations of memory/naïve T cells, regulatory and activated T cells, natural killer (NK) and NK-T cells were to be examined to determine if changes are seen with BG00012 treatment.
- RA disease markers: hsCRP, rheumatoid factor (RF; at screening only), serum MMP3, CXCL13, and MMP-1

Safety:

- Monitoring of adverse events (AEs) and serious adverse events (SAEs), physical examinations and vital sign measurements, 12-lead electrocardiograms (ECG), monitoring of concomitant therapy
- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count (with differential), and platelet count
- Blood chemistry: sodium, potassium, chloride, glucose, total bilirubin, calcium, magnesium, phosphate, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), blood urea nitrogen (BUN), uric acid, creatinine, and bicarbonate; abbreviated blood chemistry was to include total bilirubin, ALT, AST, alkaline phosphatase, BUN, and creatinine
- Serum lipid profile: blood total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride levels
- Prothrombin time (PT) and partial thromboplastin time (PTT)
- D-dimer
- Urinalysis: color, specific gravity, pH, protein, glucose, blood, ketones, and microscopy
- Urine cytology
- Urinary β2-microglobulin, microalbumin, and urine aliquot for exploratory biomarker analysis

Statistical Methods:

- Demographics and Safety: Descriptive statistics and summary tables were used to depict demographics, subject background information, baseline information, safety information (including physical examination, vital signs, ECGs and AEs) and laboratory evaluations.
- Efficacy: Descriptive statistics, summary tables and graphical representations were used to summarize the efficacy of study treatment. Cochran-Mantel-Haenszel (CMH) test was used to evaluate the primary efficacy outcome.
- Pharmacokinetics: Summary statistics were to be presented for monomethyl fumarate (MMF) concentrations by collection time and by treatment group.

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- Pharmacodynamics: Graphical representations were used to summarize the PD data.

Results:

Subject disposition:

- One hundred fifty-three subjects were enrolled and randomized in Study 109RA201. Of those, 1 subject withdrew prior to dosing. Of the 152 subjects dosed, 51 received placebo, 49 subjects received BG00012 BID, and 52 subjects received BG00012 TID.
- Thirty-five subjects dosed (23%) in this study discontinued study treatment, with 25 subjects (16%) discontinuing due to an AE. An additional subject discontinued due to RA disease progression, which was included as an AE in the analysis of safety data (see below). Of these 25 subjects, 7 subjects (14%) received placebo, and 5 subjects (10%) and 13 subjects (25%) were administered BG00012 BID or BG00012 TID, respectively. Other reasons for discontinuation among the total subject group included: RA disease progression (< 1%), lost to follow-up (1%), consent withdrawn (3%), and other reasons (2%). Twenty-four of the 25 subjects who discontinued study treatment due to an AE also withdrew from the study. In total, 34 subjects (22%) withdrew from the study, and 118 subjects (78%) completed the study.

Demographics and baseline disease characteristics:

- Subjects were predominantly white (81%) and female (81%), with a median age of 54 years (range 29 to 75 years). Subjects had a median weight of 70 kg (range 38 to 113 kg).
- The subjects enrolled in this study were representative of the typical RA patient population. The median SJC (66 joints) was 14, and the median TJC (68 joints) was 24.5. The median HAQ-disability index score for all subjects, assessed on a scale from 0 being best to 3 being worst, was 1.50. The median CRP concentration among all subjects was 0.581 mg/dL (ULN is 1 mg/dL). The median ESR among all subjects was 36.5 mm/h. The median Disease Activity Score, 28 joint version (DAS28) value (based on ESR) among all subjects was 6.515. Overall, 67% of subjects were positive for RF, and 70% of subjects were positive for anti-cyclic citrullinated peptide-2 (anti-CCP2) antibody. Baseline disease characteristics were balanced between groups, with a slight imbalance in CRP levels and RF positivity: the median baseline CRP value and percentage of subjects positive for RF were slightly lower in the BG00012 TID group compared to the placebo group.
- Distribution of RA functional class diagnosis was balanced among the cohorts, with the majority of subjects (68% overall) meeting Class II criteria. Subjects in the BG00012 TID group had a medical history at baseline which included more subjects with a history of gastrointestinal (GI) disorders (37%) compared to the placebo group (16%). Subjects in the BG00012 TID group also had a longer duration of RA at baseline than the placebo group and had been on MTX for a longer duration of time compared to either the BG00012 BID or placebo group. These imbalances between treatment groups were mild and not considered clinically significant.

Efficacy:

- Relative to placebo, treatment with BG00012 did not exhibit significant efficacy based on ACR or DAS28 criteria. The study did not meet its primary endpoint of BG00012 superiority to placebo in the proportion of subjects with an ACR20 response at Week 12. At Week 12, 33% of subjects in the BG00012 BID and 29% of subjects in the BG00012 TID group achieved an ACR20 response compared to 22% in the

placebo group. For the secondary endpoints, 4% of subjects in the BG00012 BID group, and 12% of subjects in the BG00012 TID group achieved an ACR50 response compared to 10% of the placebo group, and no subjects in the BG00012 BID group and 2% of subjects in the BG00012 TID group achieved an ACR70 response compared to 6% in the placebo group. The only ACR core set parameter with a greater median percentage change reduction from baseline compared to placebo at Week 12 in the BG00012 treatment groups was CRP (-22.71 BG00012 BID and -15.78 BG00012 TID versus 4.92 placebo). No changes were noted between BG00012 and placebo groups in change from baseline for DAS28 based on ESR or CRP or in EULAR response rates based on DAS28-ESR at Week 12.

- A greater separation between the BG00012 groups and the placebo group was observed in the ACR 20 response in subgroups of subjects who were RF positive, had a CRP level of ≥1 mg/dL at baseline, or most notably in subjects who were both RF positive and had a CRP level of ≥1 mg/dL at baseline. As in the overall analyses above, in these subgroup analyses, similar ACR20 response rates were observed at both doses of BG00012.

Pharmacokinetics:

- Due to logistical matters, it was decided not to enroll subjects in the PK/PD sub-study; therefore, no PK measurements were performed.

Pharmacodynamics:

- There was clear evidence of activation of Nrf-2 pathway markers upon treatment with BG00012, as well as data that suggest an anti-inflammatory effect of BG00012.
- There was an upward trend relative to baseline for NQO-1 and HO-1 markers with BG00012 treatment. NQO-1 levels were significantly elevated in the BG00012 TID treatment group at Week 12 compared to placebo. HO-1 levels also showed elevation at Week 12 in the BG00012 TID group compared to placebo; however this difference was not statistically significant.
- Of the multiplex panel of biomarkers tested, the A-SAA, E-Selectin, and MMP-3 inflammatory biomarkers show a downward trend after BG00012 treatment; however, these trends were not statistically significant. There is some evidence of cytokine downregulation as well, as indicated by a decrease in IL-6 levels in subjects treated with BG00012. No trends in CXCL13 or MMP-1 upon treatment with BG00012 were observed.
- In the exploratory FACS analyses, there were no significant differences between treatment groups in T and NK cell populations after 12 weeks of treatment with BG00012 in combination with MTX; however, a downward trend was noted in the BG00012 TID group compared to the placebo and BG00012 BID groups in the NK or NK-like cell types.
- No notable trends were observed in BG00012-treated subjects compared to placebo-treated subjects in the levels of KIM-1 or Cystatin C, which are urinary toxicology biomarkers used in the early detection of acute kidney injury.

Safety:

All subjects who received at least 1 dose of study treatment were included in the safety analyses. Data are presented by individual BG00012 treatment group and for the combined total BG00012 group ("total BG00012").

- Overall, the incidence of AEs was higher in the BG00012-treated subjects (69%) than in placebo-treated

subjects (55%). The most common AEs (incidence of 5% or more) in BG00012-treated subjects were nausea (11% BG00012, 2% placebo), abdominal pain (7% BG00012, 4% placebo), diarrhea (7% BG00012, 4% placebo), increased alanine aminotransferase (6% BG00012, 0% placebo) vomiting (6% BG00012, 0% placebo), flushing (5% BG00012, 0% placebo), nasopharyngitis (5% BG00012, 2% placebo), pruritus (5% BG00012, 0% placebo), and urinary tract infection (5% BG00012, 6% placebo).

- There was no difference in the incidence of severe events between the treatment groups: one subject (2%) in each treatment group had a severe AE.
- Forty-one subjects (41%) in the total BG00012 group and 8 subjects (16%) in the placebo group reported events that were considered related to study treatment. There was no notable difference between BG00012 treatment groups in the incidence of AEs considered related to study treatment (BG00012 BID [43%] and BG00012 TID [38%]). The most common AEs (≥5%) considered related to total BG00012 were nausea (8%); abdominal pain, diarrhea, vomiting and ALT increase (6%); and flushing (5%).
- There were no deaths reported in this study.
- There were no SAEs in the total BG00012 group, and one SAE (2%) in the placebo group of gastric ulcer.
- The number of subjects who discontinued treatment due to an AE was similar between the BG00012 (18%) and placebo (16%) groups. The most common events that led to discontinuation in either the total BG00012 group or the placebo group were GI disorders. There were differences between the two BG00012 treatment groups in the number of subjects who discontinued treatment due to an AE (BG00012 BID [10%] and BG00012 TID [25%]). However, there were more subjects with a history of GI disorders at baseline in the BG00012 TID group, which may account for this difference. Most subjects who discontinued due to a GI event had a history of GI disorders. Twenty-five of the 26 subjects who discontinued study treatment due to an AE also withdrew from the study.
- There were no hepatic, hematologic, cardiac, renal, or infection AEs of significance in this study.
- There was an increased incidence of flushing-like events in the total BG00012 group (12%) compared to the placebo group (2%). However, the incidence of flushing-like AEs was lower in BG00012-treated subjects who were on baseline corticosteroids (5% versus 23%).
- There was an increased incidence of GI events in the total BG00012 group (28%) compared to the placebo group (12%). Most GI events were mild or moderate in severity. In a subanalysis, the incidence of GI events was higher in BG00012-treated subjects on baseline GI-protective agents, such as protein pump inhibitors or H2 antagonists (36% versus 7%).
- No malignancies were reported in this study.
- No pregnancies were reported in this study.
- There was an increased incidence of shifts to high in ALT or AST in the total BG00012 group (51% and 38%, respectively) compared to the placebo group (16% and 11%, respectively). The majority of the shifts to high in ALT and AST were ≤3×ULN. Three subjects (3%) in the total BG00012 group had an ALT or AST elevation >5×ULN. Two of these 3 subjects had elevated ALT or AST values (>ULN) at screening or baseline and none of the elevations in ALT and AST were accompanied by elevations of total

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bilirubin (>1.5×ULN). All of the subjects with elevations of ALT or AST values >3×ULN returned to their baseline values.

- In other blood chemistry tests, trends for lipid profile components were minor from a clinical standpoint, but were favorable for BG00012 relative to placebo.

Conclusion(s):

- BG00012 did not exhibit significant efficacy, although a greater separation between the BG00012 and the placebo groups in ACR20 response rates was observed in certain subgroups of subjects.
- Activation of the Nrf-2 pathway upon BG00012 treatment was demonstrated by an increase in levels of the NQO-1 and HO-1 markers in BG00012-treated subjects. There was also a downward trend in some inflammatory markers and cytokines.
- Overall, BG00012 was well tolerated when administered for 3 months in this patient population. No new safety signals for BG00012 were observed.
- The PD and safety results of this study support the development of BG00012 in other indications.

Publication(s) Based on the Study:

None

Date of Report: 10 March 2011