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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Titles of Studies:

104RA203: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of BG9924 When Given in Combination With Methotrexate to Subjects With Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Anti-TNF Therapy

104RA205: An Open-Label Extension Study to Evaluate the Safety and Efficacy of BG9924 When Given in Combination With Methotrexate to Subjects With Rheumatoid Arthritis Who Previously Participated in Study 104RA203

Principal Investigator/Coordinating Investigator for the Studies:

[redacted] US

Study Period: Date of first treatment: **104RA203**: 29 March 2007 **104RA205**: 29 August 2007 Date of last subject last visit: **104RA203**: 08 January 2009 **104RA205:** 02 January 2009 Date of early study termination: 09 October 2008	**Phase of Development:** 2b

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Study Objective(s):

Study 104RA203

Primary objective(s):

- To evaluate the efficacy of BG9924 when administered in combination with methotrexate (MTX) to subjects with active rheumatoid arthritis (RA) who have had an inadequate response to anti-TNF therapy.

Secondary objective(s):

- To assess the safety and tolerability of BG9924 in this patient population.
- To assess the pharmacokinetic (PK) and pharmacodynamic profile of BG9924 in this patient population.

Study 104RA205

Primary objective(s):

- To determine the safety and durability of efficacy response of long-term treatment with BG9924 when administered with a stable dose of MTX to subjects with RA who previously participated in Study 104RA203.

Secondary objective(s):

- To assess the immunogenicity of long-term treatment with BG9924 in this patient population.

Study Design:

Study 104RA203

This was a randomized, double-blind, placebo-controlled, multicenter study. Approximately 120 subjects were to be enrolled at approximately 40 sites. Subjects could participate in this study for up to 26 weeks. Over the treatment period, subjects were to receive 200 mg BG9924 or placebo by subcutaneous (SC) injection, every other week for 12 weeks, with a follow-up visit 2 weeks after the last dose (Visit 9/Week 14). Subjects who continued in the study until Week 14 were offered the option to enter a safety extension study (Study 104RA205). Subjects who did not enroll in the extension study were to be followed for safety assessments for an additional 12 weeks (Visit 12/Week 26) under this protocol.

Study sites could choose to participate in an optional PK sub-study. Approximately 20 subjects were to have 6 additional visits for blood draws following Visits 1, 3, and 8. Blood samples for fluorescence-activated cell sorter (FACS) analysis were also to be taken from subjects participating in this sub-study.

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Study Design (continued):

Study 104RA205

This was an open-label extension study of BG9924 in subjects who had previously participated in Study 104RA203. Subjects could enter the study on or after the Visit 9/Week 14/Early Withdrawal Visit in Study 104RA203, but no later than the Visit 12/Week 26/Late Withdrawal Visit in Study 104RA203.

Subjects could participate in this study for up to 54 months (study extended beyond 18 months by Version 5 protocol amendment). Over the treatment period, subjects were to receive 200 mg BG9924 by SC injection, every other week for approximately 51 months, with study visits decreasing in frequency over time. Follow-up visits were to occur at Weeks 206, 210, and 218 (2, 6, and 14 weeks, respectively, after the last dose).

Subjects in this study were to switch to dosing with BG9924-C (a new liquid formulation of BG9924) from BG9924-B (the lyophilized powder formulation of BG9924) during the course of the study. Study sites could choose to participate in an optional PK sub-study evaluating PK comparability of BG9924-C with BG9924-B. Approximately 20 subjects were to have 3 additional visits for 4 PK blood draws after 3 consecutive doses of BG9924-C. The 4 PK blood samples were to be drawn within the same week.

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Early Termination of Studies

Based on the results of a dose-finding Phase 2b study (102RA202) of BG9924 in subjects with RA who have had an inadequate response to conventional disease-modifying anti-rheumatic drug (DMARD) therapy, in which the study did not meet its primary efficacy endpoint, as well as on preliminary results of Study 104RA203, Biogen Idec decided to suspend dosing of BG9924 and close Studies 104RA203 and 104RA205 on 09 October 2008. Subjects were to schedule an Early Withdrawal (104RA203) or End of Treatment (104RA205) visit immediately, and a modified follow-up visit at least 8 weeks after their last dose of BG9924.

Number of Subjects (Planned and Analyzed):

Study 104RA203

Planned: Approximately 120 subjects

Randomized: 115 subjects

Dosed: 114 subjects

Analyzed: 114 subjects

Study 104RA205

Planned: Approximately 120 subjects

Randomized: Not applicable; 74 subjects entered the study

Dosed: 74 subjects

Analyzed: 74 subjects

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Study Population:

Study 104RA203

Main inclusion criteria:

- Aged 18 to 75 years old, inclusive, at the time of informed consent.
- Must have had a diagnosis of adult onset RA according to the 1987 Revised American Rheumatism Association Criteria for the Classification of Rheumatoid Arthritis (Functional Class I to III) for at least 6 months prior to Day 0.
- Must have been treated with, and be tolerating, MTX (≥10 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 experienced an inadequate response to previous treatment with etanercept, infliximab, or adalimumab because of inadequate efficacy (etanercept for ≥3 months at 25 mg twice a week, at least 4 infusions of infliximab at ≥3 mg/kg, or adalimumab for ≥3 months at 40 mg every other week) or toxicity.
- Must have had a Swollen Joint Count (SJC) ≥8 and a Tender Joint Count (TJC) ≥8 (66/68 joint count at Screening).
- Must have had elevated hsCRP ≥1.5 times the upper limit of normal (ULN) *or* ESR ≥28 mm/hr at Screening.

Main exclusion criteria:

Medical History

- Subjects with rheumatic autoimmune disease other than RA, or significant systemic involvement secondary to RA (including, but not limited to vasculitis, pulmonary fibrosis, or Felty's syndrome). Secondary Sjogren's syndrome or secondary limited cutaneous vasculitis within RA was permitted.
- Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., pneumonia, septicemia) within 3 months prior to Day 0 (Visit 1/Week 0).
- Primary or secondary immunodeficiency (history of or currently active), including known history of HIV infection.
- History of *recurrent* infections requiring oral or parenteral anti-infective drug treatment.
- History of tuberculosis (TB) or positive purified protein derivative (positive Mantoux test defined as ≥10 mm of induration [size of raised lump, not redness], or equivalent positive TB test result as per country clinical standards) during the screening period.

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Laboratory Tests

- Clinically significant lab tests at Screening; or
- Positive for hepatitis C antibody or hepatitis B (HBsAg) at Screening.

Study 104RA205

Main inclusion criteria:

- Must have been a subject from Study 104RA203 who received at least 6 doses of study treatment and completed the Visit 9/Week 14/Early Withdrawal Visit or the Visit 9/Week 14 Visit and the Visit 12/Week 26/Late Withdrawal Visit in that study.
- Must have been receiving treatment with MTX (≥10mg/week to ≤25mg/week) for RA for the duration of the study.

Main exclusion criteria:

- Subjects with a significant change in medical history from their previous BG9924 study (Study 104RA203).

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

BG9924 is a fusion protein consisting of the extracellular domain of the human lymphotoxin beta receptor (LTβR) fused to the hinge, C_H2 and C_H3 regions of human IgG_1.

Study 104RA203: Subjects were to receive 200 mg BG9924 by SC injection every other week for 12 weeks. Doses administered were from Lot #[redacted]

Study 104RA205: Subjects were to receive 200 mg BG9924 by SC injection, every other week for approximately 51 months. BG9924-B doses administered were from Lot #[redacted] BG9924-C doses administered were from Lot #[redacted]

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

The comparator drug was placebo, sterile normal saline (0.9% Sodium Chloride for Injection), and was administered by SC injection.

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Duration of Treatment and Follow-Up:

Study 104RA203

Treatment period: 12 weeks

Follow-up period: Visit 2 weeks after the last dose; also, visits at 6, 10, and 14 weeks after the last dose for subjects who did not enroll into Study 104RA205

Study 104RA205

Treatment period: 51 months

Follow-up period: Visits at 2, 6, and 14 weeks after the last dose

A protocol amendment to extend Study 104RA205 beyond 18 months (Version 5) was approved by the central ethics committee but never implemented; therefore, some subjects completed Study 104RA205 with follow-up visits at Weeks 60, 64, and 72 as initially planned.

Study termination modified follow-up: All active subjects were seen at least 8 weeks after their last dose of BG9924.

Criteria for Evaluation

Efficacy:

- American College of Rheumatology (ACR) Core Data Set measurements (SJC, TJC, subject's and Physician's global assessments, health assessment questionnaire [HAQ], pain visual analog scale [VAS], C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]).
- Short Form 36 [SF-36] and Functional Assessment of Chronic Illness Therapy [FACIT-F] questionnaires; and Sjogrens syndrome assessments if applicable (subject-reported dryness including VAS [ocular, vaginal, skin, and oral] and Ocular Surface Disease Severity Index [OSDI]).

BG9924 concentration measurements:

- Serum concentrations of BG9924 were measured to support the PK evaluations in these studies. From these data, a number of exposure measures were calculated via both noncompartmental and compartmental analysis, such as: area under the time-concentration curve from pre-dose to the last measurable value within a dosing interval ($AUC_{(0\text{-}14\ days)}$), area under the time-concentration curve from pre-dose to infinity (AUC_{inf}), maximum concentration (C_{max}), time of the maximum concentration (T_{max}), terminal half-life ($T_{1/2}$), clearance (CL), volume of distribution (V), etc.

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Criteria for Evaluation (continued)

Pharmacodynamics:

- FACS analysis in subjects who took part in the optional intensive PK study (*Study 104RA203 only)*
  - Leukocyte subset analysis: CD3+, CD4+, CD8+, CD19+, CD16+, CD56+, and CD14+ *(Study 104RA203 only)*
  - Unswitched memory B cells: CD19+, IgD+, IgM+, and CD27+
- Cytokine panel (IL-1β, IL-6, IL-8, TNF-α, and IFN-γ) (*Study 104RA203 only)*
- RA disease markers (hsCRP, ESR, Rheumatoid factor (RF), anti-cyclic citrullinated peptide-2 (CCP-2) antibody, cartilage oligomeric matrix protein (COMP), calgranulin, matrix metalloproteinase 3 (MMP3), serum B cell activation factor from the TNF family [BAFF])
- Biomarkers (LIGHT ligand)

Safety:

- Physical examination, vital signs, electrocardiogram, monitoring of adverse events (AEs), monitoring of concomitant therapy.
- Hematology (hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count, absolute and differential counts, and platelet count).
- Blood chemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, total protein, albumin, cholesterol, total bilirubin, blood urea nitrogen, uric acid, creatinine, lactate dehydrogenase [LDH], potassium, sodium, chloride, calcium, phosphorous, bicarbonate, and glucose).
- Blood chemistry (fasting [12-hours]) cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides were to be tested. (*Study 104RA203 only*)
- International normalized ratio (for anticoagulant monitoring [INR]), prothrombin time (PT), and activated partial thromboplastin time (aPTT). (*Study 104RA203 only*)
- Urinalysis (protein, glucose, ketones, occult blood, and WBCs by dipstick and microscopic examination, if indicated).
- Serum anti-BG9924 antibody assay.
- Anti-nuclear antibody (ANA) and anti-dsDNA antibody assays. (*Study 104RA203 only*)
- Quantitative Ig (total IgA, IgG, and IgM). (*Study 104RA203 only*)

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Statistical Methods:

Descriptive statistics (all sections), analysis of variance (pharmacodynamics), and Cochran-Mantel-Haenszel test (efficacy).

Pharmacokinetics: Two complementary approaches to the analysis of the pharmacokinetic (PK) data were taken: (i) a population PK analysis of the combined dataset from studies 104RA203 and 104RA205 (All subjects PK dataset); and (ii) a noncompartmental analysis (NCA) of the data gathered from the intensive sampling groups in study 104RA203 (PK Subset 1) and 104RA205 (PK Subset 2). The PK was evaluated for the possible influence of various factors on the disposition of BG9924.

Results:

Subject disposition:

Study 104RA203 Placebo-Controlled Experience

- There were 115 subjects enrolled and randomized in Study 104RA203. Of those, 1 subject withdrew prior to dosing. Of the 114 subjects dosed, 38 received placebo and 76 received BG9924.
- Eighty-one subjects (71%) completed the treatment period. Sixteen subjects (14%) discontinued treatment for a variety of reasons, the majority of which were the Sponsor terminating the study. Nine subjects (8%) discontinued treatment due to an AE (8 subjects, [11%] in the BG9924 group and 1 subject, [3%] in the placebo group). Most subjects who discontinued treatment also withdrew from the study for the same reasons. Seventy-three subjects (64%) withdrew to enter Study 104RA205. Six subjects (5%) completed the study.

Study 104RA205 Open-Label Extension

- There were 74 subjects who entered and were dosed in Study 104RA205. Of these subjects, 30 had received placebo in Study 104RA203 and 44 had received BG9924 in Study 104RA203, which represents 79% of the subjects who received placebo in Study 104RA203 and 58% of the subjects who received BG9924.
- All of the 74 subjects who were dosed discontinued study treatment. Forty-six subjects (62%) discontinued for a variety of reasons, the majority of which were the Sponsor terminating the study. Most of these subjects also withdrew from the study. No subjects discontinued study treatment due to an AE. Only 3 subjects (4%) were able to complete the study (at the Week 72 follow-up visit as per Version 4 of the protocol).

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Demographics and baseline disease characteristics (Study 104RA203)

- Subjects were predominantly white (82%) and female (81%), with a median age of 55 years (range 24 to 74 years), and a median weight of 78.5 kg (range 43.3 to 228.2 kg).
- The subjects enrolled in this study were generally representative of a population with RA. Baseline disease characteristics were balanced between treatment groups. Among all subjects, the median SJC (66 joints) was 14.5, and the median TJC (68 joints) was 25. The median HAQ-disability index score for all subjects, assessed on a scale from 0 being best to 3 being worst, was 1.500. The median CRP concentration among all subjects was 1.165 mg/dL (ULN is 0.287 mg/dL). The median ESR among all subjects was 36.0 mm/h. The median Disease Activity Score, 28 joint version (DAS28) value (based on ESR) among all subjects was 6.409. Overall, 61% of subjects were positive for rheumatoid factor, and 66% of subjects were positive for anti-cyclic citrullinated peptide-2 (anti-CCP) antibody.
- The median time since RA onset was 9.50 years, ranging from 1.2 to 55.7 years. There was a slightly longer time since disease onset in the BG9924 group (10.8 years) compared to the placebo group (6.2 years). Overall, 9 subjects (8%) were RA functional class I, 68 subjects (60%) were class II, and 37 subjects (32%) were class III. No differences in disease history were observed between the treatment groups.

Efficacy:

- Treatment of subjects with BG9924 in Study 104RA203 was not efficacious when compared to subjects treated with placebo. At Week 14, the ACR50 response rates for BG9924 relative to placebo were 11% vs 5%. Similarly at Week 14, no significant changes were seen in the BG9924 group relative to placebo for secondary endpoints of ACR20 (14% vs 13%), ACR70 (1% vs 3%), or mean change from baseline DAS28 scores (-0.64 *vs* -0.67). Analysis of individual ACR core parameters showed no notable differences between BG9924 and placebo though slight trends towards improvement were seen in the BG9924 group for SJC and TJC.
- Assessments of fasting serum cholesterol, HDL, LDL, and triglycerides were added to Study 104RA203 via protocol amendment. In this subgroup of subjects, favorable clinical trends were noted at Week 6 for BG9924 relative to placebo, including mean percentage changes from baseline in LDL (-5.3% vs 2.2 %) and HDL (6.6% vs -1.0%).
- Exploratory endpoints included change in Sjogrens assessments in subjects with secondary Sjogrens syndrome: subject-reported dryness, including VAS (ocular, vaginal, skin, and oral) and OSDI. Due to very limited sample sizes, no formal conclusions can be made.

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Pharmacokinetics:

- The PK of BG9924 was consistent and predictable across the participating subjects. The concentration time profiles followed single compartment kinetics and reached steady-state levels at or after 6 weeks of dosing. The PK properties of BG9924 - low CL (population mean 0.458 L/day) and V (population mean 8.99 L), long half-life (approximately 13 days), fairly slow, but complete absorption (approximate T_{max} of 4.23 days; C_{max} of 17,200 ng/mL) - were in line with those expected with a molecule of this class.
- An influence of the immunogenicity on the exposure was observed yielding a CL increase for antibody-positive subjects by 43%, compared to antibody-negative subjects. Despite this effect, the steady-state concentration levels for antibody-positive individuals (43% lower compared to antibody-negative subjects) were still sizeable.
- No influence of the dosing material (BG9924-B vs BG9924-C) on the PK was captured by the PK data analyses performed.

Pharmacodynamics:

- There was clear evidence that BG9924 was biologically active based on peripheral blood lymphocyte counts, FACS data, and serum LIGHT data.
- Notable increases in lymphocyte counts were seen as early as Week 2 in Study 104RA203. The mean percentage change from baseline was 2.16 for the placebo treatment group and 30.93 for the BG9924 treatment group ($p<0.001$). FACS analysis data were available for 4 subjects in the placebo treatment group and 8 subjects in the BG9924 treatment group. These data suggest that the increase in lymphocyte counts was largely accounted for by an increase in CD3+ T cells, though it was not noted to be driven preferentially by either CD4+ or CD8+ T cells. Pharmacological effects of BG9924 treatment were additionally observed via increases in CD19+ cell counts, as well as increases in circulating IgD+ unswitched memory B cells and monocytes (CD14+ cell counts).
- There were also notable increases of serum LIGHT levels in Study 104RA203. The median value changed from approximately 80 pg/mL at baseline to about 350 pg/mL at Week 6 and 360 pg/mL at Week 14. For the placebo group, the median LIGHT levels remained at approximately 70 pg/mL at all 3 visits.
- No significant changes in cytokines (IL-1β, IL-6, IL-8, TNF-α, and IFN-γ) were observed.

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Safety:

All subjects who received at least 1 dose of study treatment were included in the safety analyses. Safety data was analyzed by treatment group for the placebo-controlled experience in Study 104RA203, by cumulative dosing of BG9924 200 mg every other week across Studies 104RA203 and 104RA205, and by first exposure of BG9924 in Study 104RA205. In general, the safety profile of BG9924 was similar between the different analyses, and data from the placebo-controlled and cumulative BG9924 experience is presented below.

Placebo-Controlled Experience (Study 104RA203)

- Overall, the incidence of AEs was slightly higher in the BG9924-treated subjects (72%) than in placebo-treated subjects (61%). The most common AEs (incidence of 10% or more) in BG9924-treated subjects were upper respiratory tract infection (17% BG9924 vs 5% placebo), rheumatoid arthritis (16% BG9924 vs 26% placebo), injection site erythema (11% BG9924 vs 0 placebo), and nausea (11% BG9924, 11% placebo). The majority of AEs were mild to moderate in severity. The incidence of severe events was similar between the 2 treatment groups (9% BG9924, 5% placebo).
- There was an increased incidence of serious adverse events (SAEs) in the BG9924-treated group, with SAEs reported by 5 subjects (7%), and by no subjects who received placebo. The majority of the events were considered unlikely or not related to study treatment. The only SAE considered related to study treatment was macular edema. Two cardiac events of myocardial infarction were reported. One subject had an ongoing history of cardiac risk factors and reported a pulmonary embolism, myocardial infarction, and subsequent worsening congestive heart failure. Other SAEs included pneumonia in one subject, and RA and gastric ulcer perforation in one subject.
- There were no deaths during Study 104RA203.
- Five percent of the placebo group and 13% of the BG9924 group discontinued treatment due to an AE; with the most common event being RA.
- The incidence of infection in BG9924-treated subjects (30%) was higher than that observed in the placebo group (21%). The most common infection after BG9924 treatment was upper respiratory tract infection (17% BG9924 vs 5% placebo). All infections were considered mild or moderate. One infection in the BG9924 group, pneumonia, was reported as an SAE. There were no opportunistic infections.
- No subjects developed malignancies during the study.
- There were no pregnancies during the study.
- There was an increased incidence of high WBC (37%) and lymphocyte (25%) counts in BG9924-treated subjects compared to placebo-treated subjects (20% and 3%, respectively). These increases are consistent with the expected biologic effect of BG9924 on cellular trafficking.
- The incidence of shifts to high in ALT (10% BG9924 vs 9% placebo) and AST (9% BG9924 vs 9% placebo) were similar in the BG9924 and placebo-treated groups. The majority of the shifts were less than 3 times the upper limit of normal, and none were associated with increases in total bilirubin. Overall, there was no evidence of hepatic or renal toxicity.

- Over the course of the study, 2 subjects (5%) in the placebo group were positive for anti-BG9924 antibodies, while 6 of 74 subjects (8%) in the BG9924 group were positive. Of subjects who tested positive for anti-BG9924 antibodies, none of the subjects in the placebo group were positive for blocking (neutralizing) antibodies, while 2 of the 6 subjects (33%) in the BG9924 group were positive for blocking antibodies. Thus, the overall incidence of blocking antibodies in the BG9924 group was 2 of 74 subjects (3%) evaluated for antibody levels. None of the 6 subjects with anti-BG9924 antibodies had AEs characteristic of those associated with anti-drug antibodies. An influence of the immunogenicity on the exposure was observed (see PK section above). The clinical relevance of anti-BG9924 antibodies is unknown.

Cumulative BG9924 Experience (Studies 104RA203 and 104RA205) for Subjects Receiving BG9924 in Study 104RA203

- The overall AE profile with cumulative BG9924 dosing was similar to that seen in the placebo-controlled study. Overall, 84% of subjects reported at least 1 AE. The most common AEs (≥10%) were RA, upper respiratory tract infection, nausea, headache, and injection site erythema.
- During the extension study, 2 additional subjects in the BG9924 group reported SAEs. The SAEs were considered unlikely or not related to study treatment. One subject with multiple cardiac risk factors reported coronary artery stenosis and experienced a post-procedure hemorrhage of the femoral artery. Another subject reported multiple SAEs as a complication of MTX toxicity, including epididymitis, renal failure, necrotizing fasciitis, drug toxicity, and sepsis. The subject died of multiple organ system failure, approximately 3 months after the last dose of BG9924. The event was assessed as not related to study treatment. This was the only death in the study.
- The incidence of infections was 45%. The only infections reported in ≥5% of BG9924-treated subjects were upper respiratory tract infection (24%) and sinusitis (5%).
- The incidence of subjects positive for anti-BG9924 antibody did not change with cumulative dosing (8 of 74 subjects, 11%). The overall incidence rate of blocking antibodies in the cumulative treatment group was 3%, which did not change from Study 104RA203.

Comparison of BG9924-B and BG9924-C

There was no difference in the incidence or types of AEs after administration of the stable liquid formulation of the drug product, BG9924-C.

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: Baminercept (BG9924)	**Name of Active Ingredient:** Baminercept (BG9924) hLTBR-hIgG1	**Study Indication:** Rheumatoid Arthritis

Conclusion(s):

In conclusion, in subjects with active RA who have had an inadequate response to anti-TNF therapy:

- BG9924 did not exhibit efficacy in subjects with RA refractory to TNF inhibitors.
- The PK of BG9924 was consistent and predictable across the participating subjects. An influence of the immunogenicity on the exposure was observed, yielding a 43% CL increase for antibody-positive subjects. No influence of the dosing material (BG9924-B vs BG9924-C) on the PK was captured by the PK data analyses performed.
- Analysis of peripheral blood lymphocyte counts, FACS data, and serum LIGHT data provided compelling evidence of LTBR biologic activity.
- Overall, BG9924 appears to be well tolerated when administered in combination with MTX in RA subjects. There was a slight increase in infections, most commonly upper respiratory tract infections. During the dosing period, there was an increased incidence of elevations of WBCs and lymphocytes consisted with the postulated mechanism of action. There did not appear to be evidence of hepatic or renal toxicity.
- The PK, pharmacodynamics, and safety results of these studies support the development of BG9924 in other indications. The BG9924-C formulation of the drug product appears to be suitable for use in future studies of BG9924.

Publication(s) Based on the Study:

None.

Date of Report: 25 November 2009