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

Title of Studies:

104RA202: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Finding 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 Conventional DMARD Therapy

EudraCT number: 2006-005466-39

104RA204: A Blinded 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 104RA202

EudraCT number: 2007-000733-19

Principal Investigator/Coordinating Investigator:

[redacted]
UK [redacted]

Study Period: Date of first treatment: **104RA202:** 11 July 2007 **104RA204:** 15 November 2007 Last Subject, Last Visit: **104RA202:** 09 October 2008 **104RA204:** 13 January 2009 Date of early study termination: 09 October 2008 (104RA204 only)	**Phase of Development:** 2b

Study Objective(s):

<u>Study 104RA202</u>

Primary objective(s):

- To evaluate the efficacy of 5 dose regimens of BG9924 (5 mg every other week [eow], 70 mg eow, 200 mg eow, 70 mg monthly, and 200 mg monthly) when administered in combination with methotrexate (MTX) to subjects with active rheumatoid arthritis (RA) who have had an inadequate response to conventional disease-modifying anti-rheumatic drug (DMARD) therapy.

Secondary objective(s):

- To assess the safety and tolerability of these 5 dose regimens of BG9924 in this subject population.
- To assess the pharmacokinetic (PK) and pharmacodynamic (PD) profile of these 5 dose regimens of

BG9924 in this subject population.

Study 104RA204

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 104RA202.

Secondary objective(s):

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

Study Design:

Study 104RA202

This was a randomized, double-blind, placebo-controlled, multicenter, dose-finding study. Approximately 380 subjects were to be enrolled at approximately 60 sites. Subjects could participate in this study for up to 26 weeks. Over the treatment period, subjects were to receive BG9924 (1 of 5 dosing regimens) or placebo by subcutaneous (SC) injection, eow for 12 weeks (including a loading dose, with the first half given at Week 0 and the second half at Weeks 1 or 2), 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 to be offered the option to enter a safety extension study (104RA204). Subjects who did not enroll in the extension study were to be followed for safety assessments for an additional 12 weeks (until Visit 12/Week 26) under this protocol.

Study sites could choose to participate in an optional PK sub-study. Approximately 50 consenting subjects were to have 6 additional visits for blood draws following Visits 1 (Visits 1a and 1b), 3 (Visit 3a), and 8 (Visits 8a, 8b, and 8c). Blood samples for fluorescence-activated cell sorter (FACS) analysis were also to be taken from subjects participating in this sub-study.

Study 104RA204

This was a blinded extension study of BG9924 in subjects with active RA who had previously participated in Study 104RA202. Subjects could enter the study on or after the Visit 9/Week 14/Early Withdrawal Visit in Study 104RA202, but no later than the Visit 12/Week 26/Late Withdrawal Visit in Study 104RA202. Depending on when a subject entered the study, either the Study 104RA202 Week 14 visit or Week 26 visit served as the Study Entry Visit for this extension study.

Up to 380 subjects were to be enrolled at approximately 60 sites. Subjects could participate in this study for up to 18 months. Over the treatment period, subjects were to receive BG9924 by SC injection, every other week for approximately 15 months, with follow-up visits at Weeks 60, 64, and 72 (2, 6, and 14 weeks, respectively, after the last dose).

Early Termination of Studies:

Based on the results of the double-blind, placebo-controlled dose finding study (104RA202), in which the study did not meet its primary efficacy endpoint, as well as on preliminary results of Study 104RA203 (a Phase 2b study in subjects with RA who have had an inadequate response to anti-tumor necrosis factor therapy), Biogen Idec decided to suspend dosing of BG9924, close the extension study (104RA204), and terminate all additional ongoing

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clinical studies on 09 October 2008. All subjects entered a modified safety follow-up and were seen at least 8 weeks after their last dose of BG9924, with the last subject seen on 13 January 2009.

Number of Subjects (Planned and Analyzed):

Study 104RA202

Planned: Approximately 380 subjects
Randomized: 391 subjects
Dosed: 391 subjects
Analyzed: 391 subjects

Study 104RA204

Planned: Approximately 380 subjects
Randomized: Not applicable; 339 subjects entered the study
Dosed: 339 subjects
Analyzed: 339 subjects

Study Population:

Study 104RA202

Main inclusion criteria:

- Aged 18 to 75 years old, inclusive, at the time of informed consent.
- Must have a diagnosis of adult onset RA according to the 1987 Revised American Rheumatism Association Criteria for the Classification of Rheumatoid Arthritis (Functional Class I – III) for at least 6 months prior to Day 0.
- Must have active disease defined as Swollen Joint Count (SJC) ≥8 and a Tender Joint Count (TJC) ≥8 (66/68 joint count at Screening).
- Must have 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.
- Must have been treated with, and tolerated, 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 had an inadequate response to at least 1 conventional DMARD therapy (i.e., MTX, leflunomide, sulfasalazine, etc.) due to inadequate efficacy or toxicity.
- Must have been willing to receive oral folate (≥5 mg/week) for the duration of the study.

Main exclusion criteria:

- 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 or positive purified protein derivative test during the screening period.

Laboratory Tests:

- Clinically significant laboratory tests at screening.
- Positive for hepatitis C antibody or hepatitis B infection (defined as positive for HBsAg and/or positive for HBcAb IgM) at Screening.

Study 104RA204

Main inclusion criteria:

- Must have been a subject from Study 104RA202 who received at least 6 doses of study treatment.
- Must have been receiving treatment with MTX (≥10 mg/week to ≤25 mg/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 104RA202).

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

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

Study 104RA202: BG9924-B was given by SC injection at doses of 5 mg eow, 70 mg eow, 200 mg eow, 70 mg monthly, and 200 mg monthly for 12 weeks. Doses administered were from Lot [redacted]

Study 104RA204: Subjects were to receive BG9924 by SC injection at doses of 70 mg eow, 200 mg eow, 70 mg monthly, and 200 mg monthly for approximately 15 months. 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

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administered by SC injection.

Duration of Treatment and Follow-Up:

Study 104RA202

Treatment period: The duration of treatment was to be 12 weeks.

Follow-up period: One visit 2 weeks after the last dose. Subjects who did not enroll in the extension study were to be followed for safety assessments for an additional 12 weeks.

Study 104RA204

Treatment period: The duration of the study was to be 15 months.

Follow-up period: One visit 2 weeks after the last dose was required. The remaining visits (6, 10, and 14 weeks after the last dose) were optional.

Study termination modified safety follow-up: subjects were seen at least 8 weeks following 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-DI], subject's assessment of pain on visual analog scale [VAS], CRP, and ESR).
- Quality of life (Short Form-36, Functional Assessment of Chronic Illness Therapy-Fatigue) and Sjogrens assessments were to be performed.
- Disease Activity Score, 28 joint version (DAS28) in study 104RA202 only.

BG9924 Concentration Measurements:

Serum concentrations of BG9924 were to be measured to support the pharmacokinetic (PK) evaluations in these studies. From these data, a number of exposure measures were to be calculated via both noncompartmental and compartmental analyses, such as: area under the time-concentration curve from pre-dose to the last measurable value within a dosing interval (AUC_{tau}); area under the time-concentration curve from pre-dose to infinity (AUC_{inf}); maximum concentration (C_{max}), reported as the highest observed concentration; time of the maximum concentration (T_{max}); terminal half-life ($t_{1/2}$); clearance (Cl); and, volume of distribution (V). These parameters were calculated after a single (first) dose and at steady state.

Pharmacodynamics (PD):

PD measurements, including disease markers, as well as markers for drug activity, were to be reviewed for the existence of patterns with time and drug exposure. If applicable, the maximum or minimum values and times to achieve those maximum and minimum values were to be documented and reported.

RA disease markers

- hsCRP
- Erythrocyte sedimentation rate (ESR)

- Rheumatoid factor (RF)
- Anti-cyclic citrullinated peptide-2 (CCP-2) antibody
- Serum BAFF (B cell activation factor from the TNF family)
- Cartilage oligomeric matrix protein (COMP)
- Calgranulin
- Matrix metalloproteinase 3 (MMP3)

PD Assessments (104RA202 only)

- Quantitative FACS analysis (only in those subjects taking part in the optional intensive PK sub-study):
    - Leukocyte subset analysis: CD3+, CD4+, CD8+, CD19+, CD16+, CD56+, and CD14+
    - Increased unswitched memory B cells: CD19+, IgD+, IgM+, and CD27+
- Cytokine panel (including but not limited to IL-1β, IL-6, IL-8, TNF-α, and IFN-γ)

Genetic DNA Testing (104RA204 only)

Genetic DNA testing was to be an optional study assessment and could include the following parameters:

- Genes known to be associated with RA (including but not limited to HLA-shared epitope, PTPN22, CTLA4, and PAD14) and other autoimmune diseases (including but not limited to CCR2, CCR3, CCR5, CD14, TLRs, IL-1, IL-10, IL-13, IL-4, IRF5, KIM1, runx1, and SLC22A4)
- Genes associated with the lymphotoxin pathway (LTβ, LTα, LTBR, and additional genes in the LTBR signaling pathway)
- Genes associated with binding of Fc fusion proteins to cells (including but not limited to Fc receptors)

Safety:

The following clinical and laboratory tests were to be performed to assess the safety profile of BG9924**:**

Clinical

- Physical examination (PE)
- Vital signs
- Electrocardiogram (ECG)
- Monitoring of adverse events (AEs)
- Monitoring of concomitant therapy

Laboratory

- Urinalysis (protein, glucose, ketones, occult blood, and white blood cells by dipstick and microscopic examination, if indicated)
- Blood chemistry (Alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, total protein, albumin, cholesterol, total bilirubin, blood urea nitrogen, uric acid, creatinine, lactate dehydrogenase, potassium, sodium, chloride, calcium, phosphorous, bicarbonate, and glucose)
- Hematology (hemoglobin, hematocrit, red blood cell count, white blood cell [WBC] count [absolute and differential counts], and platelet count)

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- Serum anti-BG9924 antibody assay
- **104RA202 only**: International normalized ratio (for anticoagulant monitoring [INR]), prothrombin time (PT), and activated partial thromboplastin time (aPTT); anti-nuclear antibody (ANA) and anti-dsDNA antibody assays; quantitative Immunoglobulin (Ig; total, IgA, IgG, and IgM); and leukocyte subset analysis: CD3+, CD4+, CD8+, CD19+, CD16+, CD56+, and CD14+

Statistical Methods:

Demographics and Safety: Descriptive statistics and summary tables were used to depict subject demographics and background information, safety information (PE, vital signs, ECG, AEs), and laboratory evaluations.

Efficacy: Descriptive statistics, including bar chart summaries, and the Cochran-Mantel-Haenszel test were used to evaluate the efficacy of BG9924. Summary statistics, including graphical displays, and an analysis of variance were used to assess the PD properties of BG9924.

Pharmacokinetics: Two complementary approaches to the analysis of the PK data were taken: (i) a population PK analysis of the all subject dataset (All PK dataset), and (ii) a noncompartmental analysis of the data gathered from the intensive sampling group in Study 104RA202 (PK subset). The PK was evaluated for the possible influence of various factors on the disposition of BG9924.

Results:

Subject disposition:

Study 104RA202

There were 391 subjects randomized to receive study treatment and none withdrew prior to dosing. Of the 391 subjects dosed, 79 received placebo and 312 were administered BG9924. The numbers of subjects by dose of BG9924 were as follows: 78 (5 mg eow); 78 (70 mg eow); 78 (200 mg eow); 39 (70 mg monthly); and 39 (200 mg monthly). Of the 391 subjects dosed, 365 (93%) completed the treatment period. There were 26 subjects (7%) who discontinued study treatment. Of these subjects, 9 (11%) received placebo, and the remaining 17 (5%) were administered BG9924. The most common reason for discontinuation in the placebo and BG9924-treated groups was an AE, reported in 3 (4%) and 6 (2%) of subjects, respectively. Of the 315 withdrawals from the study, 286 subjects (73%) entered the safety extension study (104RA204). There were 13 subjects (3%) who withdrew consent, 8 subjects (2%) who withdrew due to an AE, 4 subjects (1%) who were lost to study follow-up, and 2 subjects (<1%) each who withdrew due to disease progression or on the basis of an Investigator decision.

Study 104RA204

Three-hundred thirty-nine subjects who participated in the placebo-controlled study were entered and dosed in the extension study. Sixty-six of these subjects received placebo in the placebo-controlled study (first exposure to BG9924 in the extension study), and 273 subjects either remained on the same dose of BG9924 that they received in the placebo controlled study, or were administered a higher dose of BG9924.

Demographics and baseline disease characteristics:

- Subjects were predominantly white (88%) and female (86%), with a median age of 51 years (range 19 to 75 years), and a median weight of 69.8 kg (range 49 to120 kg).
- The subjects enrolled in this study were generally representative of a population with RA. Baseline

disease characteristics were balanced between treatment groups in this study.

- The median time since RA onset was 5.3 years, ranging from 0.5 to 42.4 years. There was a slightly longer time since disease onset in the BG9924 group (5.6 years) compared to the placebo group (4.1 years). Overall, 35 subjects (9%) were RA functional class I, 252 subjects (64%) were class II, and 104 subjects (27%) were class III. No remarkable differences in disease history were observed between the treatment groups.
- The medians for SJC and TJC were 15 and 26, respectively. HAQ-DI, CRP, and ESR median values were 1.625, 1.06 mg/dL, and 45 mm/hr, respectively. DAS28 median scaled score was 6.849, with a range from 3.82 through 8.64.
- The number of RF positive subjects was 312 (80%). The number of Anti-CCP2 positive subjects was 313 (80%).

Efficacy:

- Treatment with BG9924 in Study 104RA202 was not efficacious compared to treatment with placebo based on ACR or DAS28 criteria. There was no statistically significant difference between any BG9924 treatment group (14%, 14%, 12%, 8%, and 18% for 5 mg, 70 mg, or 200 mg eow, and 70 mg or 200 mg monthly, respectively) and placebo (11%) in the percentage of subjects achieving ACR50 at Week 14. Similarly, at Week 14 there was no statistically significant difference between BG9924 treatment groups relative to placebo for secondary endpoints of ACR20, ACR70, or change from baseline in the individual ACR core set parameters and DAS28 scores based on ESR.

Pharmacokinetics:

- The PK of BG9924 was consistent and predictable across the dosing arms and the participating subjects. The concentration time profiles followed single compartment with first order absorption kinetics and reached steady state (SS) levels at or after 6 weeks of dosing. The PK properties of BG9924, such as low Cl (population mean 0.512 L/day) and V (population mean 9.02 L), long half-life (approximately 13.2 days), and fairly slow, but complete absorption (T_{max} approximately 4.24 days), 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 (Ab) positive subjects. Despite this effect, the SS concentration levels for Ab-positive subjects in the highest dose arms (70 mg and 200 mg eow) were still sizeable.
- The observed PK variability was moderate to high, probably enhanced by the antibody-dependent exposure.

Pharmacodynamics:

- There was clear evidence that BG9924 was biologically active.
- Treatment with Baminercept resulted in a notable dose-dependent increase in total blood lymphocytes from baseline relative to placebo by Week 2. The mean percentage change from baseline was 15.31 for the placebo treatment group, 14.34 for the 5 mg eow treatment group ($p=0.874$ for comparison versus placebo), 34.85 for the 70 mg eow treatment group ($p=0.002$), 37.54 for the 200 mg eow treatment group ($p<0.001$), 23.05 for the 70 mg monthly treatment group ($p=0.311$), and 35.82 for the 200 mg monthly

treatment group (p=0.006). These increases were maintained through the 12 week treatment period.

- There were notable increases of serum LIGHT levels with all doses of BG9924 compared to placebo. The median LIGHT levels continued to increase up to Week 14, with the exception of the 5 mg BG9924 eow dose group, which had median LIGHT levels similar to baseline.
- No significant changes in cytokine levels (IL-1β, IL-6, IL-8, TNF-α, and IFN-γ) were observed.

Safety:

Safety data have been summarized by treatment group for the placebo-controlled experience in Study 104RA202, cumulative dosing by treatment group in Studies 104RA202 and 104RA204, first exposure by treatment group in Study 104RA204, and the overall BG9924 experience by exposure which included data from all subjects who received BG9924 at any time in Studies 104RA202 and 104RA204. In general, the safety profile for BG9924 was similar between the different analyses, and data from the placebo-controlled and overall BG9924 experience is presented below:

- Overall, BG9924 appeared well tolerated when administered in combination with MTX to RA subjects with an inadequate response to DMARD therapy.
- In the placebo-controlled experience, the incidence of AEs was similar in placebo-treated subjects (56%) and BG9924-treated subjects (57%). Compared to placebo, AEs reported with an increased incidence in BG9924-treated subjects (difference of 3% or more) included influenza (1% versus 5%), pyrexia (0% versus 5%), nasopharyngitis (1% versus 4%) and upper respiratory tract infection (0% versus 3%), respectively. The majority of AEs were mild to moderate in severity. The incidence of severe AEs was balanced between placebo- and BG9924-treated subjects (5% each). No dose relationship was observed.
- During the overall BG9924 experience, 67% of BG9924-treated subjects experienced at least 1 AE. The most common AEs (≥5%) were rheumatoid arthritis, headache, pyrexia, cough, upper respiratory tract infection, influenza, nasopharyngitis, nausea, diarrhea, and injection site pain. The incidence of AEs was similar across the different dosing groups and did not increase in a dose-dependent manner.
- In the placebo-controlled experience, the incidence of discontinuations of study treatment (5% versus 3%) and withdrawal of study treatment (5% versus 2%) due to AEs was low and similar between placebo-treated subjects and BG9924-treated subjects, respectively.
- In the placebo-controlled experience, 4 (5%) placebo-treated subjects and 12 (4%) BG9924-treated subjects reported at least 1 SAE. During the overall BG9924 experience, a total of 25 (7%) BG9924-treated subjects reported a SAE. The majority of SAEs were considered unlikely or not related to study treatment. SAEs considered possibly related or related to study treatment included pneumonia in the placebo group and hypersensitivity reaction, RA flare, esophageal candidiasis, liver disorder, tuberculosis, and injection site vasculitis/necrotizing vasculitis in the BG9924 group.
- In the placebo-controlled experience, the incidence of infections was slightly increased in BG9924-treated subjects (27%) compared to placebo-treated subjects (23%). Infections seen at a higher incidence in BG9924-treated subjects compared to placebo-treated subjects (difference of 3% or more) included influenza (5% versus 1%), nasopharyngitis (4% versus 1%), and upper respiratory tract infection (3% versus 0%).
- During the overall BG9924 experience, 36% of BG9924-treated subjects experienced at least 1 infection.

Infections reported in ≥5% of subjects included upper respiratory tract infection (6%), influenza (5%), and nasopharyngitis (5%).

- In the placebo-controlled experience, serious infections were reported in 1 (1%) placebo-treated subject and 2 (<1%) BG9924-treated subjects. Serious infections included pneumonia in the placebo-treated subject and atypical pneumonia and esophageal candidiasis in the BG9924-treated subjects. During the overall BG9924 experience, a total of 5 serious infections (1%) were reported in BG9924-treated subjects. The 3 additional serious infections in BG9924-treated subjects included tuberculosis, gastroenteritis, and dengue fever.
- During the overall BG9924 experience, there were 2 subjects with reported hypersensitivity reactions. One subject with a history of asthma had a serious hypersensitivity reaction after the third dose of study treatment in the extension study that was characterized by bronchospasm, tachycardia, and hypotension that was treated with IV steroids, fluids, and inhaled salbutamol. Another subject with history of Sjogren's syndrome had a moderate episode of skin rash and facial edema after the first dose of study treatment in the extension study. The event responded to dexamethasone.
- During the placebo-controlled experience, there were no deaths in the study. During the overall BG9924 experience, there were 2 deaths, both of which were assessed as unlikely or not related to study treatment. One subject, who lived in an endemic area, developed dengue fever and died from dengue shock syndrome. A second subject, who discontinued study treatment due to tuberculosis, died after the end of study. The Investigator stated that the death was not related to tuberculosis or to study treatment.
- There was 1 malignancy reported in a subject who was diagnosed with breast cancer after her third dose of BG9924 (70 mg monthly) in the placebo-controlled study. The Investigator assessed this event as not related to BG9924.
- There were no pregnancies reported during the study.
- In the placebo-controlled and overall BG9924 experience, there were notable increases in WBC, lymphocytes, and neutrophils in BG9924-treated subjects compared to placebo-treated subjects during the dosing period. These increases are consistent with an expected effect of BG9924 on cellular trafficking.
- There were no clinically significant changes in coagulation tests (INR, PT, and aPTT) in BG9924-treated subjects compared to placebo.
- In the placebo-controlled experience, the incidence of shifts to high in ALT (28% versus 17%) and AST (14% versus 13%) were similar in placebo-treated subjects and BG9924-treated subjects, respectively. The majority of shifts was less than 3 times the upper limit of normal, transient in nature, and not associated with increases in total bilirubin. One subject reported an SAE of liver disorder characterized by high levels of ALT and AST greater than 10 times the upper limit of normal without any associated changes in total bilirubin or hepatic dysfunction that occurred 3 weeks after the last dose of study treatment. The Investigator assessed this event as related to study treatment, methotrexate, and sulfasalazine. Overall, there was no clear evidence of hepatotoxicity.
- There were no clinically significant changes in urinalyses, vital signs, physical exams, and ECGs.
- In the placebo-controlled and overall BG9924 experience, there was no clinically significant changes in total immunoglobulins (Igs), immunoglobulin subclasses (IgM, IgA and IgG), or protective antibody titers

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to tetanus toxoid.

- No significant changes from baseline were detected in the number of subjects with positive ANA results.
- In the placebo-controlled experience, anti-BG9924 antibodies were detected at any time in 4% (3/79) of placebo-treated subjects and 37% (114/309) of BG9924-treated subjects. Of subjects who tested positive for anti-BG9924 antibodies at any time, blocking antibodies were detected in none (0/3) of the placebo-treated subjects and in 41% (47/114) of the BG9924-treated subjects. There was an inverse correlation in the incidence of anti-BG9924 antibodies and dose.

Conclusion(s):

- BG9924 did not exhibit efficacy when given in combination with MTX to subjects with active RA who had an inadequate response to conventional DMARD therapy.
- Analyses of peripheral blood lymphocyte counts, FACS data, and serum LIGHT data provided compelling evidence that BG9924 was biologically active.
- Overall, BG9924 appeared to be well tolerated when given in combination with methotrexate to RA subjects with prior inadequate response to DMARDs. The incidence of AEs, SAEs, and serious infections was similar between placebo- and BG9924-treated subjects. However, there was a slight increase in infections, most commonly influenza, nasopharyngitis and upper respiratory tract infections. Increases in WBCs, lymphocytes and neutrophils were observed, consistent with an expected effect of BG9924 on cell trafficking. There was no clear evidence of hepatotoxicity or renal toxicity.
- The PK of BG9924 is consistent and predictable across the dosing arms and participating subjects. A marked influence of the immunogenicity on the exposure was observed yielding a Cl increase for Ab-positive subjects. Despite this effect, the SS concentration levels for Ab-positive individuals in the highest dose arms (70 mg and 200 mg eow) were still sizeable.

Publication(s) Based on the Study:

None to date

Date of Report: 4 December 2009