These Clinical Study Results are provided for informational purposes only.

The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the overall results obtained across the product development. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult prescribing information for the product approved in their country.

2. STUDY SYNOPSIS

Name of Sponsor/Company: Biogen MA Inc./Biogen Idec Research Limited	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: BIIB023	**Name of Active Ingredient:** BIIB023	**Study Indication:** Lupus Nephritis

Title of Study:

A Dose-Blinded, 2-Dose Level, Parallel-Group, Multicenter, Long-Term Extension Study to Evaluate the Long-Term Safety, Efficacy, and Immunogenicity of BIIB023 in Subjects With Lupus Nephritis

Number of Study Sites and Countries:

Forty-two Investigators at 42 sites located in 19 countries participated in this study.

Study Period:	**Phase of Development: 2**
Date of first treatment: 22 November 2013 End of study date: 15 January 2015 Date of early study termination: 08 October 2015	

Study Objective(s):

The primary objective was analyzed for this abbreviated clinical study report (CSR). Study 211LE202 was terminated based on the review of results following the pre-specified, blinded futility analysis of Study 211LE201, which did not demonstrate sufficient efficacy to warrant continuation of the studies. The study was not terminated based on safety considerations.

Primary Objective

The primary objective of the study was to evaluate the long-term safety and tolerability of BIIB023 in subjects with lupus nephritis (LN).

Additional Objectives

Additional objectives of this study were not analyzed due to early study termination.

Primary Endpoints

1. Incidence of adverse events (AEs) and serious adverse events (SAEs).
2. Discontinuation of study treatment or withdrawal from the study due to an AE.

Study Design:

Study 211LE202 was a dose-blinded, 2-dose level, parallel-group, multicenter, long-term extension study for all subjects who completed Study 211LE201 through Week 52 and did not discontinue BIIB023 or placebo. Eligible subjects from Study 211LE201 were followed for up to 108 weeks, provided that BIIB023 continued to have a positive benefit/risk ratio in the overall study population.

This study was expected to be conducted at approximately 160 sites globally. Approximately 220 subjects were planned to be enrolled to the Dose-Blinded, 2-Dose Level Treatment Period. Subject eligibility was determined at

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Baseline (Day 1 of Study 211LE202) and was based on laboratory assessments conducted at Week 48 of Study 211LE201 and on the urine pregnancy test assessed at Baseline (Day 1). Subjects were expected to complete 28 study visits over the course of the study (including the Baseline Visit). Subjects were to report to the study site every 4 weeks (Q4W) up to Week 108.

Subjects were enrolled at Baseline (Day 1) after confirmation of eligibility. For subjects enrolled in Study 211LE202, it was preferred that the Week 52 Visit of Study 211LE201 served as the Baseline (Day 1) Visit of Study 211LE202, such that laboratory, efficacy, and safety assessments conducted for the Week 52 Visit of Study 211LE201 could be used as Baseline (Day 1) assessments of Study 211LE202. In the event that the visits could not occur on the same day, the Baseline Visit in Study 211LE202 must have occurred within 14 days of the Week 52 Visit in Study 211LE201 and Baseline assessments must have been conducted on their day of enrollment.

Subjects randomized to 3 or 20 mg/kg BIIB023 intravenous (IV) infusion in Study 211LE201 remained on their blinded randomized treatment as an add-on treatment to background therapy (including mycophenolate mofetil [MMF] and oral corticosteroids [prednisone or equivalent]) through Week 100 in Study 211LE202. Subjects who were randomized to placebo in Study 211LE201 were randomized in a 1:1 ratio to 3 or 20 mg/kg BIIB023 IV infusion as add-on to background therapy (including MMF and oral corticosteroids [prednisone or equivalent]) through Week 100 in Study 211LE202. Subjects were to receive their first administration of study treatment in Study 211LE202 on the day of randomization.

As part of their standard of care, all subjects enrolling in the extension study were treated with MMF and an oral corticosteroid (prednisone or equivalent) according to the treating physician (MMF dose up to a maximum dose of 3 g/day; no minimum dose of MMF and no minimum or maximum dose of oral corticosteroids was required to remain in the study). Eligible subjects were to receive IV infusions of 3 or 20 mg/kg BIIB023 (as add-on treatment to background therapy) Q4W from Baseline (Day 1) through Week 100. Study treatment was administered by IV infusion over 1 hour, followed by at least a 1-hour observation period for safety assessments.

There were 4 treatment groups in this study:

1. Treatment Group 1 (placebo/3 mg BIIB023): subjects who received placebo during Study 211LE201 and were randomized to receive 3 mg/kg BIIB023 in Study 211LE202
2. Treatment Group 2 (3 mg/3 mg BIIB023): subjects who received 3 mg/kg BIIB023 during Study 211LE201 and were continued on the same dose in Study 211LE202
3. Treatment Group 3 (placebo/20 mg BIIB023): subjects who received placebo during Study 211LE201 and were randomized to receive 20 mg/kg BIIB023 in Study 211LE202
4. Treatment Group 4 (20 mg/20 mg BIIB023): subjects who received 20 mg/kg BIIB023 during Study 211LE201 and were continued on the same dose in Study 211LE202

Follow-Up Visits were to occur at Week 104 (End of Treatment/Early Withdrawal Visit) and Week 108 (Safety Follow-Up Visit/End of Study Visit).

Subjects who prematurely discontinued study treatment and withdrew from the study should have performed Early Withdrawal study assessments at the time of withdrawal. In addition, subjects who permanently discontinued study treatment and withdrew from the study were encouraged to return for a Follow-Up Visit 8 weeks following their last dose of study treatment to perform all End of Study assessments. Subjects who prematurely discontinued

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study treatment were withdrawn from the study.

Number of Subjects (Planned and Analyzed):

Planned: The planned enrollment for the study was approximately 220 subjects at approximately 160 sites globally.

Analyzed: Of the 87 enrolled subjects, all were randomized to the Dose-Blinded, 2-Dose Level Treatment Period. Fourteen subjects (16%) were in the placebo/3 mg BIIB023 treatment group, 33 subjects (38%) were in the 3 mg/3 mg BIIB023 treatment group, 13 subjects (15%) were in the placebo/20 mg BIIB023 treatment group, and 27 subjects (31%) were in the 20 mg/20 mg BIIB023 treatment group.

Study Population:

Main Inclusion Criteria

1. Subjects who completed Week 52 of Study 211LE201 and did not discontinue BIIB023 or placebo study treatment.

Main Exclusion Criteria

1. Any significant change in medical history in subjects from Study 211LE201, including laboratory tests or current clinically significant condition that, in the opinion of the Investigator, would have excluded the subjects' participation. The Investigator must have re-reviewed the subject's medical fitness for participation and considered any diseases that would have precluded treatment under this study.
2. Subjects from Study 211LE201 who discontinued BIIB023 or placebo treatment prior to Week 52 of Study 211LE201.
3. Previous participation in Study 211LE202; subjects who were enrolled in Study 211LE202 and consequently withdrew for any reason are prohibited from re-entering the study.
4. Subjects who were prescribed MMF >3 g/day during Study 211LE201 and/or subjects for whom the Investigator was planning to prescribe MMF >3 g/day during this study.
5. Subjects having received disallowed concomitant medication during Study 211LE201, including the following:
   - Immunosuppressant used for therapy of LN (cyclophosphamide, nitrogen mustard, chlorambucil, vincristine, procarbazine, etoposide, mycophenolic acid, azathioprine, cyclosporine, methotrexate, atacicept, or any biologic B-cell-depleting therapy (e.g., anti-CD20 [rituximab], anti-CD22 [epratuzumab], or anti-BLyS/B-cell activating factor [e.g., belimumab] therapy)
   - Treatment with Campath® (alemtuzumab)
   - Anti-tumor necrosis factor (infliximab, adalimumab, etanercept, efalizumab, or alefacept) treatment

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- Cyclophosphamide, calcineurin, or a calcineurin inhibitor (i.e., cyclosporine A or tacrolimus)

6. Subjects with the following laboratory test results at Week 48 of Study 211LE201:
   - Absolute neutrophil count $<1.5 \times 10^3/\mu L$
   - Platelet count <20,000/µL; subjects with platelet count >20,000/µL and <150,000/µL who were experiencing, or were at high risk for developing, clinically significant bleeding or organ dysfunction requiring therapy (as determined by the Investigator)
   - Hemoglobin <8.5 g/dL
   - Aspartate aminotransferase (AST)/serum glutamate oxaloacetate transaminase or alanine aminotransferase (ALT)/serum glutamate pyruvate transaminase >2 × upper limit of normal (ULN) established by the central laboratory

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

Subjects randomized to 3 or 20 mg/kg BIIB023 IV infusion in Study 211LE201 were to remain on their allocated treatment as an add-on to background therapy (MMF and oral corticosteroids) through Week 100 of Study 211LE202. Subjects who were randomized to placebo in Study 211LE201 were randomized in a 1:1 ratio to 3 or 20 mg/kg BIIB023 IV infusion as add-on treatment to background therapy through Week 100 of Study 211LE202. All subjects enrolled in Study 211LE202 were blinded to their dose level. Subjects were to receive administration of BIIB023 at 26 study visits (Day 1 [Baseline], Week 4, Week 8, and Q4W thereafter through Week 100).

The lot numbers of the BIIB023 100-mg/mL vials used in this study were [redacted].

Comparator Therapy/Therapies, Dose, Mode of Administration, Batch Numbers:

Open-label MMF was provided to all of the study sites. The batch numbers for the MMF 500-mg tablets used in this study at sites in the United States were [redacted].The lot numbers for the MMF 500-mg tablets used in this study at sites in the rest of the world were [redacted].

Corticosteroid therapy was specified as prednisone doses, but equivalent doses of other corticosteroids were permitted. The subjects were to obtain corticosteroid therapy by prescription.

Duration of Treatment and Follow-Up:

Subjects were enrolled at Baseline (Day 1) after confirmation of eligibility. Laboratory assessments conducted at Week 48 of Study 211LE201 and the urine pregnancy test assessed at Baseline (Day 1) were used to determine eligibility for Study 211LE202. For subjects who were enrolled in Study 211LE202, the Week 52 Visit of Study 211LE201 could serve as the Baseline (Day 1) Visit of Study 211LE202, such that laboratory, efficacy, and safety assessments conducted for the Week 52 Visit of Study 211LE201 could be used as Baseline (Day 1) assessments of Study 211LE202. In the event that the visits could not occur on the same day, the Baseline Visit of Study 211LE202 must have occurred within 14 days of the Week 52 Visit in Study 211LE201, and baseline assessments must have been conducted on the subject's day of enrollment.

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Subjects randomized to 3 or 20 mg/kg BIIB023 in Study 211LE201 remained on their blinded randomized treatment through Week 100 of Study 211LE202. Subjects who were randomized to placebo in Study 211LE201 were randomized at a 1:1 ratio to 3 or 20 mg/kg BIIB023 IV infusion through Week 100 of Study 211LE202. Subjects were to receive their first administration of study treatment on the day of randomization.

As part of their standard of care, all subjects enrolling in the extension study were treated with MMF and an oral corticosteroid (prednisone or equivalent) according to the treating physician (MMF dose was up to a maximum dose of 3 g/day; no minimum dose of MMF and no minimum or maximum dose of oral corticosteroids were required to remain in the study). Eligible subjects were to receive monthly IV infusions of 3 or 20 mg/kg BIIB023 (as an add-on treatment to background therapy) Q4W from Baseline (Day 1) through Week 100. Study treatment was administered by IV infusion for 1 hour, followed by at least a 1-hour observation period for safety assessments.

Subjects who prematurely discontinued study treatment and withdrew from the study should have performed Early Withdrawal study assessments at the time of withdrawal. In addition, subjects who permanently discontinued study treatment and withdrew from the study were encouraged to return for a Follow-Up Visit 8 weeks after their last dose of study treatment to perform all End of Study assessments. Subjects who prematurely discontinued study treatment were withdrawn from the study.

Subjects who withdrew from Study 211LE202 for any reason were prohibited from re-entering the study and re-starting study treatment.

Criteria for Evaluation:

The following is a description of all efficacy and safety assessments that were originally planned for this study.

Efficacy:

- Proportion of subjects who develop antibodies to BIIB023
- Incidence of partial renal response
- Incidence of complete renal response
- Time to complete renal response in subjects without complete renal response at baseline
- Duration of renal response
- Proportion of subjects who experience a new renal flare
- Time to renal flare
- Time to first nonrenal systemic lupus erythematosus (SLE) flare
- Time to a major adverse renal event defined as the occurrence of one of the following:
  - New renal flare during the Dose-Blinded Treatment Period
  - Sustained doubling (present in 2 consecutive visits at least 4 weeks apart) of serum creatinine from Baseline (Day 1)
  - Initiation of rescue therapy for LN

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  - End-stage renal disease
  - Death from any cause

- Changes in the SLE index: Safety of Estrogens in Lupus Erythematosus – National Assessment Systemic Lupus Erythematosus Disease Activity Disease Activity Index and Systemic Lupus International Collaborating Clinics/American College of Rheumatology
- Steroid use
- MMF use

Pharmacokinetics:

Pharmacokinetics (PK) was not evaluated due to early study termination.

Immunogenicity:

- Serum antibodies to BIIB023

Safety:

The safety assessments included, but were not limited to, the following:

- Physical examination
- Weight
- Vital signs
- 12-Lead electrocardiogram
- Hematology
- Coagulation panel
- Blood chemistry
- Urinalysis
- Serum and urine pregnancy tests
- Total immunoglobulin
- AEs, SAEs, and AEs leading to study treatment discontinuation or study withdrawal
- Concomitant therapy

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Statistical Methods:

Planned Analyses:

Safety

All AEs, laboratory data, and vital signs were evaluated. Safety analyses focused on the 108-week extension study. Safety data for subjects who received BIIB023 during Study 211LE201 could also have been summarized in combination with safety data from Study 211LE202.

All AEs were analyzed based on the principle of treatment emergence. An AE was regarded as treatment-emergent if it was present prior to receiving the first administration of study treatment in Study 211LE202 and then subsequently worsened in severity or was not present prior to receiving the first administration of study treatment in Study 211LE202 but subsequently appeared in this study.

The incidence of treatment-emergent adverse events (TEAEs) was summarized by treatment group and overall, by severity, and by relationship to study treatment.

Laboratory data were analyzed using shift tables. The shift from baseline to the maximum postbaseline value and the shift from baseline to the minimum postbaseline value were to be presented for each laboratory test by treatment group. In addition, shifts from baseline to high/low status for hematology and blood chemistry parameters and shifts from baseline to high/positive status for urinalysis were to be presented as well.

Efficacy

Analysis of efficacy was planned to be focused on all subjects who received at least 1 dose of study treatment during Study 211LE202. Additional analyses were to be performed on the efficacy-evaluable population of subjects compliant with the dosing regimen and on subgroups of subjects.

The treatment groups were planned to be compared using logistic regression analysis for binary responses and using analysis of covariance for continuous responses, adjusting for region (Asia, Latin America, and all other regions), race (black and non-black), and renal response before the first study treatment (partial response and nonresponse). For the binary responses, a sensitivity analysis using a Cochran-Mantel-Haenszel test adjusting for the same variables as above was planned to be performed.

Time to event (such as the time to first complete/partial response and time to first sustained complete/partial response) was planned to be assessed using Kaplan-Meier methods for combined data from Study 211LE201.

A Kaplan-Meier plot and 90% confidence intervals were planned to be provided for each treatment group. Modeling using Cox proportional hazards may have been performed.

Pharmacokinetics

The PK analysis population was to be defined as all subjects who received at least 1 dose of study treatment during Study 211LE202 and have at least 1 measurable drug concentration. Descriptive statistics and graphical presentations were to be presented for each PK assessment, as appropriate.

Immunogenicity

Analyses were planned to be based on all subjects who received at least 1 dose of BIIB023 during Study 211LE202.

The incidence of anti-BIIB023 antibodies was planned to be presented by time for subjects without positive

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antibody prior to treatment in Study 211LE202 and for all enrolled subjects in Study 211LE202.

Interim Analysis:

No interim analyses were performed.

Sample Size Calculations:

There was no formal sample size calculation. The number of subjects eligible for this study was determined by the number of subjects randomized in Study 211LE201. Study 211LE201 was terminated early.

Changes in the Planned Analysis:

Due to the early termination of Study211LE202, only the primary objective was analyzed for this abbreviated CSR.

Results:

Subject Accountability:

A total of 87 subjects were randomized to the Dose-Blinded, 2-Dose Level Treatment Period. Forty-seven subjects (54%) received 3 mg/kg BIIB023. Of these, 14 subjects (30%) had received placebo in Study 211LE201 and 33 subjects (70%) had received 3 mg/kg BIIB023 in Study 211LE201. All 14 subjects (100%) in the placebo/3 mg BIIB023 treatment group discontinued BIIB023 and withdrew from the study due to early study termination.

Of the 33 subjects in the 3 mg/3 mg BIIB023 treatment group, 32 subjects (97%) discontinued BIIB023; 27 subjects (82%) discontinued BIIB023 due to early study termination, 3 subjects (9%) due to consent withdrawn, 1 subject (3%) due to an AE, and 1 subject (3%) due to Investigator decision. One subject (3%) completed the study.

Forty subjects (46%) received 20 mg/kg BIIB023. Of these, 13 subjects (33%) had received placebo in Study 211LE201 and 27 subjects (67%) had received 20 mg/kg BIIB023 in Study 211LE201. Of the 13 subjects in the placebo/20 mg BIIB023 treatment group, 12 subjects (92%) discontinued BIIB023; all 12 subjects (100%) discontinued BIIB023 due to early study termination. One subject (8%) completed the study.

Of the 27 subjects in the 20 mg/20 mg BIIB023 treatment group, 25 subjects (93%) discontinued BIIB023; 24 subjects (89%) due to early study termination, and 1 subject (4%) due to death. One subject (4%) completed the study.

The first dose of BIIB023 was administered on 22 November 2013, and the last visit of the study (end of study date) was conducted on 15 January 2015. The date of early study termination was 08 October 2015.

Demographics and Baseline Disease Characteristics:

Subjects' ages ranged from 19 to 58 years, with a median of 31.0 years. The majority of subjects were females (75 86%] females vs. 12 [14%] males). The majority (41%) of subjects were White; 34% were Asian, 20% were of Other race, and 2% were Black or African-American. Race was not reported for 2% of the subjects because of confidentiality regulations.

Baseline Disease Characteristics:

All subjects were required to have a documented diagnosis of SLE according to current American College of Rheumatology criteria and a diagnosis of International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Class III or IV LN with either active or active/chronic disease, which was confirmed by biopsy within

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3 months prior to Screening for Study 211LE201. Subjects were permitted to have co-existing Class V LN.

Lupus Nephritis Classification:

Overall, the most common LN ISN/RPS classification at study entry was Class IV with 67 subjects (77%). Of these classifications, Class IV-G (A) was the most common subclass with 41 subjects (47%). This was consistent with the enrolled population in the parent Study 211LE201. Comparing subjects in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups with subjects in the placebo/20 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, a greater proportion of subjects in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups had Class III (5 subjects [36%] and 7 subjects [21%], respectively, vs. 1 subject [8%] and 7 subjects [26%], respectively) and Class IV LN ISN/RPS classification (9 subjects [64%] and 26 subjects [79%], respectively, vs. 12 subjects [92%] and 20 subjects [74%], respectively). A smaller proportion of subjects in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups had co-existing Class V classification (2 subjects [14%] and 8 subjects [24%], respectively, vs. 4 subjects [31%] and 6 subjects [22%], respectively).

Efficacy:

Efficacy was not evaluated.

PK and pharmacodynamics were not evaluated.

Safety:

Overall Summary

Overall, 53 subjects (61%) reported a TEAE. Four subjects (29%) and 23 subjects (70%) reported a TEAE in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups, respectively. Seven subjects (54%) and 19 subjects (70%) reported a TEAE in the placebo/20 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, respectively.

Overall, 23 subjects (26%) reported a moderate or severe TEAE. Two subjects (14%) and 12 subjects (36%) reported a moderate or severe TEAE in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups, respectively. Three subjects (23%) and 6 subjects (22%) reported a moderate or severe TEAE in the placebo/20 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, respectively.

Overall, 8 subjects (9%) reported a severe TEAE. No subjects (0%) and 4 subjects (12%) reported a severe TEAE in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups, respectively. One subject (8%) and 3 subjects (11%) reported a severe TEAE in the placebo/20 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, respectively.

Overall, 11 subjects (13%) reported a TEAE related to dose-blinded treatment. One subject (7%) and 5 subjects (15%) reported a TEAE related to dose-blinded treatment in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups, respectively. One subject (8%) and 4 subjects (15%) reported a TEAE related to dose-blinded treatment in the placebo/20 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, respectively. Of these 11 subjects, 1 subject in the 3 mg/3 mg BIIB023 treatment group (Subject [redacted]) had an SAE of tuberculosis reported as related to study treatment in the clinical trial database but the Investigator changed the event to not related to study treatment in the safety database after database lock.

Overall, 21 subjects (24%) reported a TEAE related to MMF. Two subjects (14%) and 8 subjects (24%) reported a TEAE related to MMF in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups, respectively. Two subjects (15%) and 9 subjects (33%) reported a TEAE related to MMF in the placebo/20 mg BIIB023 and

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20 mg/20 mg BIIB023 treatment groups, respectively.

Overall, 15 subjects (17%) reported a serious TEAE. One subject (7%) and 7 subjects (21%) reported a serious TEAE in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups, respectively. Four subjects (31%) and 3 subjects (11%) reported a serious TEAE in the placebo/20 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, respectively.

Overall, 4 subjects (5%) reported a serious TEAE related to dose-blinded treatment. No subjects (0%) and 2 subjects (6%) reported a serious TEAE related to dose-blinded treatment in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups, respectively. One subject (8%) and 1 subject (4%) reported a serious TEAE related to dose-blinded treatment in the placebo/20 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, respectively.

Overall, 6 subjects (7%) reported a serious TEAE related to MMF. No subjects (0%) and 3 subjects (9%) reported a serious TEAE related to MMF in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups, respectively. One subject (8%) and 2 subjects (7%) reported a serious TEAE related to MMF in the placebo/20 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, respectively.

Overall, 1 subject (4%) experienced a fatal TEAE. The fatal TEAE was reported in the 20 mg/20 mg BIIB023 treatment group (1 subject [4%]); no fatal TEAEs were reported in the other 3 treatment groups.

No subjects (0%) discontinued treatment due to a TEAE.

Overall, 3 subjects (3%) withdrew from the study due to a TEAE. No subjects (0%) and 2 subjects (6%) withdrew from the study due to a TEAE in the placebo/3 mg BIIB023 and 3 mg/3 mg BIIB023 treatment groups, respectively. No subjects (0%) and 1 subject (4%) withdrew from the study due to a TEAE in the placebo/20 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, respectively.

There were fewer SAEs and severe AEs in subjects who were in the placebo/3 mg BIIB023 and placebo/20 mg BIIB023 treatment groups. The most common events reported during this study in all treatment groups were non-serious infections (bronchitis [11 subjects (13%)], upper respiratory tract infection [7 subjects (8%)], urinary tract infection [6 subjects (7%)], and nasopharyngitis and influenza [4 subjects (5%) each]). Headache was reported in 6 subjects (7%). One serious event of tuberculosis (Subject [redacted] in the 3 mg/3 mg BIIB023 treatment group) was reported on Day 483 and considered initially unrelated to BIIB023 and unrelated to MMF by the Investigator; this assessment was updated to possibly related to BIIB023 and was later changed unrelated to BIIB023 in the safety database after database lock. Subject [redacted] had been on study treatment, MMF 1000 mg orally twice daily (BID), and oral prednisone 10 to 40 mg once daily (QD) throughout the duration of participation in the study. One fatality due to a serious event of gastroenteritis and septic shock, which progressed to multi-organ failure, was reported (Subject [redacted] in the 20 mg/20 mg BIIB023 treatment group) in a subject who had eaten street market food that may have been contaminated just prior to the onset of symptoms; the events were considered not related to BIIB023. In the placebo/3 mg BIIB023 treatment group, the type and severity of 2 events were unknown.

The system organ classes (SOCs) with the highest incidence of TEAEs (≥15% of subjects overall) were Infections and Infestations (40 subjects [46%]), Gastrointestinal (GI) Disorders (15 subjects [17%]), and Musculoskeletal and Connective Tissue Disorders (14 subjects [16%]).

The SOCs with the highest incidence of TEAEs (≥20% of subjects within a treatment group) in each treatment group are presented below:

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- Placebo/3 mg BIIB023: Infections and Infestations, 4 subjects (29%)
- 3 mg/3 mg BIIB023: Infections and Infestations, 19 subjects (58%); GI Disorders, 8 subjects (24%); and Musculoskeletal and Connective Tissue Disorders, 7 subjects (21%)
- Placebo/20 mg BIIB023: Infections and Infestations, 6 subjects (46%); Nervous System Disorders, 5 subjects (38%); Musculoskeletal and Connective Tissue Disorders, 4 subjects (31%); and GI Disorders and Skin and Subcutaneous Tissue Disorders, 3 subjects (23%) each
- 20 mg/20 mg BIIB023: Infections and Infestations, 11 subjects (41%)

The most commonly reported TEAEs in the Infections and Infestations SOC (≥5% of subjects within a treatment group) in each treatment group are present below. Note that because of the small number of subjects in the placebo/3 mg BIIB023 and placebo/20 mg BIIB023 treatment groups, events that occurred in 1 or 2 subjects will have an incidence ≥5%.

- Placebo/3 mg BIIB023: bronchitis, upper respiratory tract infection, nasopharyngitis, and herpes zoster (1 subject [7%] each)
- 3 mg/3 mg BIIB023: bronchitis and upper respiratory tract infection (5 subjects [15%] each); viral upper respiratory tract infection, urinary tract infection, influenza, onychomycosis, oral herpes, and pneumonia (2 subjects [6%] each)
- Placebo/20 mg BIIB023: urinary tract infection (4 subjects [31%]); influenza, gastroenteritis Norovirus, and pharyngitis (1 subject [8%] each)
- 20 mg/20 mg BIIB023: bronchitis (5 subjects [19%]); nasopharyngitis and gastroenteritis (2 subjects [7%] each)

TEAEs in the GI Disorders SOC were reported in the 3 mg/3 mg BIIB023 treatment group (8 subjects [24%]). No subjects (0%) in the placebo/3 mg BIIB023 treatment group reported TEAEs in the GI Disorders SOC. TEAEs in the GI Disorders SOC were reported in the placebo/20 mg BIIB023 treatment group (3 subjects [23%]) and in the 20 mg/20 mg BIIB023 treatment group (4 subjects [15%]). The most frequently reported preferred terms (PTs) were abdominal pain, mouth ulceration, and diarrhea.

Renal and Urinary Disorders SOC TEAEs were reported with 4 subjects (12%), 2 subjects (15%), and 3 subjects (11%) in the 3 mg/3 mg BIIB023, placebo/20 mg BIIB023, and 20 mg/20 mg BIIB023 treatment groups, respectively. No subjects (0%) in the placebo/3 mg BIIB023 treatment group reported a TEAE in the Renal and Urinary Disorders SOC. LN and dysuria were the most frequently reported PTs contributing to this difference.

Investigations SOC TEAE of increased hepatic enzyme was reported in 2 subjects (2 events) and 3 subjects (8 events) in the 3 mg/3 mg BIIB023 and 20 mg/20 mg BIIB023 treatment groups, respectively, and in 1 subject (1 event) in the placebo/3 mg BIIB023 and 1 subject (1 TEAE) in the placebo/20 mg BIIB023 treatment group. None of these cases had ALT or AST >3 × ULN and concomitant total bilirubin >2 × ULN.

The most frequently reported TEAEs during the Dose-Blinded Period (≥5% of subjects overall) were bronchitis (11 subjects [13%]); upper respiratory tract infection (7 subjects [8%]); headache (6 subjects [7%]); urinary tract infection (6 subjects [7%]); abdominal pain (5 subjects [6%]); and arthralgia, hepatic enzyme increased, influenza, and nasopharyngitis (4 subjects [5%] each). Other frequently reported AEs were dysuria, gamma-glutamyltransferase (GGT) increased, gastritis, gastroenteritis, hypertension, LN, mouth ulceration, pain in

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extremity, rhinorrhea, and viral upper respiratory tract infection (3 subjects [3%] each).

Analysis by Relationship to Study Treatment

Overall, a total of 11 subjects (13%) experienced a TEAE that was considered by the Investigator to be related to study treatment. These included 1 subject (7%) in the placebo/3 mg BIIB023 treatment group, 5 subjects (15%) in the 3 mg/3 mg BIIB023 treatment group, 1 subject (8%) in the placebo/20 mg BIIB023 treatment group, and 4 subjects (15%) in the 20 mg/20 mg BIIB023 treatment group. In the placebo/3 mg BIIB023 treatment group, the relationship to study treatment was not coded for 2 events.

Overall, the most commonly reported TEAEs considered to be related to study treatment (≥2% of subjects overall) were herpes simplex (2 [2%]), GGT increased (2 [2%]), and nasopharyngitis (2 [2%]).

Analysis by Relationship to MMF

Overall, a total of 21 subjects (24%) experienced a TEAE that was considered by the Investigator to be related to MMF. These included 2 subjects (14%), 8 subjects (24%), 2 subjects (15%), and 9 subjects (33%) in the placebo/3 mg BIIB023, 3 mg/3 mg BIIB023, placebo/20 mg BIIB023, and 20 mg/20 mg BIIB023 treatment groups, respectively.

Overall, the most commonly reported TEAEs considered by the Investigator to be related to MMF (≥5% of subjects overall) were bronchitis (6 subjects [7%]) and hepatic enzyme increased (4 subjects [5%]).

Safety Conclusions

Overall, BIIB023 was well tolerated in this study. Overall, AE incidence was similar between subjects treated with 3 mg BIIB023 and 20 mg BIIB023 during the Dose-Blinded Period of Study 211LE202. A smaller proportion of subjects in the placebo/3 mg BIIB023 treatment group reported TEAEs; however, the proportion of subjects with TEAEs was similar between the other 3 treatment groups (3 mg/3 mg BIIB023, placebo/20 mg BIIB023, and 20 mg/20 mg BIIB023). Given the small number of subjects in each treatment group, ranging from 14 to 33 subjects, small differences between treatment groups were not interpreted to indicate any true difference, and the overall incidence of AEs and SAEs was considered to be comparable between treatment groups.

The incidence and types of TEAEs reported were generally consistent with the known toxicities of the background therapies MMF, which was received by all subjects during Study 211LE201 and Study 211LE202, and oral corticosteroids, and the significant morbidity associated with the underlying disease in the population studied. The most common events reported during this study were non-serious infections (bronchitis, upper respiratory infection, and nasopharyngitis), and a few cases of urinary tract infection, oral herpes, and cellulitis were reported.

A single case of septic shock due to severe acute gastroenteritis following ingestion of street market food that may have been contaminated was reported in a [redacted]-year-old [redacted] in the 20 mg/20 mg BIIB023 treatment group. [redacted] received MMF 1000 mg orally BID and 10 mg oral prednisone QD. This subject had a rapid progression to multi-organ failure, and the case was fatal on Day 21 of treatment, 1 day after the event onset. The subject was at increased risk of developing serious infections due to [redacted] pre-existing lupus with nephrotic syndrome and significant hypoalbuminemia, and [redacted] concomitant immunosuppressive medications (prednisone and MMF). It is not known if these events were related to BIIB023. However, a contributory role of BIIB023 cannot be excluded. One case of tuberculosis was reported in a subject in the 3 mg/3 mg BIIB023 treatment group after 16 months of treatment in Study 211LE202, which was considered not related to BIIB023 by the Investigator. Complete medical history and diagnostic information were not available. The Sponsor assessed this case as not related to study treatment, and it was confounded by treatment with MMF. Whether BIIB023 treatment could have

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had an added immunosuppressive effect cannot be determined from these data, although there is no evidence to suggest a dose-response relationship.

Three subjects experienced TEAEs leading to withdrawal from the study; 2 subjects (severe LN and severe tuberculosis) from the 3 mg/3 mg BIIB023 treatment group and 1 subject (severe multi-organ failure) from the 20 mg/20 mg treatment group. No pattern of TEAEs by dose level or length of exposure was evident from these data.

Conclusions:

- Baseline demographic data and LN disease activity were well balanced among the 4 treatment groups.
- The primary objective and additional objectives could not be fully assessed due to early study termination and subsequent small sample size. Study 211LE202 was terminated based on the review of results following a pre-specified, blinded futility analysis of Study 211LE201, which did not demonstrate sufficient efficacy to warrant continuation of the studies. The study was not terminated based on safety considerations.
- BIIB023 administered for up to approximately 70 weeks appears to have an acceptable safety profile. The incidence and types of AEs reported were generally consistent with the known toxicities of the background therapies MMF and oral corticosteroids, and the significant morbidity associated with the underlying disease in the population studied. Considering the small sample size, there was no apparent relationship between the duration of exposure to BIIB023 and the incidence of TEAEs. In general, the safety profile of BIIB023 in Study 211LE202 is consistent with the findings in Study211LE201.

Date of Report: 26 August 2016

Version: 1.0