2. BCDJ Synopsis

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Clinical Study Report Synopsis: Study H9B-MC-BCDJ

Title of Study: Multiple Subcutaneous Doses of LY2127399, an Anti-BAFF Human Antibody, in Subjects with Relapsing Remitting Multiple Sclerosis

Number of Investigators: This multicenter study included 71 principal investigators.

Study Centers: This study was conducted at 71 study centers in 15 countries.

Publication Based on the Study: None at this time

Length of Study:
Date of first patient enrolled: 08 May 2009
Date of last patient completed: 13 June 2012

Phase of Development: 2

Objectives:

The primary objective of this study was to test the hypothesis that patients with relapsing-remitting multiple sclerosis (RRMS) in at least 1 tabalumab group would have statistically significantly fewer cumulative total gadolinium (Gd)-enhancing magnetic resonance imaging (MRI) lesions over Weeks 12, 16, 20, and 24 compared to patients in the placebo group.

The secondary objectives of the study were as follows:

- To determine safety and tolerability of tabalumab compared to placebo.
- To determine whether:
  - Total number of Gd-enhancing MRI lesions,
  - Total number of new Gd-enhancing MRI lesions,
  - Total number of new or newly enlarging T2-weighted MRI lesions,
  - Total volume of T2-weighted MRI lesions, and

  were statistically significantly less in at least 1 tabalumab group compared to placebo over the 48-week duration of the study.
- To determine whether the time to first relapse was statistically significantly longer in 1 or more tabalumab groups compared to placebo.
- To determine whether the proportion of relapse-free patients was greater in 1 or more tabalumab groups compared to placebo at Weeks 24 and 48.
- To test the hypothesis that patients in at least 1 tabalumab group would have a smaller annualized relapse rate over 24 and 48 weeks compared to placebo.
- To determine proportion of patients with anti-tabalumab antibodies at the end of the study.
- To evaluate the pharmacodynamics (PD) of selected peripheral B cell subsets following administration of tabalumab compared to placebo.
- To evaluate the serum pharmacokinetics (PK) of tabalumab after multiple doses in patients with multiple sclerosis (MS).
- To evaluate the effect of treatment with tabalumab compared to placebo on the Expanded Disability Status Scale (EDSS; Kurtzke 1983).
- To evaluate the effect of treatment with tabalumab compared to placebo on the Multiple Sclerosis Functional Composite Scale (MSFC; Fisher et al. 1999).
- To evaluate the effect of treatment with tabalumab compared to placebo on Visual Analog Scale (VAS) of Wellbeing.
- To evaluate the effect of treatment with tabalumab compared to placebo on the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36; Ware and Sherbourne 1992).
- To evaluate the effect of treatment with tabalumab compared to placebo on the 16-Item Quick Inventory for Depressive Symptomatology Self Report (QIDS SR16; Rush et al. 2003).

Study Design: This was a multicenter study in patients with RRMS. The study was a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study. Patients were randomized to a placebo group or 1 of 6 dose groups of tabalumab and were administered subcutaneous (SC) treatment once every 4 weeks (Weeks 0, 4, 8, 12, 16, and 20) for a total of 6 doses or were administered 4 mg or 120 mg SC once every 12 weeks (at Weeks 0 and 12) for a total of 2 doses, and placebo at Weeks 4, 8, 16, and 20. Patients were followed through Week 72.

Number of Patients:

Planned: 245 patients randomized to 1 of 6 dose groups of tabalumab or placebo (approximately 35 patients per treatment group)

Randomized: 210 patients randomized to tabalumab (4 mg every 4 weeks [Q4W]: 35 patients; 12 mg Q4W: 34 patients; 40 mg Q4W: 34 patients; 120 mg Q4W: 36 patients; 4 mg every 12 weeks [Q12W]: 36 patients; 12 mg Q12W: 35 patients), 35 randomized to placebo

Treated (at least 1 dose): 210 patients in all tabalumab dose groups combined (4 mg Q4W: 35 patients; 12 mg Q4W: 34 patients; 40 mg Q4W: 34 patients; 120 mg Q4W: 36 patients; 4 mg Q12W: 36 patients; 12 mg Q12W: 35 patients), 35 patients in the placebo group

Completed: 181 patients in all tabalumab dose groups combined (4 mg Q4W: 27 patients; 12 mg Q4W: 26 patients; 40 mg Q4W: 30 patients; 120 mg Q4W: 31 patients; 4 mg Q12W: 28 patients; 12 mg Q12W: 28 patients), 27 patients in the placebo group

Diagnosis and Main Criteria for Inclusion: To be included in the study, patients had to meet the following main criteria: RRMS diagnosed prior to Visit 2; a Kurtzke EDSS score of 0 through 5.0; at least 1 documented clinical relapse within 12 months prior to Visit 2 OR show evidence of Gd-enhancing lesion(s) of the brain or spine by MRI performed within 12 months prior to Visit 2; and were 18 to 64 years of age, inclusive.

Tabalumab, Dose, and Mode of Administration:

Tabalumab, 4 mg, 12 mg, 40 mg, and 120 mg, given every 4 weeks (Q4W; Weeks 0, 4, 8, 12, 16, and 20) as SC injection for a total of 6 doses and 4 mg or 120 mg SC once every 12 weeks (Q12W; at Weeks 0 and 12) for a total of 2 doses.

Placebo, Dose, and Mode of Administration: Placebo given every 4 weeks as SC injection for a total of 6 doses or placebo at Weeks 4, 8, 16, and 20 as SC injection for a total of 4 doses (for tabalumab group with treatment Q12W).

Duration of Treatment:

20 weeks

Tabalumab, Q4W or Q12W: 20 weeks

Placebo, Q4W or at Weeks 4, 8, 16 and 20 for Q12W tabalumab groups: 20 weeks

Variables:

Efficacy and Pharmacodynamic: Number of total cumulative Gd-enhancing MRI lesions per scan, averaged over scans at Weeks 12, 16, 20, and 24; total number, and total number of new of Gd-enhancing MRI lesions at Weeks 4, 8, 12, 16, 20, 24, 36, and 48; total number of new or newly enlarging T2-weighted lesions at Weeks 4, 8, 12, 16, 20, 24, 36, and 48; total volume of T2-weighted MRI lesions at Weeks 4, 8, 12, 16, 20, 24, 36, and 48; time to first relapse at Week 24, Week 48 and during the period between Weeks 24 and 48; proportion of relapse-free patients at Week 24, Week 48 and the end of the study; annualized relapse rate at Weeks 24 and 48; to determine proportion of patients with anti-tabalumab antibodies at the end of the study; Kurtzke EDSS at Weeks 12, 24, and 48; MSFC at Weeks 12, 24, and 48; patient VAS at Weeks 12, 24, and 48; applicable flow cytometry measures and other disease-related biomarkers.

Safety: Adverse events (AEs), clinical laboratory test results, vital signs, and electrocardiograms (ECGs)

Bioanalytical: Serum concentrations of tabalumab were measured.

Pharmacokinetic (PK): Population PK parameters for tabalumab were estimated.

Health Outcomes: Observed values and changes from baseline in Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and 16-Item Quick Inventory for Depressive Symptomatology – Self Report ($QIDS\text{-}SR_{16}$).

Statistical Methods:

Efficacy and Pharmacodynamic: The primary efficacy endpoint was the number of total cumulative Gd-enhancing MRI lesions (whether the lesion was new or pre-existing, unchanged or enlarged from previous scans) summed over Weeks 12, 16, 20, and 24. For statistical analyses, the primary efficacy variable was the number of total cumulative Gd-enhancing MRI lesions per scan, averaged over scans at Weeks 12, 16, 20, and 24.

Primary analyses utilized 1-tailed tests (alpha level of 0.05) examining the alternative hypothesis that at least 1 treatment group had superior results compared to placebo. The number of cumulative total Gd-enhancing MRI lesions per scan over Weeks 12, 16, 20, and 24 was analyzed using a 1-way analysis of variance (ANOVA) model with treatment group (all dose level groups including placebo) as the main effect. Since the data were most likely negative binomial distributed, i.e., over dispersed, all data were log-transformed first using log (count + .25) before an analysis was to be carried out. A preliminary overall F-test was conducted prior to pairwise comparisons with placebo. If this overall F-test was significant at the alpha level of 0.05, each of the 6 active treatment groups was then to be compared to placebo based on 6 linear contrasts. All the pairwise tests of treatment effects were conducted at a 1-sided alpha level of 0.05 as a follow up to the preliminary dose response test unless otherwise stated. The primary efficacy analysis of the cumulative number of total Gd-enhancing MRI lesions per scan over Weeks 12, 16, 20, and 24 was to be based on all patients with at least 1 available Gd-enhancing MRI scan among Weeks 12, 16, 20, or 24. Missing data were not imputed for this analysis since the average per scan was used for this analysis. In addition, robust analysis using negative binomial regression were to be carried out since the data were expected to be negative binomial distributed.

For the secondary efficacy variables, analysis of each variable was based on patients with available data at respective timepoints used in defining the specific secondary efficacy variable. In general, missing data were not imputed. All analyses of efficacy were performed reporting the level of significance (alpha), using 1-tailed tests. The 1-sided alternative hypothesis was that the active treatment group has superior efficacy compared with the placebo group during the post infusion study period.

Each treatment group was compared to placebo at the 0.05 level of significance (alpha) with 1-tailed tests. Secondary analyses were performed comparing the placebo group to each of the 6 active dose groups at each evaluation visit and at endpoint. As these were exploratory analyses, no adjustments were made for multiplicity.

Safety: The incidence of AEs and treatment-emergent AEs (TEAEs) for each treatment is summarized by severity and by association with study drug as perceived by the investigator. All clinical laboratory results are descriptively summarized by treatment group. Individual results that are outside of normal range are flagged and changes from baseline are summarized by treatment. Categorical variables are summarized by frequency and percentage of patients in corresponding categories. ECG measurements and vital signs are tabulated and summarized. Observed values and changes from baseline (predose or Visit 1 if missing) for QT interval are descriptively summarized by treatment group and time point. An analysis similar to that proposed for the efficacy variables were used for the change from baseline measurements (with 90% confidence intervals). Changes from baseline in vital signs were analyzed using a mixed-effects model.

Pharmacokinetic: Tabalumab concentration-time data were analyzed using a population approach.

Health Outcomes: Observed values and changes from baseline in SF-36 and QIDS-SR_{16} were to be analyzed similarly to secondary efficacy endpoints.

Summary:

A total of 245 patients entered the study entry period and were randomized to receive study treatment; 210 of these patients were randomized to 1 of the 6 tabalumab groups (4 mg every 4 weeks [Q4W]: 35 patients; 12 mg Q4W: 34 patients; 40 mg Q4W: 34 patients; 120 mg Q4W: 36 patients; 4 mg every 12 weeks [Q12W]: 36 patients; 12 mg Q12W: 35 patients), and 35 patients were randomized to the placebo group. Across all treatment groups, 48 patients discontinued the study and 33 discontinued the study treatment. The most common reason for discontinuation of study or study treatment in all treatment groups was Subject Decision. There were no notable differences between all tabalumab dose groups combined (hereafter referred to as the all tabalumab group) and the placebo group in the percentage of patients who discontinued the study or the reasons for discontinuation. There were no statistically significant differences in any demographic or baseline characteristic between any of the tabalumab groups and placebo or between the all tabalumab group and the placebo group.

Efficacy:

The efficacy results of this study indicate that treatment with tabalumab did not result in fewer cumulative total Gd-enhancing MRI lesions over Weeks 12, 16, 20, and 24 compared to patients in the placebo group. There was no statistically significant difference overall or between any of the tabalumab groups and placebo.

Similarly, there was no statistically significant difference overall or between any of the tabalumab groups and placebo for the following:

- Total number of Gd-enhancing MRI lesions,
- Total number of new Gd-enhancing MRI lesions,
- Total number of new or newly enlarging T2-weighted MRI lesions,
- Total volume of T2-weighted MRI lesions,
- Time to first relapse,
- Proportion of relapse-free patients at Week 24, Week 48, end of treatment, or at end of study, and
- Annualized relapse rate over 24 and 48 weeks analyzed using ANOVA. However, Poisson regression analysis of annualized relapse rate showed statistical significance for the model term treatment (p=.043) at Week 24, but not at Week 48.

Conclusions based on the PK analysis results are as follows:

- The population PK of LY2127399 administered as SC injection were adequately described by a 2-compartment open model with constant (linear) as well as saturable (nonlinear) clearance.
  Results from the base model development showed minor differences in the inter-compartmental clearance and peripheral compartment volume components of the PK model compared to previous studies in patients with rheumatoid arthritis, thus disease state does not appear to affect the PK of tabalumab.

Tabalumab exhibited pharmacologic activity as evidenced by dose-dependent changes in peripheral blood B cell parameters. In general, B cell changes noted in both 4 mg dose groups were minimal throughout the study.

There were no meaningful differences between the tabalumab groups and placebo with regard to EDSS, MSFC, VAS of Wellbeing, SF-36; or QIDS SR16 at any timepoint.

Safety:

Tabalumab was generally safe and well tolerated at doses of 4 mg, 12 mg, 40 mg, and 120 mg, given every 4 weeks as SC injection for a total of 6 doses or 4 mg or 120 mg SC once every 12 weeks for a total of 2 doses, as evidenced by the following:

- A total of 2 deaths occurred during this study; 1 was treatment-emergent (multiple sclerosis, tabalumab 12mg Q4W dose group) and 1 was non-treatment emergent (heart disease congenital; tabalumab 120mg Q12W dose group).
- A total of 4 patients in the all tabalumab group and none in the placebo group experienced at least 1 AE that was reported as reason for discontinuation of treatment. The events were acute psychosis, hepatitis B, multiple sclerosis, and toxic skin eruption, each event led to discontinuation of treatment for a single patient. The events of acute psychosis and multiple sclerosis also led to discontinuation from the study, both events were reported for patients in a tabalumab group.
- There was a higher proportion of patients with at least 1 TEAE in the all tabalumab group, (68.1%) compared with the placebo group (48.6%). There was a higher incidence in the all tabalumab group

compared with placebo (>5% difference) of fatigue (8.1% versus none in placebo) and multiple sclerosis relapse (5.7% versus none in placebo). The proportion of patients with at least 1 FEAEs was 41.9% in the all tabalumab group and 34.3% in the placebo group. There was a higher incidence in the all tabalumab group compared with placebo (>2% difference) of dizziness (2.9% versus none in placebo), nasopharyngitis (2.4% versus none in placebo), and viral infection (2.4% versus none in placebo). There was no clear pattern of a dose-response relationship with the incidence of any TEAE or FEAE.

- A total of 25 patients experienced at least 1 SAE during the study; 23 patients in the all tabalumab group and 2 patients in the placebo group. Each preferred term was experienced by a single patient, except for the event of multiple sclerosis relapse. Fifteen patients (7.1%) in the all tabalumab group and 1 patient (2.9%) in the placebo group experienced multiple sclerosis relapse. The SAEs, as well as TEAEs, of multiple sclerosis relapse were carefully evaluated by the Data Monitoring Committee and internal safety review committees. There was no dose relationship and no relationship with the time at which relapses occurred, either during treatment or post-treatment follow-up.
- No unexpected changes in safety-related laboratory analytes were observed.
- No clinically meaningful differences between tabalumab and placebo were observed in change from baseline in vital signs or in ECG parameters.

Conclusions: The efficacy results of this study indicate that treatment with tabalumab is not efficacious in reducing Gd-enhancing MRI lesions, time to relapse, or proportion of relapse-free patients. The population PK of LY2127399 administered as subcutaneous injection were adequately described by a 2-compartment open model with constant (linear) as well as saturable (nonlinear) clearance. The patients with MS studied had similar exposure profiles to those observed in earlier phase II rheumatoid arthritis studies, suggesting no clinically significant PK differences in these populations. Tabalumab was generally safe and well tolerated at doses of 4 mg, 12 mg, 40 mg, and 120 mg, given every 4 weeks as SC injection for a total of 6 doses or 4 mg or 120 mg SC once every 12 weeks for a total of 2 doses in patients with RRMS.