2. BCDG Synopsis

Approval Date: 05-Feb-2013 GMT

Clinical Study Report Synopsis: Study H9B-MC-BCDG

Title of Study: A Phase 2 Study of Multiple Intravenous Doses of LY2127399, an Anti-BAFF Human Antibody, in Patients with Rheumatoid Arthritis on Concomitant Methotrexate and an Inadequate Response to TNFα Inhibitor Therapy	
Number of Investigators: This multicenter study included 43 principal investigators.	
Study Centers: This study was conducted at 43 study centers in 8 countries.	
Publications Based on the Study: None at this time.	
Length of Study: Date of first patient enrollment: 16 July 2008 Date of last patient completion: 27 May 2010	**Phase of Development:** 2
Objectives: The primary objective was to evaluate LY2127399 efficacy assessed by the proportion of patients who achieved an American College of Rheumatology (ACR)50 (see definition below) response compared to placebo at 16 weeks in patients with rheumatoid arthritis (RA), who had had an inadequate response or intolerance to treatment with at least 1 biologic tumor necrosis factor (TNF)α inhibitor therapy. The secondary objectives of the study were as follows: to evaluate LY2127399 efficacy compared to placebo over the 16-week study period as assessed by the individual components of the ACR Core Set, Disease Activity Score based on the 28-joint count (DAS28), and European League Against Rheumatism Responder index based on the 28-joint count (EULAR28); to evaluate LY2127399 safety and tolerability compared to placebo; to evaluate pharmacodynamics (PD) of disease-related biomarkers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and selected peripheral B cell subsets following administration of LY2127399 as compared to placebo; to explore the potential associations between selected biomarkers (baseline and response to study treatment) and selected disease activity measures; to characterize LY2127399 pharmacokinetics (PK) in RA patients with inadequate response or intolerance to TNFα inhibitor therapy; and to evaluate the impact of LY2127399 compared to placebo over the 16-week study period on patient-reported outcomes as measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale and the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).	
Study Design: This was a Phase 2, multicenter, parallel-group, double-blind, randomized, fixed-dose, outpatient, proof-of-concept clinical study comparing LY2127399 with placebo in the treatment of patients with active RA and a history of an inadequate response or intolerance to at least 1 TNFα inhibitor therapy. Placebo, or 30 or 80 mg of LY2127399, was administered as a single intravenous (IV) infusion over 30 minutes at 0, 3, and 6 weeks. The planned minimum duration of the study was 40 weeks. In accordance with Protocol Amendment D, B cell follow-up monitoring for patients whose B cell levels had not recovered at Week 40 continued until Week 68. The total possible follow-up period was at least 52 weeks after the last dose.	
Number of Patients: Planned: 33 per LY2127399 dose group (66 total), 33 in placebo group Randomized: 35 in LY2127399 30-mg group, 30 in LY2127399 80-mg group, 35 in placebo group Treated (at least 1 dose): 35 in LY2127399 30-mg group, 30 in LY2127399 80-mg group, 35 in placebo group Completed: 30 in LY2127399 30-mg group, 24 in LY2127399 80-mg group, 29 in placebo group	
Diagnosis and Main Criteria for Inclusion: Ambulatory male and female patients 18 to 75 years of age (inclusive) with active RA (at least 5/28 swollen joints and at least 5/28 tender joints) and a screening CRP value of at least the upper limit of normal (ULN) or screening ESR of at least 28 mm/hr. Patients were on a stable dose of methotrexate and could also have been receiving stable doses of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (doses not exceeding 10 mg/day of prednisone or its equivalent), hydroxychloroquine, and/or sulfasalazine. Inadequate response or intolerance to at least 1 biologic TNFα inhibitor treatment.	
Study Drug, Dose, and Mode of Administration: LY2127399 30 or 80 mg in a 100 mL IV infusion with 0.9% sodium chloride given over 30 minutes. Lot [redacted].	

Reference Therapy, Dose, and Mode of Administration: Placebo was a 100 mL IV infusion of 0.9% sodium chloride given over 30 minutes.

Duration of Treatment: Blinded study drug was administered at Weeks 0, 3, and 6. Patients who had not responded to therapy at their Week 16 assessments (did not have an improvement of at least 20% in either their tender or their swollen joint counts, based on 28 joints), could receive an additional 30-minute infusion of LY2127399 80 mg as open-label therapy.

Variables:

Efficacy: Efficacy endpoints in this study included ACR response. An ACR"X" responder was a patient who had ≥X% improvement in both tender and swollen joint counts and in 3 of the following 5 criteria: physician global assessment, patient global assessment, functional ability measure (Health Assessment Questionnaire-Disability Index [HAQ-DI]), visual analog pain scale, and CRP. The primary efficacy variable was ACR50 response. Secondary efficacy variables included ACR20 response, ACR70 response, ACR-N; ACR core set (tender joint count, swollen joint count, patient's assessment of joint pain, patient's assessment of disease activity, physician's assessment of disease activity, HAQ-DI, CRP, Disease Activity Score [based on 28-joint count; DAS28], European League Against Rheumatism Responder Index [EULAR28] response). Patient-reported outcomes included morning stiffness, Functional Assessment of Chronic Illness Therapy Fatigue Scale [FACIT] score, and Medical Outcomes Study 36-item Short Form Health Survey [SF-36].

Safety: Adverse events (AEs), clinical laboratory evaluations, vital signs, 12-lead electrocardiograms (ECGs), cluster of differentiation (CD)20^+ B cells, CD19+ B cell subsets, disease-related biomarkers (rheumatoid factor [RF], CRP, anti-cyclic citrullinated peptide antibody [anti-CCP], and ESR), anti-LY2127399 immunogenicity, and serum immunoglobulins.

Bioanalytical: Serum samples for LY2127399 analysis.

Pharmacokinetic: Parameters reported included constant clearance (CL), saturable clearance (CLSAT), intercompartmental clearance (Q), Michaelis-Menten constant (C50), central volume (V1), and peripheral volume (V2). Patient factors including body weight, age, gender, ethnic origin, baseline BAFF level, and creatinine clearance were evaluated as covariates to LY2127399 PK.

Pharmacodynamic**:** $CD20^+$ B cell counts, B cell activating factor (BAFF) levels, $CD19^+$ B cell subsets (mature naïve [$CD19^+$, $CD27^-$, IgD+], immature/transitional [CD19+, IgD-, CD27-], switched memory [CD19+, IgD-, CD27+], and nonswitched memory [$CD19^+$, IgD+, CD27+]), T cells (CD3+, CD4+, and CD8+), and natural killer cells (CD16+ and CD56+).

Evaluation Methods: Assuming a placebo ACR50 rate of 10% and an ACR50 rate of 33% for treated patients at Week 16, a sample size of 33 evaluable patients per arm (33 total placebo, 66 total LY2127399 treated) had 83% power to detect a 23% absolute difference in ACR50 response rates between the placebo and combined LY2127399 treatment groups (without continuity correction, one-sided hypothesis, 5% type I error rate). Continuous variables were summarized using descriptive statistics and were analyzed using parametric or non-parametric tests as applicable based on the distribution of the variable. Discrete variables were summarized using frequencies and percentages and were analyzed using Chi Square tests.

Efficacy: Primary analyses were performed comparing placebo to the combined LY2127399 groups. Analyses were also performed comparing placebo to each LY2127399 treatment group separately. All analyses of the following efficacy endpoints were performed at the 0.05 level of significance (α) using one-sided tests: ACR20, ACR50, ACR70, ACR-N, DAS28, and EULAR28. Analyses of all other efficacy endpoints were performed at the 0.05 level of significance (α) using two-sided tests.

Safety: All safety data were descriptively summarized by treatment groups.

Bioanalytical and Pharmacokinetic/Pharmacodynamic: Serum samples were analyzed for LY2127399 concentrations using a validated immunoassay method. PK parameters for LY2127399 were estimated by population PK analysis method with a two-compartment open model using NONMEM based on data in both Study BCDG and Study BCDH. Model selection was performed using various quantitative and graphical methods including the goodness-of-fit criteria and visual predictive checks. Simulation was conducted using final population PK model to predict steady-state pharmacokinetics of LY2127399. For PD assessments, the visit

values and change from baseline values were summarized and compared across treatments (two-sided tests) using similar methods to those described for the continuous secondary efficacy variables. Spearman-rank correlation analyses were used to compare selected biomarkers with continuous measures of clinical response at various time points.

Summary:

A total of 98 patients (placebo: 35 patients; LY2127399 30 mg: 35 patients; LY2127399 80 mg: 28 patients) were included in the efficacy analyses. The safety population included 100 patients. The patient population was predominately female and Caucasian with a mean age of approximately 52 years. Demographic and baseline characteristics of the treatment groups were broadly comparable. The mean duration of disease was 10 years in the combined LY2127399 group, compared with 11 years in the placebo group. Patients were in ACR functional class I, II, or III at baseline.

Although the primary endpoint, ACR50 response at Week 16 (non-responder imputation/last observation carried forward; NRI/LOCF) was not met, the ACR50 response rate for the primary endpoint was 10% higher for LY2127399-treated patients in comparison with placebo-treated patients (13% vs 3%). At Week 9, the ACR50 response rate was 24% for LY2127399-treated patients vs 0% for placebo-treated patients, and the difference was statistically significant. As observed for ACR50 response, the proportions of patients who were ACR20 or ACR70 responders were larger for LY2127399-treated patients vs placebo-treated patients at Week 16, but the differences were not statistically significant. Statistically significant differences in favor of LY2127399 were observed, however, for ACR20 and ACR70 response at Week 9. Statistically significant differences in favor of LY2127399 for ACR-N response were observed for LY2127399 at Week 16 (LOCF) and also at Week 9. In general, a trend toward greater improvement in the signs and symptoms of RA was observed for LY2127399-treated patients relative to placebo-treated patients in other secondary efficacy measures (eg, DAS28 and EULAR28) and patient-reported outcome measures (for example, fatigue and mental health) and the differences were statistically significant for some parameters including patient-reported outcome measures (for example, morning stiffness and physical health) over the course of the study. The PK parameters of LY2127399 were characterized by a 2-compartment open model, with linear and nonlinear elimination parameterized with first-order constant (linear) clearance and saturable (nonlinear) clearance, respectively. CL and CLSAT were estimated to be 5.25 and 15.5 mL/hr, respectively. Body weight was found to have statistically significant effects on the PK of LY2127399, with CL increasing with body weight; however, the effect was not deemed to be clinically relevant. Age, gender, ethnic origin, baseline BAFF level, and creatinine clearance had no significant effect on PK of LY2127399. Simulation of LY2127399 concentration profiles following 30 or 80 mg IV infusion once every three weeks suggested that steady state is reached at approximately 12 weeks or following the fourth once-every-three-week dose.

The trends of early increases in CD20+ and CD19+ cells with LY2127399 treatment followed by decreases to levels below baseline observed in this study were comparable to those observed in other studies of LY2127399. Increases were seen in total CD20+ B cells in LY2127399 groups at Week 1 and at Week 3, then decreased toward approximately baseline levels at Week 9 and continued to trend downward. The CD20+ B cell counts (absolute) in LY2127399-treated patients were statistically significantly decreased compared with placebo-treated patients at Week 16. The percent decreases of CD20+ B cell counts were also statistically significant compared with placebo (22.21) in the 30-mg group (-6.40; $p = 0.003$), the 80-mg group (-5.60; $p = 0.014$), and the combined LY2127399 group (-6.04; $p = 0.002$) at Week 16 (LOCF). No statistically significant changes in T cell or natural killer cell numbers in the LY2127399-treated groups were observed. Significant correlations were observed between efficacy outcomes (DAS28 and ACRN) and B-cells but no other biomarker (except for one Spearman-Rank correlation with BAFF levels).

Immunoglobulin group mean values showed statistically-significant, dose-related reductions from baseline for IgM in both dose groups and the combined LY2127399 group compared with placebo for observed and LOCF Week 16 values. Comparable decreases from baseline were observed for IgG and IgA at Week 16 for the 80-mg and combined LY2127399 groups versus placebo. No statistically significant differences between the placebo group and LY2127399-treated patients were observed for RF, anti-CCP, or ESR levels.

No patient died during the study. The incidence of serious adverse events (SAEs) and AEs that led to discontinuation of study drug was low. The 3 SAEs reported for patients treated with LY2127399 were worsening of active RA and Crohn's disease in the 80-mg group and spondylolisthesis (after Week 16) in the 30-mg group. Two patients discontinued the study due to an AE (arrhythmia in the 30-mg group, ovarian cyst in the 80-mg group). The overall incidence of TEAEs was higher in the LY2127399 80-mg group vs the 30-mg group (77% vs 66%) through Week 16. No trend in nature of TEAEs by dose of LY2127399 was apparent. The most frequently observed TEAEs in the combined LY2127399 group were RA (exacerbation; 10.8% vs 25.7% for placebo), URTI (7.7% vs 0% for placebo), headache (6.2% vs 5.7% for placebo), and upper abdominal pain (6.2% vs 0% for placebo). No clinically significant differences between treatment groups were observed in laboratory results, vital signs measurements, or ECGs. No treatment-emergent immunogenicity (anti-drug antibody, ADA) was observed for any LY2127399-treated patients. One LY2127399-treated patient developed transient follow-up emergent immunogenicity that was non-neutralizing. This patient did not report any TEAEs or FEAEs. No assessment of ADA effect on efficacy or PK could be performed since the only occurrence of ADA was during the follow-up period and efficacy and PK were not collected at that time. Eight LY2127399-treated patients and 1 placebo treated patient had a total B cell count >43 cells/µL at baseline which dropped below <43 cells/µL post baseline (Weeks 0 to 24). Of the 9 patients, 2 patients also experienced mild to moderate infections (22%) at or near the time of the low total B cell count. The frequency of treatment-emergent infectious events in patients with a low B cell count postbaseline during the treatment period (2/9 or 22%) is not greater than the frequency of infectious events reported for any LY2127399 dose group (20% in placebo, 31.4% in 30 mg group and 30.0% in 80 mg group reported infections.

Conclusions:

No statistically significant difference between LY2127399 and placebo was observed at Week 16 for ACR50 response rate, therefore the primary endpoint of the study was not reached. Among the secondary efficacy endpoints, the DAS28, but not the ACR20, ACR50, or EULAR28 (good+moderate) response rates, showed a statistically significant difference between LY2127399 and placebo at Week 16. However, many efficacy outcome assessments showed statistically significant differences between LY2127399 and placebo at Week 9. This apparent loss of efficacy between Week 9 and Week 16 in Study BCDG contrasts with the sustained clinical efficacy observed until Week 24 in the previous Study BCDF. While several factors have been posited to explain the differences between Study BCDF and BCDG, the actual cause of these differences is unknown.

The population PK of LY2127399 administered as IV infusion were adequately described by a 2-compartment open model with constant (linear) as well as saturable (nonlinear) clearance. Body weight was found to have statistically significant effects on the PK of LY2127399, with CL increasing with body weight; however, the effect was not deemed to be clinically relevant. Age, gender, ethnic origin, baseline BAFF level, and creatinine clearance had no significant effect on PK of LY2127399. The trends of early increases in CD20+ and CD19+ cells with LY2127399 treatment followed by decreases to levels below baseline observed in this study were comparable to those previously observed for LY2127399. Immunoglobulin group mean values showed statistically significant, LY2127399 dose-related reductions from baseline. No new safety issues were reported with LY2127399 treatment.