2. BCDI Synopsis

Clinical Study Report Synopsis: Study H9B-MC-BCDI

Title of Study: An Open-Label Extension Study of Multiple Subcutaneous Doses of LY2127399, an Anti-BAFF Human Antibody, in Patients with Rheumatoid Arthritis

Number of Investigators: This multicenter study included 67 principal investigators.

Study Centers: This study was conducted at 67 study centers in 14 countries.

Publications Based on the Study:

Greenwald MW, Szczepanski L, Kennedy AC, Lee CH, Polasek E, Veenhuizen M, Jones-Taha R, Berclaz P. Long-term safety and efficacy of tabalumab, an anti-B cell activating factor monoclonal antibody, in patients with rheumatoid arthritis: a 52-week, open-label extension study [abstract]. In the Arthritis and Rheumatism abstract supplement for the 2012 Annual Meeting of The American College of Rheumatology, Nov 9-11, 2012; Washington, DC. Arthritis and Rheumatism. 2012;64(10S):S193.

Greenwald MW, Veenhuizen M, Komocsar W, Jones-Taha R, Lee CL, Berclaz P. Changes in B cell populations and serum immunoglobulins and their relationship to infections in a 1-year, uncontrolled, open-label study of tabalumab [abstract]. In the Arthritis and Rheumatism abstract supplement for the 2012 Annual Meeting of The American College of Rheumatology, Nov 9-11, 2012; Washington, DC. Arthritis and Rheumatism. 2012;64(10S):S545

Length of Study: Date of first patient visit: 12 February 2009 Date of last patient visit: 13 January 2012	**Phase of Development:** 2

Objectives:

The primary objective was to evaluate the safety and tolerability of LY2127399 60 mg administered as SC injections Q4W for 48 weeks in patients with RA who completed at least 24 weeks of participation in Study H9B-MC-BCDG (BCDG) or Study H9B-MC-BCDH (BCDH) and received at least 6 weeks or 12 weeks of study drug, respectively. Safety and tolerability assessments included: treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs); discontinuation of study drug; and clinical laboratory evaluations (including hematology, clinical chemistry, and urinalysis).

The secondary objectives of the study were as follows:

- To evaluate the long-term efficacy of LY2127399 compared to baseline as assessed by the:
  - Individual components of the American College of Rheumatology (ACR) Core Set, as well as ACR20, ACR50, ACR70, and ACR-N;
  - Disease Activity Score based on the 28 joint count (DAS28);
  - European League Against Rheumatism Responder Index based on the 28 joint count (EULAR28);
- To evaluate the impact of long term administration of LY2127399 on patient-reported outcomes as measured by the:
  - Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale;
  - Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).
- To evaluate the long term impact of LY2127399 administration on selected peripheral blood biomarkers, including anti-cyclic citrullinated peptide antibody (anti-CCP antibody), rheumatoid factor (RF), immunoglobulins, B cells, and selected peripheral B cell subsets.
- To explore the potential associations between selected biomarkers (baseline and response to treatment) and selected disease activity measures.
- To explore the potential development of anti-LY2127399 antibodies following long-term dosing.

continued

Study Design:
Study H9B-MC-BCDI (BCDI) was a multi-center, 52-week, open-label, flexible-dose extension study that enrolled RA patients who completed one of two 24-week randomized controlled trials (BCDG and BCDH) of LY2127399 versus placebo and had received at least 3 doses of study drug.
Patients were to participate in monthly visits to the study site. Safety was evaluated at all study visits while evaluation of RA disease activity was conducted periodically through the end of the study, as specified in the Study Schedule. Additional visits beyond Week 72 could be scheduled if needed to assess patient safety, including monitoring B cell counts. The first visit in Study BCDI was on or within 3 days of the Week 24 visit in Studies BCDG or BCDH.

Number of Patients: Planned: The expected maximum sample size was approximately 249 patients (given approximate sample sizes of 99 patients for Study BCDG and 150 patients for Study BCDH). It was anticipated that between 187 and 236 patients would enroll in Study BCDI.
Randomized and Treated (at least 1 dose): A total of 182 patients received LY2127399, 60 patients in the LY2127399 60-mg only group, 121 patients in the LY2127399 60/120-mg group and 1 patient in the LY2127399 60/120/60-mg group.

Diagnosis and Main Criteria for Inclusion:
[1] Had participated for at least 24 weeks in either Study BCDG or Study BCDH and received at least 6 weeks or 12 weeks of study drug, respectively. Visit 1 of Study BCDI had to be completed within 3 days of the Week 24 visit of the previous study.
[2] Women who were pregnant, breastfeeding, or at risk to become pregnant during study participation were not included; a negative pregnancy test was required. Women of childbearing potential had to use a medically permitted form of contraception during the whole study.
[3] Had given written informed consent approved by Lilly or its designee and the Investigational Review Board/Ethical Review Board (IRB/ERB) governing the site.

Study Drug, Dose, and Mode of Administration: LY2127399 was administered to patients at doses of 60 mg (or 120 mg at the investigator's discretion starting at Visit 4 or later) SC Q4W for 48 weeks. Investigators could increase the LY2127399 dose to 120 mg at Visit 4 or any visit thereafter based on their clinical judgment and if a patient had at least 4 tender and 4 swollen joints. Investigators could decrease the LY2127399 dose at any visit after having increased the LY2127399 dose based on their clinical judgment and safety profile of the patient. Only 1 dose increase to 120 mg and 1 dose decrease to 60 mg were permitted per patient; no further adjustments of the LY2127399 dose were allowed. Lots [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted]

Reference Therapy, Dose, and Mode of Administration: Not applicable

Duration of Treatment: The total duration of treatment was 48 weeks, that is, 13 administrations of study drug.

Variables:
Efficacy:
Primary efficacy variable:
- ACR 50% responder index ACR50.

Secondary efficacy variables:
- ACR20, ACR70, ACR-N, and ACR core set (tender joint count (TJC) [28/68], swollen joint count (SJC) [28/66], patient's assessment of joint pain, patient's global assessment of disease activity, physician's global assessment of disease activity, Health Assessment Questionnaire – Disability Index [HAQ-DI], DAS28 and EULAR28). Additional variables were the maintenance of clinical improvement as measured by ACR Functional Class, FACIT Fatigue score, SF-36 domain scales (physical health component summary (PCS) and mental health component summary (MCS) scores), and C-reactive protein (CRP).

continued

Safety:
Adverse events (AEs), clinical laboratory evaluations, vital signs, 12-lead electrocardiograms (ECGs).
Pharmacokinetic: Graphical analysis was performed to compare the 1,997 LY2127399 serum concentrations collected from 182 patients in this study to predictions based on the BCDG and BCDH data and analysis.
Pharmacodynamics**:**
Cluster of determination (CD)20+ B cell counts, CD19+ cell counts, CD19+ B cell subsets (mature naïve [CD19+, CD27-, IgD+], immature/transitional [CD19+, IgD-, CD27-], memory [CD19+, IgD-, CD27+], and nonswitched memory [$CD19^+$, IgD+, CD27+]), disease-related biomarkers (RF, CRP, anti-CCP), and erythrocyte sedimentation rate (ESR), and serum immunoglobulins.

Evaluation Methods: Descriptive statistics including the number of patients, mean, standard deviation (SD), median, minimum, and maximum were provided for continuous variables, and frequency counts and percentages were tabulated for categorical variables.

Efficacy:

For the ACR20, ACR50, and ACR70 response analyses, patients who discontinued from the study prior to Week 52 were imputed as non-responders (non-responder imputation [NRI]/last observation carried forward [LOCF]). For patients who reached the Week 52 visit, but had 1 or more of the 7 parameters missing at Week 52, LOCF was used to impute the missing values. For all other measures, the LOCF approach was used.
The primary efficacy endpoint was the ACR50 responder index at Week 52 (NRI/LOCF).
The secondary efficacy endpoints – ACR50 at all other time points; and ACR20, ACR70 and EULAR28 at all-time points – were summarized and analyzed similarly to the primary efficacy endpoint. The continuous secondary efficacy endpoints (ACR-N and ACR components, ie, TJC, SJC, patient's assessment of joint pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI, CRP, and DAS28 score) were summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) by treatment group at all applicable time points. The health outcomes questionnaires used in this study (SF-36 and the FACIT fatigue scale) were summarized and analyzed as described above for the continuous secondary efficacy endpoints.

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

Bioanalytical and Pharmacokinetic and Pharmacodynamics: Steady-state and single dose PK profiles were simulated and a 90% prediction interval created using the final model derived from BCDG and BCDH data. Graphical analysis was used for comparison of the model predictions with the observed BCDI data. For pharmacodynamic (PD) assessments, the visit values and change from baseline values were summarized using similar methods as 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 timepoints.

Summary

Patient Characteristics

A total of 182 patients received LY2127399, 60 patients in the LY2127399 60-mg only group, 121 patients in the LY2127399 60/120-mg group and 1 patient in the LY2127399 60/120/60-mg group.
This study was conducted in an international population with 42.0% of the patients enrolled in North America, 33.1% in Eastern Europe, 14.4% in South America, 5.5% in Asia, and 5.0% in Western Europe.
Mean values for physician's global assessment of disease activity, patient's assessment of disease activity, patient's assessment of joint pain, DAS28 scores as well as CRP, ESR, RF, and anti-CCP antibody values were higher at BCDI baseline in the LY2127399 60/120-mg group than in the LY2127399 60-mg group, supporting the need for an increase to LY2127399 120 mg in these patients.

Efficacy

The overall ACR50 response rate at Week 52 (NRI/LOCF) was 20.0% in the ITT population by Study BCDI treatment assignment and assessed by pre-LY2127399 baseline. The ACR50 response rate at Week 52 (NRI/LOCF) in the LY2127399 60-mg group was 33.9% and 13.3% in the LY2127399 60/120-mg group, demonstrating clinical improvement in patients receiving LY2127399 over the 52-week period. The ACR50 response rate at Week 72

assessed by pre-LY2127399 baseline was 22.1% among patients remaining in the study at that time. The overall ACR20 response rate at Week 52 (NRI/LOCF) was 43.3%. The ACR20 response rate at Week 52 (NRI/LOCF) was 66.1% in the LY2127399 60-mg group and 32.5% in the LY2127399 60/120-mg group. The overall ACR70 response rate at Week 52 (NRI/LOCF) was 10.6%, that is, only a few patients achieved an ACR70 response. For ACR50, similar results were found for the PP Population as for the ITT Population.

The correlation analysis showed statistically significant negative correlations between ACR-N and CRP levels and between ACR-N and the percentage of CD20+ B cells. The higher the ACR-N, the lower were both the relative proportion of CD20+ B cells and the CRP levels. The patients in the LY2127399 60/120 mg group, despite treatment with the increased dose, had higher baseline disease severity and did not achieve response rates equivalent to the 60 mg group patients for these disease improvement indices.

The mean (SD) change in FACIT fatigue score from baseline to Week 52 (LOCF) was 0.7 (9.8) points in all patients; 1.8 (7.3) points were reported in the LY2127399 60-mg group and 0.2 (10.8) points in the LY2127399 60/120-mg group. The mean (SD) changes in the SF-36 PCS and MCS scores from baseline to Week 52 (LOCF) in all patients were 1.2 (8.8) points for PCS and -0.1 (10.1) points for MCS, 1.7 (7.0) points for PCS and 1.2 (10.0) points for MCS in the LY2127399 60-mg group, and 1.0 (9.6) points for PCS and -0.7 (10.2) points for MCS in the LY2127399 60/120 mg group. Long-term (up to 52 weeks) efficacy was observed in both the LY2127399 60-mg and 60/120 mg groups as measured by the percentage of patients who achieved ACR20, ACR50, and ACR70 response, as well as by ACR-N, EULAR responses, change in DAS28, and change in HAQ-DI.

Pharmacokinetics

Pharmacokinetic concentrations of LY2127399 for patients in study BCDI show close alignment with established model predictions. The PK model was previously developed using data from studies BCDG and BCDH, which are the originating studies for this extension study. Since the model predictions are consistent with the observed data in BCDI, this suggests the PK was time-independent over the duration of this study. In addition, presence of treatment-emergent anti-drug antibodies seem to have minimal or no impact on the PK of LY2127399, at least for the duration of this study.

Pharmacodynamics

CD20+ B cell counts gradually declined over time, but were not totally depleted by Week 52 and the effect was maintained after Week 52 with relative decreases of 40% or more both in the LY2127399 60-mg group and the LY2127399 60/120-mg group until Week 100. CD19+ B cell counts declined over time for mature naïve and immature B cells. Most patients (84%) returned to at least 43 cells/µL (the lower limit of the reference range) or at least 50% of baseline levels during the post-treatment follow-up period and using a Kaplan-Meier estimate, the median time to B cell recovery after the last injection was 40.6 weeks (confidence interval: 39.6-51.3). Mean IgG, IgM and IgA levels consistently decreased through Week 52 without clinically relevant differences among the LY2127399 treatment groups. There was no indication that reductions in B cells or in serum immunoglobulins below the lower limit of normal were associated with an increased frequency of infections. No clear relationship to treatment was indicated by changes from baseline in mean RF levels and anti-CCP antibody levels over the course of the study.

Safety

Overall, 21 (11.5%) patients had an SAE though Week 52, with 4 (6.7%) patients in the LY2127399 60-mg group, 16 (13.2%) patients in the LY2127399 60/120-mg group and 1 (100.0%) patient in the LY2127399 60/120/60-mg group. During the follow-up period, 9 (4.9%) patients had an SAE.

One patient in the LY2127399 60/120-mg group had a myocardial infarction that led to death on Day 182 of the treatment period. This SAE was not related to study drug in the opinion of the investigator. During the follow-up period, 3 additional deaths unrelated to study drug in the opinion of the investigator were reported.

The percentage of patients who experienced TEAEs through Week 52 was 66.7% in the LY2127399 60-mg group and 79.3% in the LY2127399 60/120-mg group. The system organ class (SOC) for which TEAEs were most frequently reported was infections and infestations. Overall, 44.0% of patients who received LY2127399 reported an infection/infestation through Week 52.

Overall, 75 (41.2%) patients who received LY2127399 experienced a Follow-up emergent AE (FEAE). The overall frequencies of AEs of special interest (AESI) were similar among treatment groups through Week 52 and thereafter lower in the LY2127399 60/120-mg group.

When AE rates are compared by patient years of exposure, the rate of events is marginally lower with 110.6 AEs per 100 patient years of exposure of LY2127399 60-mg compared with 118.1 AEs per 100 patient years of exposure of LY2127399 120-mg.

No clinically significant differences between groups in hematologic or chemistry values, vital signs, or ECGs were seen. The incidence of treatment-emergent, persistent anti-LY2127399 antibodies (2 dilutions/4-fold increase over baseline) was 6.2% (11/178).

Conclusions

No unexpected safety signals were observed. Despite different treatment regimens and patient populations in prior Studies BCDG and BCDH, the majority of patients in both treatment groups (LY2127399 60-mg and LY2127399 60/120 mg) appeared to maintain efficacy response with long-term (up to 52 weeks) open-label LY2127399 treatment. Treatment with LY2127399 reduced total B cells, mature naïve and immature B cells, and serum immunoglobulins, while switched memory and nonswitched memory B cells counts increased. Total B cell counts decreased without total depletion and most patients returned to either the lower limit of the reference range or at least 50% of baseline levels during the post-treatment follow-up period.