# 2. GSDB Synopsis

Approval Date: 31-Jan-2014 GMT

# Clinical Study Report Synopsis: Study I2M-MC-GSDB

**Title of Study:** A Phase 2 Randomized Study of LY2541546 versus Placebo in Postmenopausal Women with Low Bone Mineral Density: An Evaluation of the Dose Response Relationship Using Bone Mineral Density

**Number of Investigators:** This multicenter study included 13 principal investigators.

**Study Centers:** This study was conducted at 13 study centers in 5 countries.

**Publications Based on the Study:**

Benson C, Robins D, Recker R, Alam J, Chiang AY, Mitlak B, Sipos A, Hu L. Effect of blosozumab on bone mineral density: results of a phase 2 study of postmenopausal women with low bone mineral density. *Bone Abstracts.* 2013; 1:OC5.3. Abstract OC5.3.

Keaveny TM, Myers SL, Chiang AY, Alam J, Robins DA, Krege J, Sipos AA, Mitlak BH, Benson C. Effects of blosozumab on estimated spine and hip strength in postmenopausal women with low bone mineral density: finite element analysis of a Phase-II dosing study. *J Bone Miner Res.* 2013; 28(suppl 1):1023.

Matsumoto T, Robins D, Alam J, Chiang AY, Hu L, Miltak B, Sipos A, Benson C. Effect of blosozumab on bone mineral density in Japanese and non-Japanese postmenopausal women with low bone mineral density. *IBMS BoneKEy*. 2013; S9. Abstract OC02.

| **Length of Study:** | **Phase of Development:** Phase 2 |
|---|---|
| Date of first patient enrolled: 11 August 2010<br>Date of last patient completed entire study: 22 February 2013 | |

**Objectives:**

The primary objective of this study was to evaluate the dose response of LY2541546 using bone mineral density (BMD) changes from baseline, as measured by dual energy x-ray absorptiometry (DXA) of the lumbar spine at 52 weeks, compared with placebo in postmenopausal women with low BMD.

The secondary objectives of the study were:

- To evaluate the overall safety and tolerability of LY2541546 following multiple subcutaneous (SC) administrations.
- To evaluate the dose or doses of LY2541546 that increase BMD from baseline, as measured by DXA of the lumbar spine at 12 and 24 weeks, compared with placebo.
- To evaluate the dose or doses of LY2541546 that increase BMD from baseline, as measured by DXA of the proximal femur and wrist (distal radius), compared with placebo.
- To evaluate the dose effect of LY2541546 on biochemical markers of bone metabolism, bone-specific alkaline phosphatase (BSAP), serum type I collagen fragment (CTx), osteocalcin, and N-terminal extension propeptide of type I collagen (P1NP).

The exploratory objectives of the study were:

- To explore the immunogenicity of LY2541546.
- To explore the population pharmacokinetics (PK) of LY2541546 and the relationship between LY2541546 exposure and pharmacodynamic (PD) endpoints.
- To explore the effects of variants in SOST, LRP5, and additional genes in the Wnt pathway on safety and/or efficacy of LY2541546.
- To explore bone quality using quantitative computed tomography scans of the hip and spine (in a subset of patients, as described in the addendum).
- To explore cranial nerve function in a subset of patients using auditory evoked potential testing.
- To explore BMD changes in the head and body, using whole-body DXA measurement (including the head), in a subset of patients.

**Study Design:** A randomized, parallel-design, double-blind, placebo-controlled, multiple-dose, Phase 2 study evaluating the efficacy and safety of LY2541546 in postmenopausal women with low BMD (lumbar spine T-score from -3.5 to -2.0, inclusive).
There were 2 addenda added to the study that affected the study design. The first addendum added a fourth treatment arm (with additional placebo patients) of LY2541546 270 mg every 12 weeks (Q12W). The second addendum extended the follow-up period an additional 40 weeks (for a total of 52 weeks of follow-up) for all patients except those in the additional dosing group addendum.

**Number of Patients**:
Planned: 240
Randomized: 117 active drug, 37 placebo
Treated (at least 1 dose): 116 active drug, 37 placebo
Completed: 102 active drug and 34 placebo in treatment and 12-week follow-up phases; 88 treatment and placebo patients completed the 40-week follow-up extension.

**Diagnosis and Main Criteria for Inclusion:**
Ambulatory postmenopausal women, whose menopausal status was confirmed, aged 45 to 85 years, inclusive, were enrolled in the study. Women with low BMD, defined as a lumbar spine T-score from -3.5 to -2.0, inclusive, based on the local DXA report as interpreted by the investigator, were included in this study.

Patients who had previous significant exposure to another osteoporosis drug were not enrolled in the study. The following were also exclusion criteria for enrollment in the study: (a) severe vitamin D deficiency, (b) a history of osteoporotic fracture, (c) a bone disease other than osteoporosis, (d) a history of cranial nerve damage, or (e) treatment with any other therapeutic agent that may confound the interpretation of study results.

**Study Drug, Dose, and Mode of Administration:**
There were 4 dose levels/regimens of LY2541546: 180 mg every 4 weeks (Q4W), 180 mg every 2 weeks (Q2W), 270 mg Q2W, and 270 mg Q12W. For the Q4W and Q12W dosing regimens, patients received placebo on alternate dosing visits.

During the lead-in period and throughout the duration of the treatment period and follow-up period, all patients received approximately 1000 mg/day of elemental calcium and approximately 1000 IU/day of vitamin D as open label supplements.

**Reference Therapy, Dose, and Mode of Administration:** Placebo (0.9% sodium chloride injection, United States Pharmacopeia [USP]) administered SC by site personnel during study visits. During the lead-in period and throughout the duration of the treatment period and follow-up period, all patients received approximately 1000 mg/day of elemental calcium and approximately 1000 IU/day of vitamin D as open label supplements.

**Duration of Treatment:**
Treatment period: Exposure to study drug for 52 weeks (26 doses, last dose at Week 50)

**Variables:**

Efficacy: The primary endpoint was the change from baseline to endpoint (at 52 weeks) in BMD of the lumbar spine, measured by DXA.

Secondary efficacy variables included BMD changes from baseline to the following time points:

- 12 weeks: Lumbar spine
- 24 weeks: Lumbar spine and proximal femur (femoral neck, trochanter, intertrochanteric, Ward's triangle, and total hip)
- 52 weeks: Proximal femur, wrist (distal radius), whole body
- 64 weeks: Lumbar spine and proximal femur (femoral neck, trochanter, intertrochanteric, Ward's triangle, and total hip).

Changes in biochemical markers of bone metabolism, including BSAP, serum CTx, osteocalcin, and P1NP, were also assessed.

Safety: Routine safety parameters including adverse events (AEs), vital signs, electrocardiogram (ECG), safety laboratory tests, and clinical assessments were monitored throughout the study. Blinded reviews of the safety data from all enrolled patients occurred monthly throughout the study. In addition, the immunogenicity of LY2541546 was explored in blood samples collected from patients randomized to LY2541546.

Bioanalytical: Blood samples collected from patients randomized to LY2541546 were analyzed to determine sclerostin levels and concentrations of LY2541546. Sclerostin levels in patients randomized to placebo were also analyzed.

**Statistical Methods:**

Approximately 120 patients were entered into the study so that at least 80 patients were considered evaluable. An evaluable patient was defined as any randomized patient with a baseline and 24-week lumbar spine BMD measurement following study treatment. Patients who qualified for enrollment into the study were randomized in a 1:1:1:1 ratio to receive 180 mg Q4W, 180 mg Q2W, or 270 mg Q2W LY2541546, or placebo Q2W.

With 20 evaluable patients in each group, the study had 93% power to detect the overall treatment main effect among 3 doses of LY2541546 and placebo. The sample size was determined based on data from Study B3D-MC-GHAC using a simulation (with 1000 runs) at a two-sided 5% significant level, multiplicity adjusted, under the following assumptions.

- Expected changes from baseline in lumbar spine BMD for 1 of the 3 LY2541546 groups at 12-week, 24-week and 52-week visits of 0.03, 0.05, and 0.06 $g/cm^2$, respectively (corresponding to percentage increases of 3.78%, 6.22%, and 8.26%, respectively), with no difference for each of the other 2 LY2541546 groups
- Expected changes from baseline in lumbar spine BMD for placebo at 12-week, 24-week, and 52-week visits of 0, 0.01, and 0.01 $g/cm^2$, respectively
- Common standard deviation of 0.04 $g/cm^2$
- Compound symmetry variance-covariance structure with a correlation of 0.5 in the mixed-effect repeated measure model

Furthermore, to detect the treatment effect based on the 24-week lumbar spine BMD comparison of the above assumed active LY2541546 group compared to placebo, the power was 86% with Bonferroni multiplicity adjustment.

The assumptions above were consistent with the data observed in the multiple-dose study of LY2541546 (Study I2M-MC-GSDE).

The following three interim analyses occurred for this study:

- The first interim lock was conducted after all of the original GSDB patients completed Week-24 BMD.
- The second interim analysis was conducted after at least 60% of the original GSDB patients completed Week-52 BMD and at least 80% of Q12W dosing group patients completed Week-24 BMD.

- The third interim analysis was conducted when all original GSDB patients completed Week-52 BMD and 12 weeks of follow-up. The LY2541546 270 mg Q12W dosing group's data up to the cutoff date were included in the third interim, but no 3-month follow-up data were available.

The final datalock for this study was conducted once all patients enrolled in the 40-week follow-up extension (Addendum 4) had completed the Week-104 BMD.

Efficacy: The primary efficacy analysis compared the change from baseline in lumbar spine (L1 through L4) BMD at 52 weeks between each of the LY2541546 doses and placebo. This comparison was performed using a mixed-model repeated measures (MMRM) analysis of covariance. Factors in the model include treatment, time, and the interaction of treatment-by-time as fixed effects, and baseline lumbar spine BMD as a covariate. Pairwise comparison between each of the LY2541546 doses and placebo at each time point was made by constructing contrasts of the difference in lumbar spine BMD changes (two-sided 5% significant level, multiplicity-adjusted). A secondary analysis of the primary outcome was conducted by using only the lumbar spine BMD change from baseline at Week 24. Treatment effect of LY2541546 was evaluated using Dunnett's t-test at the 0.05 significance level. Another secondary analysis of the primary outcome was performed using the same model as for the primary analysis; however, this analysis also included data from the Week-12 visits. Analyses based on percent changes of lumbar spine and proximal femur BMD, and bone biochemical markers were performed to help interpret the findings.

Safety: Adverse events were analyzed as to whether they were treatment-emergent adverse events (TEAEs). For each TEAE, the severity level was recorded (mild, moderate, or severe). The frequency and percentage of TEAEs were summarized by treatment group in the treatment period and follow-up period of the study. The proportion of patients experiencing TEAEs were compared among all treatments groups. A listing of safety lab parameters and vital signs (sitting systolic blood pressure, diastolic blood pressure, and pulse rate) for each patient was provided. Summary statistics (including number of patients, mean, standard deviation, minimum, and maximum) of the raw and change from baseline values for these parameters were computed by each treatment group by visit. Vital signs were analyzed using an MMRM model. Least-squares means (LSM) were obtained from this model for each treatment group and visit, and comparisons were displayed showing the treatment difference LSM and the p-value.

For the interim analyses, lumbar spine BMD was analyzed in the same manner as described above. Analyses based on percent change of lumbar spine BMD from baseline were performed using the same model. Secondary and additional exploratory analyses of safety and efficacy parameters were performed, and details of the analyses are described in the statistical analysis plan.

Pharmacokinetic/Pharmacodynamic: Pharmacokinetic parameters for LY2541546 were estimated by population PK analysis method with a compartmental model using NONMEM. The PK parameters estimated with the model include: constant systemic clearance (CL), saturable systemic clearance (CLSAT), intercompartmental clearance (Q), Michaelis-Menten constant (C50), absorption rate constant (Ka), central volume (V), peripheral volume (V2), and absolute bioavailability (F). The terminal half-life ($t_{1/2}$) of LY2541546 was derived from the PK parameters obtained in the model. Potential factors, including but not restricted to age, body size, and immunogenicity, that have an overt effect on blosozumab exposure were explored. Population PK/PD analyses were conducted to explore exposure-response relationships between serum LY2541546 concentrations and PD endpoints including lumbar spine BMD, total hip BMD, and other biomarkers as appropriate to help understand the temporal nature of the relationship between drug concentrations and effects.

**Summary:**

There were 154 postmenopausal women randomized to Study GSDB, and 153 received at least 1 dose of study drug. Nearly all of the patients were either Caucasian (56.9%) or Japanese (42.5%). Based on the average lumbar spine T-score of -2.76, patients enrolled in Study GSDB had osteoporosis. The mean age of the population was 65.2 years. There were few drop outs from the study (11%), and there was no difference across the treatment groups in discontinuations or reasons for discontinuations.

The primary efficacy endpoint was met: There was a dose-related increase in lumbar spine BMD at 52 weeks of treatment. The increase from baseline in lumbar spine BMD was significantly different from placebo at all time periods (Weeks 12, 24, and 52) with every LY2541546 dose ($p<0.001$). The following are the key BMD changes following 52 weeks of LY2541546 treatment:

- Lumbar spine percent change from baseline: 6.83%, 8.40%, 14.89%, and 17.77% for the LY2541546 270 mg Q12W, 180 mg Q4W, 180 mg Q2W, and 270 mg Q2W groups, respectively. The placebo BMD percent change from baseline at Week 52 was -1.43%.
- Total hip percent change from baseline: 2.54%, 2.18%, 4.60%, and 6.71% for the LY2541546 270 mg Q12W, 180 mg Q4W, 180 mg Q2W, and 270 mg Q2W groups, respectively. The placebo patients had a 0.61% decrease in BMD from baseline.
- Femoral neck percent change from baseline: 2.14%, 2.79%, 3.98%, and 6.31%, for the LY2541546 270 mg Q12W, 180 mg Q4W, 180 mg Q2W, and 270 mg Q2W groups, respectively. The placebo patients had a 0.49% change in BMD from baseline.
- There was no significant BMD change from baseline for any site in the radius.

After cessation of LY2541546 treatment for 12 weeks, there was usually a decrease in lumbar spine BMD and BMD at sites in the hip compared with changes from baseline at 52 weeks of treatment; however, most changes from baseline remained significantly greater than that of placebo. After cessation of LY2541546 for an additional 40 weeks (52 weeks total), all skeletal sites had decreases in BMD compared with Week-52 treatment values; however, the change from baseline values for the 2 highest LY2541546 dose groups, 180 mg Q2W and 270 mg Q2W, usually were significantly different from placebo change from baseline, suggesting that the gains made by LY2541546 treatment were not completely eliminated 52 weeks after treatment ended.

Biochemical markers of bone metabolism supported a bone anabolic effect of LY2541546. After cessation of LY2541546 treatment, there was a slight decrease in the bone formation markers and a slight increase in the bone resorption maker, supporting the gradual decline in BMD during the follow-up period.

There was a dose-related increase in sclerostin levels, with peak levels reached between Weeks 2 and 4 for the 3 lower-dose groups. Sclerostin levels for the 270 mg Q2W group generally increased throughout the treatment part of the study, with peak levels measured at 52 weeks of treatment.

LY2541546 shows drug concentration dependent nonlinear PK, with apparent $t_{1/2}$ varying between approximately 3 and 14 days.

LY2541546 was well-tolerated at each dose level investigated in this study. No patient died during either the treatment phase or the follow-up phases of the study. The incidence of serious adverse events (SAEs) and discontinuations due to AEs was low. The only SAE or AE that led to discontinuation of more than 1 patient was breast cancer. None of the 4 reported cases of breast cancer were considered related to LY2541546 treatment. Each case had confounding factors and heterogeneous histopathology.

Injection site reaction was the only TEAE considered related to LY2541546 treatment. The injection site reactions were usually mild in severity, localized, self-limiting, and did not increase in frequency or severity upon increased exposure to study drug, nor were they associated with anti-LY2541546 antibodies.

There was an initial decrease in serum calcium levels accompanied by an increase in intact parathyroid hormone (PTH) levels. As LY2541546 treatment results in rapid increases in BMD, it is likely that the changes in calcium levels were a result of rapid bone mineral increase and that the changes in PTH were a physiological response to serum calcium levels. There were no AEs associated with the changes in calcium or PTH.

Treatment emergent anti-LY2541546 antibodies were detected in 31.9% of patients treated with LY2541546 (37of 116). Of those anti-LY2541546 antibodies, 19 were determined to be neutralizing by assay. However, only 1 patient (LY2541546 180 mg Q2W group) developed anti-LY2541546 antibodies that had an effect on LY2541546 exposure and efficacy. The development of anti-LY2541546 antibodies appeared to be inversely dependent on dose and dose frequency. There were no AEs associated with the development of anti-LY2541546 antibodies in any of the patients, including the one with reduced LY2541546 exposure.

There were no clinically significant changes in ECGs, vital signs, or brainstem auditory evoked potential tests.

**Conclusions:**

The primary efficacy endpoint was met as treatment with LY2541546 for 52 weeks resulted in a significant dose response increase in lumbar spine BMD, as well as a significant increase in total hip BMD. The increase in lumbar spine and hip BMD from baseline remained significantly greater than placebo 52 weeks after discontinuation of LY2541546 treatment for the 2 highest LY2541546 doses. Evaluation of bone turnover markers supported a bone anabolic effect of LY2541546 as the mechanism underlying the increase in BMD. LY2541546 shows drug concentration dependent nonlinear PK, with apparent $t_{1/2}$ varying between approximately 3 and 14 days. LY2541546 was well tolerated at each dose level investigated in this study. The only TEAE associated with LY2541546 was injection site reaction, which was generally mild, self-limiting, and did not increase in incidence with repeated dosing. Transient asymptomatic calcium and intact PTH laboratory changes were associated with the pharmacology of LY2541546.

LY2541546 appears to have bone anabolic effects, is well tolerated, and warrants further investigation as a treatment for osteoporosis.