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# Early Changes in Bone Turnover Markers Are Associated With Increases in BMD During Treatment With Blosozumab in Postmenopausal Women With Low BMD

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## ABSTRACT

**Background**: A randomized, blinded study evaluated the effect of treatment with blosozumab, a humanized monoclonal antibody targeted against sclerostin, on BMD and bone turnover markers (BTMs) in postmenopausal women with low BMD. The objectives of these analyses are to determine the 1) relationship between changes in BTMs (PINP, BALP, OC, and CTX) at 2, 4, and 12 weeks and changes in BMD after 1 year of treatment; 2) BTM and time point most strongly associated with 1-year changes in spine, hip, and total body BMD; and 3) proportions of patients responding to treatment based on change in BTMs.

**Method**: Multiple regression models with applied forward selection identified the strongest association between changes in BTMs and changes in spine, hip, and total body BMD after 1 year of treatment. Least significant change (LSC) in BTM was determined from within subject variability of repeated measures to define proportions of responders.

**Results:** A strong association was observed between early change in BTMs reflecting bone formation and BMD increases with 1 year of blosozumab treatment. In a model considering treatment effect and BTMs reflecting bone formation, changes in PINP at 2 and 4 weeks were significantly correlated with changes in spine (P<0.01) and hip BMD (P<0.02) at 1 year. When treatment and PINP increases were considered, CTX decrease at 2 weeks was also significantly correlated with change in hip (P=0.04) but not spine BMD. In the highest dose group, PINP at 4 weeks was correlated (P<0.01) with BMD at 52 weeks (spine r=0.51, hip r=0.56, whole body r=0.62). The LSC from post-baseline PINP measurements in the placebo group was 10 ng/mL; response rates were >95% with Q2W dosing, 52% with Q4W dosing, and 8% with placebo.

**Conclusion**: We conclude change in PINP by 4 weeks of treatment with blosozumab identifies later BMD response at 1 year of treatment.

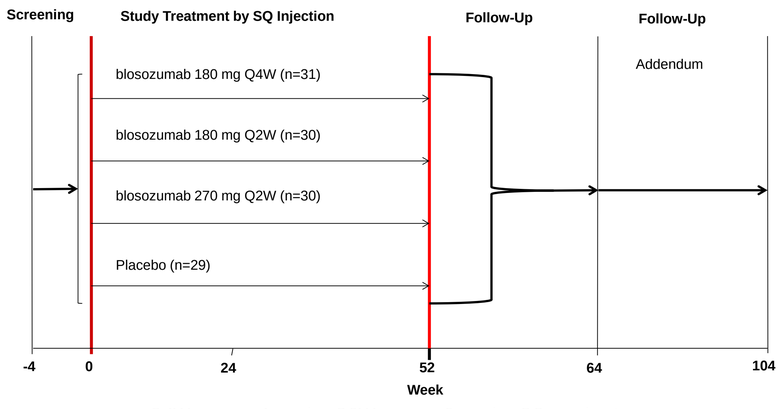
## BACKGROUND

- Osteoporosis, a condition that affects >200 million people worldwide,[1] is associated with bone fragility, risk of fracture due to low bone mineral density (BMD), altered bone microarchitecture, and reduced bone strength.[2-3]
- Contemporary anabolic treatments for severe osteoporosis are directed at preferentially stimulating osteoblastic activity over osteoclastic activity.[4]
- Biochemical tissue markers of bone turnover (BTMs) may provide clinically useful information in managing patients with severe osteoporosis.[4]
- BTMs in serum include those associated with new bone formation (N-terminal extension propeptide of type 1 collagen [PINP], bone-specific alkaline phosphatase [BALP], osteocalcin [OC]) and resorption (serum type I collagen fragment [CTX]).[5]
- Sclerostin, a negative regulator of mineralized bone matric formation and bone mass, represents a new target in the treatment of osteoporosis.[6]
- Blosozumab is a humanized monoclonal IgG4 antibody targeted to sclerostin.[7]
- A Phase 2 study that assessed the safety and efficacy of different blosozumab doses in postmenopausal women found that 52 weeks of blosozumab treatment significantly increased lumbar spine BMD and was generally well tolerated.[7]

### Study Population and Design

- Postmenopausal women with a baseline lumbar spine T-score of -3.5 to -2 were randomized to blosozumab or placebo for 52 weeks followed by a 52-week follow-up period (Figure 1)

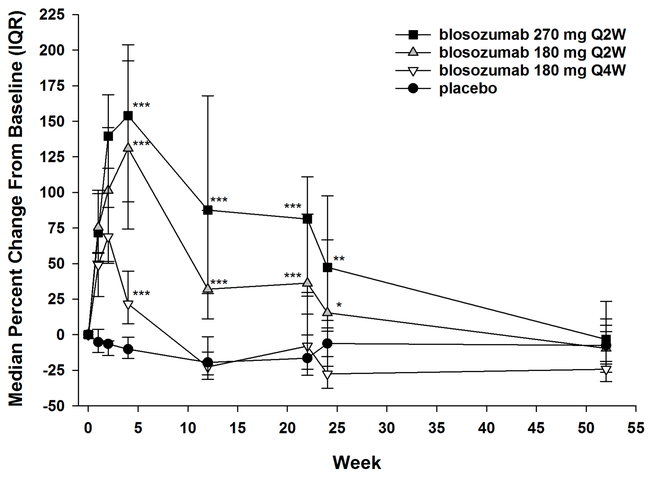
### Figure 1. Study Design and Treatment[a]




*Q4W = every 4 weeks; Q2W = every 2 weeks; SQ = subcutaneous*
*[a]One hundred six women (88.3%) completed 52 weeks of treatment.*

- Elevated bone formation and decreased bone resorption markers were observed (Figure 2).

### Figure 2. Median Percent Change in PINP from Baseline to Week 52




*IQR = interquartile range; PINP = N-terminal extension propeptide of type 1 collagen; Q2W = every 2 weeks; Q4W = every 4 weeks*
*Asterisks indicate statistically significant differences (*P<0.050, **P<0.010, ***P<0.001) for each study group as compared with placebo.*

### Objectives

- To determine:
  - Relationship between changes in BTMs (PINP, BALP, OC, and CTX) at 2, 4, and 12 weeks and changes in BMD after 52 weeks of treatment.
  - BTM and time point most strongly associated with 52-week changes in spine, hip, and total body BMD.
  - Proportions of patients responding to treatment based on changes in BTMs.

## METHODS

- Parameters analyzed:
  - BMD: spine, hip, and whole body at 52 weeks
  - BTMs: PINP, BALP, OC, and CTX at 2, 4, and 12 weeks
- Multiple regression models with forward selection were used to identify the strongest association between early changes in BTMs and 52-week changes in BMD.
  - Parameters were considered statistically significant if P<0.05.
- Least significant change (LSC) in PINP was determined from placebo group using repeated measures analysis of variance to define the smallest difference between successive measurements.
  - The LSC was derived with no intervening treatment: LSC=2.77*SD (standard deviation).

## RESULTS

- Demographics and baseline characteristics for postmenopausal women with osteoporosis were well balanced across treatment groups (Table 1).

### Table 1. Patient Demographics and Baseline Characteristics

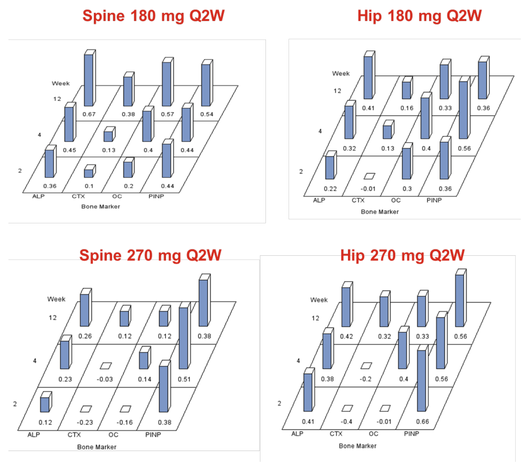
| | Treatment Group | | | |
|---|---|---|---|---|
| | Placebo (n=29) | Blosozumab 180 mg Q2W (n=30) | Blosozumab 270 mg Q2W (n=30) | Blosozumab 180 mg Q4W (n=31) |
| **Age, years (mean ± SD)** | 66.0 ± 9.2 | 64.2 ± 8.2 | 66.1 ± 7.7 | 66.8 ± 9.0 |
| **Ethnicity, n (%)** | | | | |
| Caucasian | 16 (55.2) | 17 (56.7) | 17 (56.7) | 17 (54.8) |
| Black | 1 (3.4) | 0 | 0 | 0 |
| Asian | 12 (41.4) | 13 (43.3) | 13 (43.3) | 14 (45.2) |
| **BMI, kg/m$^2$ (mean ± SD)** | 23.8 ± 5.6 | 23.7 ± 3.8 | 24.6 ± 4.7 | 23.1 ± 3.7 |
| **T-score (mean ± SD)** | | | | |
| Lumbar spine | –2.81 ± 0.54 | –2.77 ± 0.41 | –2.67 ± 0.53 | –2.79 ± 0.52 |
| Femoral neck | –2.13 ± 1.01 | –2.12 ± 0.88 | –1.94 ± 0.55 | –2.19 ± 0.72 |

*BMI = body mass index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation*

### Early Changes in BTMs and 1-Year Changes in BMD

- A strong association was observed between early changes in BTMs reflecting bone formation and BMD increases after 52 weeks of blosozumab with strongest correlations in Q2W treatment groups (Figure 3)

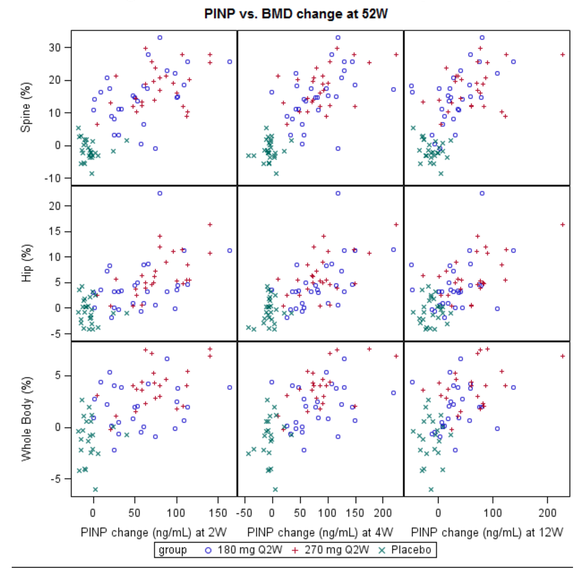
### Figure 3. Pearson's Correlations Between Absolute Changes in Bone Tissue Markers of Turnover at 2, 4, and 12 Weeks and Lumbar Spine and Hip BMD after 52 Weeks




*BMD = bone mineral density; Q2W = every 2 weeks; ALP = bone-specific alkaline phosphatase; CTX = resorption (serum type I collagen fragment); OC = osteocalcin; PINP = N-terminal extension propeptide of type 1 collagen*

- In the highest dose group (270 mg Q2W), the change in PINP at 4 weeks was highly correlated (P<0.01) with the changes in BMD at 52 weeks (spine r=0.51, hip r=0.56, whole body r=0.62) (Figure 4).

### Figure 4. Scatter Plots of Absolute Changes in PINP and Lumbar Spine, Hip, and Whole Body BMD




*BMD = bone mineral density; PINP = N-terminal extension propeptide of type 1 collagen;*
*Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; 52W = Week 52 of study*

- A series of multiple regression models with forward selection was constructed to evaluate the sequential effects of treatment alone (4 groups) plus any early changes in BTMs with BMD changes in lumbar spine and hip at 52 weeks.
- Changes in PINP at 2 and 4 weeks were the most significant predictors for both lumbar spine and hip BMD increases at 52 weeks (Table 2).
- When treatment and PINP increases were included in the model, CTX decrease at 2 weeks was also significantly correlated with change in hip BMD (P=0.04), but not lumbar spine BMD.

### Table 2. BTM Predictors of BMD Increase at 52 Weeks

| | BTM Marker | *P* value |
|---|---|---|
| **Lumbar spine** | PINP 2W | <0.0001 |
| | PINP 4W | 0.0092 |
| **Hip** | PINP 2W | <0.0159 |
| | PINP 4W | <0.0001 |

*2W = after 2 weeks of treatment; 4W = after 4 weeks of treatment;*
*BMD = bone mineral density; BTM = bone turnover marker;*
*PINP = N-terminal extension propeptide of type 1 collagen*

### Least Significant Change of PINP

- This analysis used only placebo group data and excluded baseline PINP.
- Successive PINP measures were modeled through a repeated measure analysis of variance, adjusted for time, body mass index (BMI), race, and age.
- The results showed the within-subject variability of PINP was 12 ng/mL.
- The LSC from post-baseline PINP was sqrt(12)*2.77, or approximately 10 ng/mL.

### PINP and BMD Response Rates

- For patients who had BMD measured at 52 weeks, response rates (PINP increase ≥10 ng/mL) were >95% with blosozumab Q2W dosing, 52% with blosozumab Q4W dosing, and 8% with placebo (Table 3).

### Table 3. Response Rates at Week 4

| | | Placebo (n=26) | Blosozumab 180 mg Q2W (n=29) | Blosozumab 270 mg Q2W (n=26) | Blosozumab 180 mg Q4W (n=27) |
|---|---|---|---|---|---|
| **PINP <10 ng/mL** | n (%) | 24 (92) | 1 (3) | 1 (4) | 13 (48) |
| **PINP ≥10 ng/mL** | n (%) | 2 (8) | 28 (97) | 25 (96) | 14 (52) |

*PINP = N-terminal extension propeptide of type 1 collagen; Q2W = every 2 weeks; Q4W = every 4 weeks*

## METHODS

- Parameters analyzed:
  - BMD: spine, hip, and whole body at 52 weeks
  - BTMs: PINP, BALP, OC, and CTX at 2, 4, and 12 weeks
- Multiple regression models with forward selection were used to identify the strongest association between early changes in BTMs and 52-week changes in BMD.
  - Parameters were considered statistically significant if P<0.05.
- Least significant change (LSC) in PINP was determined from placebo group using repeated measures analysis of variance to define the smallest difference between successive measurements.
  - The LSC was derived with no intervening treatment: LSC=2.77*SD (standard deviation).

## CONCLUSIONS

- Changes in PINP at 2 or 4 weeks of treatment with blosozumab was the single best predictor for spine and hip BMD increases at 52 weeks of treatment.
- A change of 10 ng/mL in PINP represents a least significant change, which was associated with the following response rates:
  - More than 95% of patients receiving 180 mg or 270 mg Q2W achieved PINP changes of ≥10 ng/mL at 4 weeks.
  - About 8% of patients receiving placebo achieved PINP changes of ≥10 ng/mL at 4 weeks.
- Data from this Phase 2 study suggest that PINP monitoring may be a useful aid in monitoring patients treated with blosozumab.

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### Acknowledgements and Disclosure:

- The authors wish to thank Teresa Tartaglione of ClinGenuity, LLC for assistance with poster creation and design.
- Conflicts of Interest: RE is a consultant for Eli Lilly and Company. All other authors are Lilly employees.
- This research was supported and funded by Eli Lilly and Company, including the preparation of this poster.