Population Pharmacokinetics and Pharmacodynamics of Blosozumab

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Objectives: Blosozumab is a humanized monoclonal antibody against sclerostin that is being evaluated as a treatment for osteoporosis. Population modeling was utilized to characterize the pharmacokinetics (PK) of blosozumab and establish pharmacodynamic (PD) exposure-response relationship for bone mineral density (BMD) changes in lumbar spine (LS) and total hip (TH).

Methods: The population PK model used data from three phase 1 studies in healthy postmenopausal (PMP) women (single or repeated intravenous infusions or subcutaneous [SC] injections of blosozumab or placebo) and one phase 2 study in osteoporotic PMP women (4 blosozumab SC regimens or placebo). The exposure-response model was constructed by jointly fitting LS and TH BMDs from the Phase 2 study. Limited covariate exploration was conducted on PK and PD parameters.

Results: Blosozumab PK data were best described by a two-compartment open model with both linear and saturable clearances (CL). In the final PK model, the linear CL was 8.82 mL/hr; volume of distribution was 3.96 L; bioavailability for the 2 SC formulations used was 54% and 69%, respectively. These values are typical for monoclonal antibodies. Body weight was found to influence the volumes and saturable CL.

The exposure-response model well described the observed changes in BMD. Briefly, blosozumab exposure was linked to a hypothetical target engagement module which led to LS and TH BMD responses through indirect response relationships. The baseline concentration of procollagen type 1 N propeptide (P1NP) was found to be a significant covariate for the production rate constant of BMD.

Conclusion: The population PK model and the exposure-response model for blosozumab adequately captured the observed PK and BMD data. By clinical trial simulations, these models support selection of appropriate regimens for future development of blosozumab.