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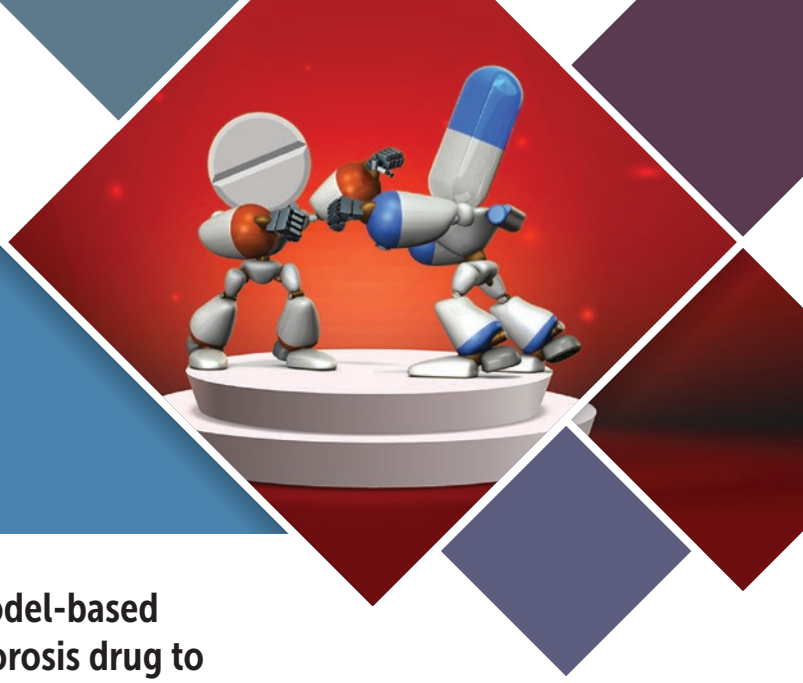

Using MBMA to Run Virtual "Head-to-head Trials"

Certara Strategic Consulting scientists used model-based meta-analysis to compare an approved osteoporosis drug to competing drugs in the same indication.

Background

Osteoporosis is a common health problem in post-menopausal women. The long-term sequelae of osteoporosis include bone fractures, particularly of the hip and vertebrae. Bone mineral density (BMD) of the lumbar spine (LS) and total hip (TH) are the canonical biomarkers for measuring the efficacy of osteoporosis drugs.

The sponsor had achieved regulatory approval in several countries for denosumab to treat this condition. Denosumab is a humanized monoclonal antibody that prevents osteoclast differentiation, activation, and survival by blocking the binding of receptor activator of nuclear factor-kappa B ligand (RANKL) to RANK. Inhibition of osteoclast-mediated bone absorption results in increased bone mass, volume, and strength.[1] Treatment with denosumab significantly decreased the risk of bone fracture in women with postmenopausal osteoporosis.[2]

Challenge

The osteoporosis drug landscape is crowded with many competitors with varying mechanisms of action (MOA). A year-long clinical trial comparing denosumab and alendronate in postmenopausal women with low bone mass suggested that denosumab treatment significantly increased LS and TH BMD compared to alendronate.[3] Denosumab has not been compared in clinical trials to other approved osteoporosis treatments.

Solution

Model-based meta-analysis (MBMA) was chosen as the most efficient method for comparing denosumab to the competition.[4] The primary goal of the MBMA was comparing the time course of LS and TH BMD changes during treatment with denosumab or other osteoporosis drugs. Comparing changes in BMD provided insight into the effect of dose, dose frequency, and route of administration.

Challenge

The sponsor needed to compare denosumab—an osteoporosis drug—to competing drugs in the same landscape.

Solution

Certara Strategic Consulting scientists used model-based meta-analysis (MBMA) to run virtual "head-to-head trials" of denosumab and other approved osteoporosis treatments.

Benefit

The MBMA analysis provided insight into how denosumab compares to other drugs approved for this indication without having to spend the time and money on running head-to-head trials.

The MBMA used data from 142 clinical trials (representing over 113,000 women) for preventing or treating postmenopausal osteoporosis. The drugs were grouped according to their MOA: bisphosphonates, selective estrogen receptor modulators (SERMs), parathyroid hormone (PTH), RANKL (denosumab), and calcitonin.

The percent change from baseline BMD was analyzed using a nonlinear least-squares random-effects meta-regression analysis. The dose-response relationship for BMD changes in the LS and TH was characterized by a maximal effect (E_{max}) model. The ratio of LS and TH BMD changes differed significantly across drug classes. The time course of BMD changes was characterized by an exponential onset with a different rate for LS and TH for each drug class.

Benefit

The dose-response relationship for denosumab showed that the approved dosing regimen resulted in maximal BMD changes. The MBMA showed that three years of treatment with denosumab resulted in bigger changes in LS and TH BMD compared to the same treatment duration with competing osteoporosis drugs approved in the US. While treatment with PTH resulted in larger increases in LS BMD compared to denosumab, treatment with the latter provided larger increases in TH BMD.

Impact

The MBMA analysis provided insight into how denosumab compares to other drugs approved for this indication without having to spend the time and money on running head-to-head trials.

References

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