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Model-based Meta-analysis: An Innovative Methodology Comes of Age

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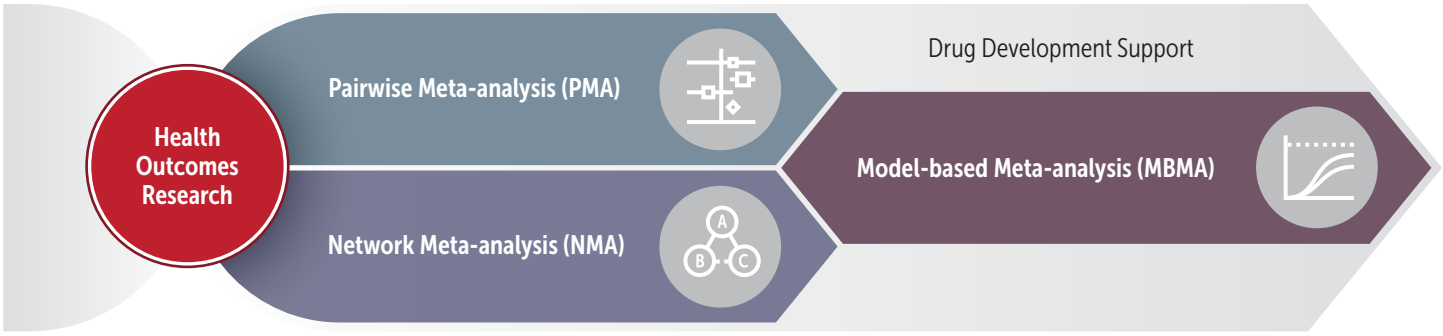
How MBMA can increase the likelihood of commercial success in drug development

Model-based Meta-analysis: What is it and why should you consider using it?

Making the right choices in drug development often means the difference between getting a new medication to patients and it ending up in the scrap heap of failed programs. If we are to progress beyond making decisions based on little more than gut feelings, we must rely on evidence to guide us. According to David Sacket and Gordon Guyatt, founders of evidence based medicine, "medical care and clinical decision making must be based on results (evidence) from empirical quantitative and systematic research." Drug development decisions are usually made with in-depth quantitative analysis of internal data from the drug candidate and a comprehensive, but less quantitative, review of public data or data from other candidates. While internally generated data is crucial, many important decisions cannot be made with internal data alone.

Today, surfeit of public information on approved drugs and those in development is available. How can sponsors turn clinical trial data into understanding that helps chart the course for investigational drugs? Moreover, most trials in drug development make comparisons against a placebo control or the standard of care (SOC). How can sponsors make head-to-head comparisons with other competing drugs approved for the same indication without spending excessive time and money? In the last decade, model-based meta-analysis (MBMA) has emerged as a methodology that quantifies clinical trial efficacy, tolerability, and safety information to enable strategic drug development decisions. It also has the advantage of yielding important insights in a timely and cost-effective manner.

Types of Meta-analysis in Drug Development



The different types of meta-analyses used in drug development

Meta-analysis combines the results of multiple clinical drug trials to generalize or strengthen the findings. Three types of meta-analysis are used in drug development: pairwise meta-analysis (PMA), network meta-analysis (NMA), and MBMA. PMA compares treatments in pairs. This approach has the advantage of being relatively fast and easy. The major drawback to PMA is that it only takes head-to-head evidence into account. Thus, it cannot make indirect comparisons of drugs that haven't been compared in a clinical trial. Network meta-analysis (NMA) combines trials with different treatments and comparators into a single framework. Thus, NMA is able to simultaneously accommodate direct and indirect comparisons. Finally, MBMA is a meta-analysis that incorporates parametric pharmacology models (eg, with dose and duration). This approach provides insights by integrating relevant pre-clinical, bio-marker, clinical safety and efficacy data of competing treatment options in a certain disease area. It can support decision making for any therapeutic area and can be used at any stage of drug development from pre-clinical to post-approval.

The MBMA approach also supports bridging across studies, thereby enabling comparing treatments that may never have been tested in the same clinical trial. In contrast, traditional meta-analysis focuses on treatments that were compared within the same trial, and on a particular dose levels for each drug.

The benefits of using MBMA

MBMA supports decision making in multiple ways. This approach can help gain a better understanding of a drug's dose-response relationship[1], support competitive positioning, elucidate endpoint-to-endpoint relationships, and increase the probability of clinical trial success.

For new drugs to be commercially successful, they must differentiate themselves from the SOC. MBMA can help predict how a new drug's safety and efficacy profile might compare to the current SOC and other competitor drugs.[2] In some cases, an analysis might suggest that the candidate drug is unlikely to provide improved benefit to patients. This could results in a "no-go" decision for the drug program due to limited commercial viability, thus enabling the sponsor to invest in programs with better likelihood of success.

Likewise, MBMA can be used to make biomarker to clinical, and short-term to long-term endpoint predictions. This approach can also be applied to scale across indications. These analyses help predict drug performance in later stage development, or in a different indication. Finally, dose-response models used in MBMA can help sponsors understand how differences in patient populations or trial design aspects may result in differential responses to a drug. The benefits of incorporating MBMA into a drug program are illustrated in the following three case studies.

Evaluating the psoriasis competitive landscape to support a best-in-class strategy

Psoriasis is an auto-immune disease characterized by abnormal patches of skin. The sponsor needed to select the dose-range for Phase 2 studies of a novel drug for psoriasis using Phase 1b data. The Phase 1b data showed a strong proof-of-concept for drug efficacy; all active treatments resulted in a maximal therapeutic effect by the end of the study. Due to limited Phase 1b data from a small number of patients, no robust PK/PD model could be established. While the sponsor determined an initially proposed dose (25-200 mg, injected subcutaneously at specified time points) range, they were concerned whether this range would allow them to characterize the dose-response relationship for the drug and determine the lowest maximum effective dose.

To borrow strength from published comparator data, MBMA was proposed for conducting a comparator analysis to enable model-based dose selection for Phase 2 studies.[3,4] This best-in-class strategy would support maximal learning in Phase 2 to help the sponsor understand the requirements for Phase 3 dosing.

The comparator analysis drew upon mean study-arm level data from five commonly used psoriasis drugs—adalimumab, etanercept, infliximab, ustekinumab, and briakunumab (Figure 1). The combined data set included information on over 10,000 patients. Before starting the comparator analysis, four critical assumptions were made. First, the maximum efficacy for the in-house compound was assumed to be similar to other compounds with similar mechanism-of-action (MOA). Next, the time-course of the onset of response was presumed to be similar across compounds. In addition, the efficacy of the Phase 1b dose regimen of the in-house compound was expected to be similar to the efficacy of the Phase 2 dose regimen. Finally, the Phase 1b and Phase 2 patient populations were assumed to be similar.

Comparative efficacy models were used to determine the time-course of the response for the drugs. The models assumed that the maximum efficacy for the in-house compound was similar to competitors with the same MOA. They also assumed that the time-course for the response onset was similar across compounds. These models showed a drug effect that gradually increases over time to a steady-state.

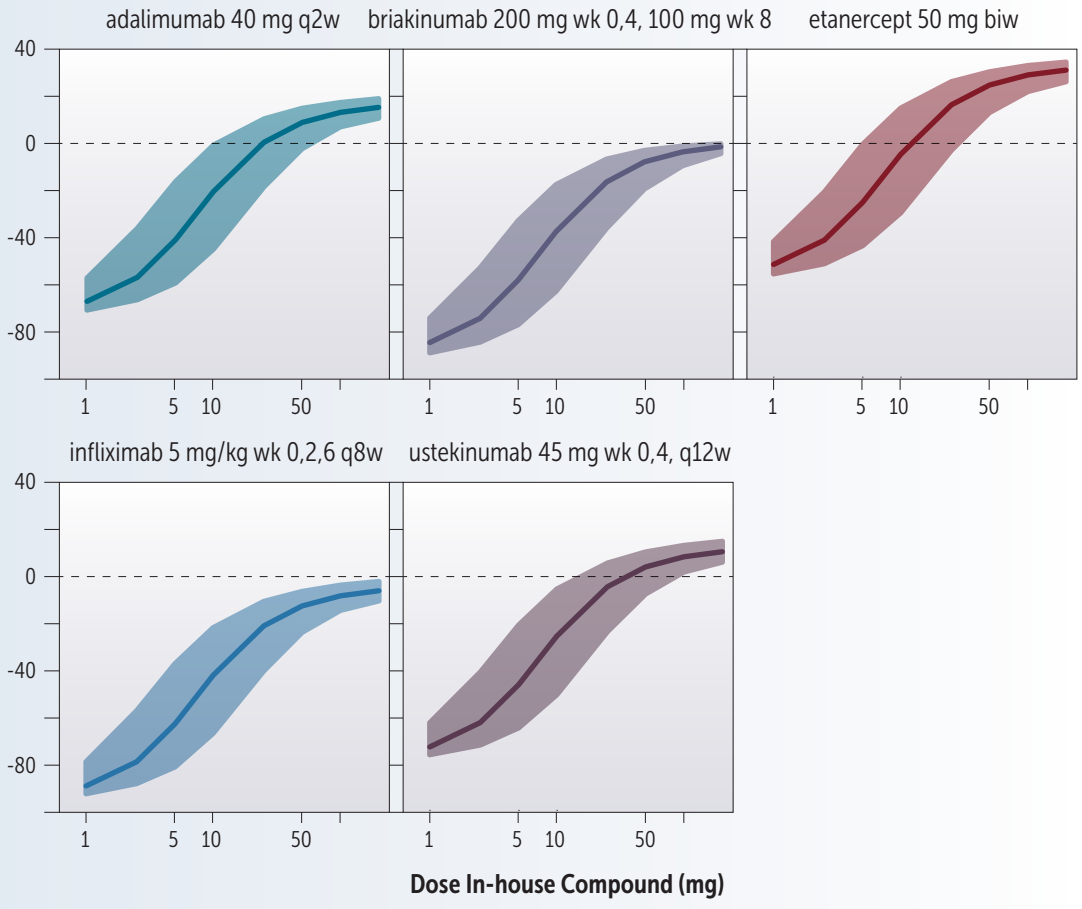
Figure 1. The comparator analysis combined mean study-arm level data from over 10,000 psoriasis patients

Compound		MoA	# Trials	# Study arms incl. plac	# Patients
Adalimumab	(Humira)	Type 1	4	9	1658
Etanercept	(Enbrel)	Type 1	9	20	2868
Infliximab	(Remicade)	Type 1	6	15	1695
Ustekinumab	(Stelara)	Type 2	5	13	2868
Briakinumab	(ABT-874)	Type2	2	6	1585
In-house compound			1	5	24

The in-house compound was then compared to competitors in dose-response models. All compounds were estimated to have different potencies. Limited Phase 1 data meant that there was a large uncertainty in determining the dose-response relationship for the in-house compound.

Dose-response models provided several insights regarding which doses to use in future trials. A near maximum effect of the drug was predicted to be achieved using the 50 mg dose. Doses of 50-200 mg were predicted to have little separation in time to reach maximum effect. Therefore, the 200 mg dose is not predicted to have a faster maximum effect. Also, by determining the median effective dose (ED50) to be approximately 8.4 mg meant that the 5 mg and 25 mg doses would be the best for further establishing the dose-response relationship.

Figure 2. Positioning the in-house compound in the competitive landscape



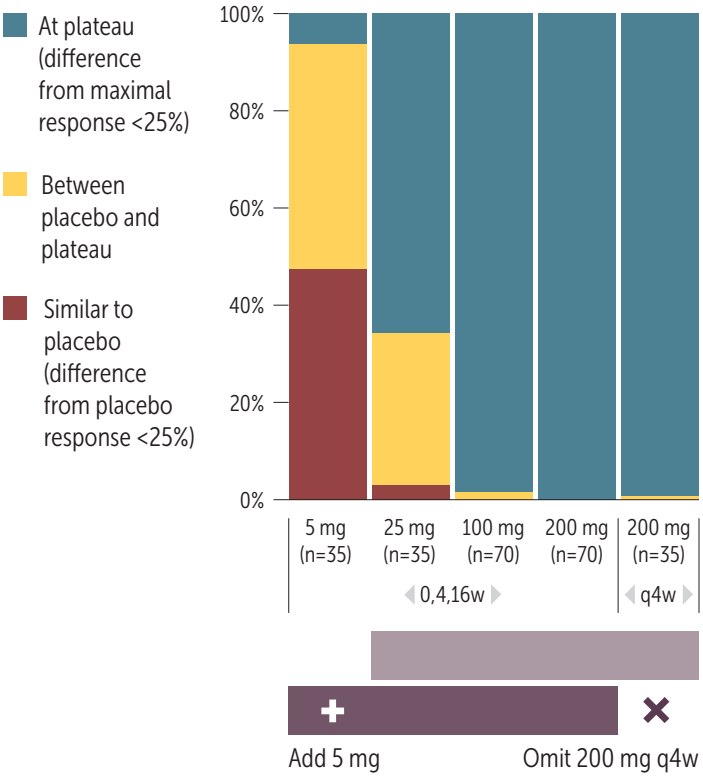
The models also supported positioning the in-house compound in the competitive landscape. Doses greater than 50 mg were predicted to be superior to etanercept, adalimumab, and ustekinumab. However, the similar potency and onset of action conferred no major competitive advantage over ustekinumab (Figure 2).

Clinical trial simulations were then used to support dose optimization for Phase 2 studies. Establishing the dose-response for a drug requires using doses between placebo and maximal effect or plateau. The doses for Phase 2 were evaluated for being "near placebo," "near maximum effect," or in between. The clinical simulations included doses near the ED_{50} in the Phase 2 trial to identify the lowest dose reaching maximum effect.

The simulations revealed that the 100 mg and 200 mg doses given on the typical schedule were predicted to be at the plateau of the dose-response relationship (Figure 3).

The monthly 200 mg dose arm was not predicted to be informative, so it was dropped. Because there was a reasonable probability that the 5 mg dose was not near plateau or placebo, this dose was added. The results of the MBMA enabled the sponsor to proceed to Phase 2 trials with a dosing range that is more likely to support identifying the best dose to carry into Phase 3 trials.

Figure 3. MBMA supports dose selection for Phase 2B study



Leveraging competitor information to predict efficacy of a novel drug formulation

Ezetimibe and atorvastatin are both used to treat dyslipidemia—an abnormally high level of lipids in the blood—by lowering levels of low-density-lipoprotein cholesterol (LDL-C). The sponsor wanted to develop a fixed-dose combination (FDC) of two previously approved drugs, ezetimibe and atorvastatin.[5] In bioequivalence (BE) trials conducted across a combined dose range of ezetimibe/atorvastatin, all parameters met traditional BE bounds except atorvastatin C_{max} at two intermediate doses (Figure 4). The FDA uses BE data as the gold standard for regulatory decisions on providing a clinical bridge for drug quality, efficacy, and safety for other similar FDCs. Thus, the agency requested data from clinical equivalence (CE) trials to evaluate the two doses that did not meet atorvastatin BE.

MBMA analyses were conducted to understand the impact of dosing regimen and formulation on low-density-lipoprotein cholesterol (LDL-C) levels, to predict the impact of changes in exposure for ezetimibe+atorvastatin FDC on efficacy, and inform the design of CE trials. Previously, a dose-response model for statin LDL-C reduction as a monotherapy and in combination with ezetimibe was developed based on publicly-available trial data.[6] This model was updated with published clinical data from over 200 statin trials involving greater than 100,000 patients.

The model-based meta-analysis predicted that the observed difference in C_{max} between an ezetimibe+atorvastatin FDC and co-administration of these drugs translates to a clinically-insignificant change in lowering of LDL-C (Figure 5). Indeed, the reduction in LDL-C associated with atorvastatin administration is more highly correlated with total daily atorvastatin dose than with the measurement of peak atorvastatin exposure. This is consistent with the biological processes regulating changes in LDL-C levels which occur over weeks and months, whereas plasma concentrations of atorvastatin peak within an hour of dosing.

The model's predictions from simulations using the BE studies and dose-exposure analysis also allowed for a more accurate estimate of the treatment difference. These insights were leveraged to design the CE trials. The sample size for the CE trials was able to be reduced by 17% while still maintaining a 90% probability of success resulting in significant time and cost savings. Both doses were found to be clinically equivalent in the CE trials. The results of the two CE trials were submitted to the FDA. The FDC attained FDA approval in 2013.[7] In the future, MBMA leveraging relevant competitor information may negate the need for dedicated CE trials after near-miss BE, thus enabling sponsors to accelerate the development of new drugs.

Figure 4. BE results for atorvastatin and ezetimibe in healthy volunteers across the dose range for the fixed-dose combination as compared with coadministration of individual components

Part (dose, mg/mg)	N	Estimated geometric mean ratio (FDC/coadministration) (90% confidence interval)			
		Atorvastatin $AUC_{0-\infty}$	Atorvastatin C_{max}	Unconjugated ezetimibe AUC_{0-last}	Unconjugated ezetimibe C_{max}
10/10	92	0.93 (0.86, 1.01)	0.90 (0.81, 0.99)	1.03 (0.99, 1.07)	1.13 (1.05, 1.22)
10/20	95	0.89 (0.83, 0.96)	0.77 (0.68, 0.87)	0.97 (0.90, 1.04)	1.00 (0.90, 1.10)
10/40	96	0.96 (0.94, 1.00)	0.81 (0.73, 0.90)	0.98 (0.93, 1.03)	1.03 (0.96, 1.10)
10/80	95	1.11 (1.06, 1.17)	1.09 (0.99, 1.20)	0.97 (0.93, 1.02)	0.99 (0.92, 1.06)

AUC, area under the concentration-time curve; BE, bioequivalence; C_{max}, peak plasma concentration; FDC, fixed-dose concentration

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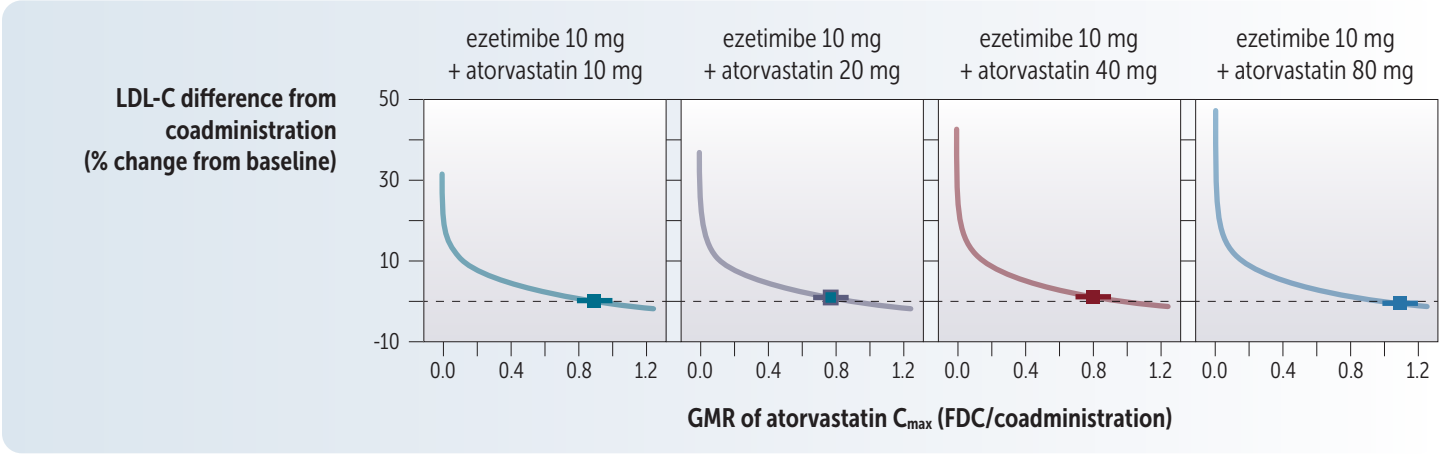
Figure 5. The impact of the differences in C_{max} between the FDCs and coadministration of individual atorvastatin and ezetimibe tablets was predicted to result in an insignificant change in efficacy



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Using MBMA to run virtual "head-to-head trials" against competing osteoporosis drugs

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) is the canonical biomarker 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.[8] Treatment with denosumab significantly decreased the risk of bone fracture in women with postmenopausal osteoporosis.[9]

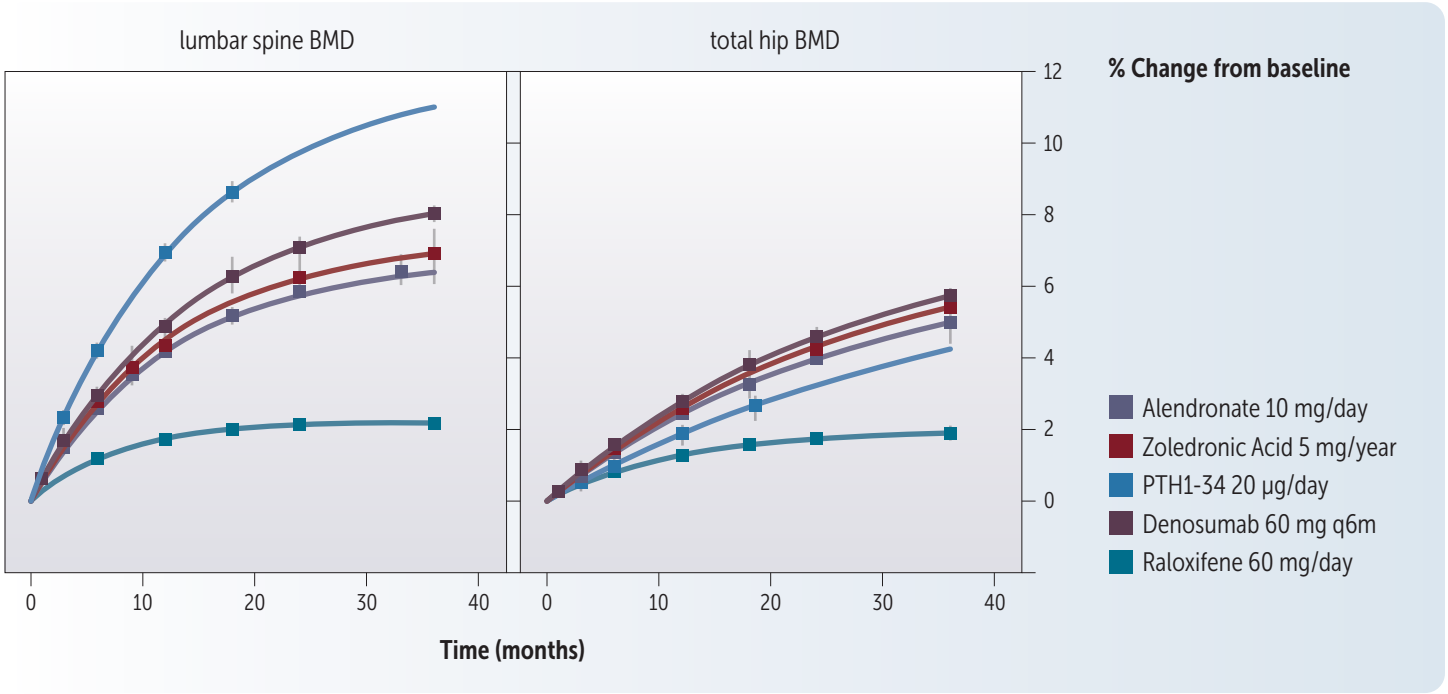
The osteoporosis drug landscape is crowded with many competitors with varying MOA. A year-long clinical trial comparing denosumab and alendronate in postmenopausal women with low bone mass suggested that denosumab treatment significantly increased LS and TH BMD compared to alendronate.[10] Denosumab has not been compared in clinical trials to other approved osteoporosis treatments. MBMA was chosen as the most efficient method for comparing denosumab to the competition.[11] 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.

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. 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 (Figure 6). While treatment with PTH resulted in larger increases in LS BMD compared to denosumab, treatment with the latter provided larger increases in TH BMD. Thus, 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.

Figure 6. Three years of treatment with denosumab resulted in bigger changes in lumbar spine (LS) and total hip (TH) bone mineral density (BMD) compared to the same treatment duration with competing osteoporosis drugs. While treatment with PTH resulted in larger increases in LS BMD compared to denosumab, treatment with the latter provided larger increases in TH BMD



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MBMA: An emerging method for gaining insights from publicly available data

MBMA integrates internal and external drug development data to inform proprietary commercial and R&D decisions. The insights gained via MBMA support designing less costly and more precise trials with an eye toward achieving commercial success for both the drug and portfolio.

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