

Population PK/PD Modeling of Lumbar Spine Bone Mineral Density Response to 12 Months of Treatment with the Cathepsin K Inhibitor, Odanacatib, and Simulations to Further Evaluate the Dose-Response Relationship

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Background and Objectives

- Cathepsin K, a cysteine protease abundantly expressed in osteoclasts, is necessary for bone collagen degradation.
- Odanacatib, a selective inhibitor of cathepsin K, has been shown to rapidly and reversibly decrease bone resorption and is in development for the treatment of osteoporosis.
- A Phase II dose-ranging study in 399 women with osteoporosis is ongoing and data out to 12 months were available for modeling [1].
- The objectives of this work were to develop a population pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) model of lumbar spine bone mineral density (LSBMD) and to use these models to further characterize the exposure-response relationship

Odanacatib Phase IIB Study Overview of Study Design

- Postmenopausal women (age 45-85) with osteoporosis
- N=399 randomized
- Treatment: PBO, 3, 10, 25, 50 mg once weekly odanacatib (plus open-label calcium + vitamin D)
- 12-month study +12-Mo extension and 6-Mo interim
- Primary endpoint: %Δ in lumbar spine BMD at 12 mos
 - Secondary endpoints: hip, total body, forearm BMD, Biomarkers
- BMD measured at baseline, Mos. 1, 3, 6, 12, 18, 24
- Biomarkers/PK measured at baseline, Wk. 1, Mos. 1, 3, 6, 9, 12, 18, 24 (Week 1 sample at trough, others unspecified time)
- 12-month data for lumbar spine BMD used to develop the BMD model; PK model based on 6-month data

PK Model Development

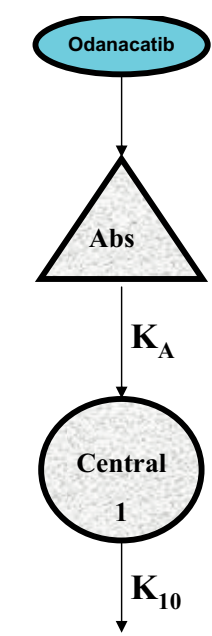
Sparsely sampled PK data out to 6-months were obtained from a Phase IIB study of the safety, tolerability and efficacy of weekly doses of placebo, 3, 10, 25 or 50 mg of odanacatib on BMD and biochemical indices of bone turnover in postmenopausal women with low BMD. Additional PK data for modeling were obtained from a 3-week Phase Ib study in healthy postmenopausal women. The population PK model consisted of a 1-compartment, saturable (dose-dependent bioavailability) absorption PK model and covariates were included to potentially account for differences in the drug lot used in differing study arms and for potential differences between healthy women and osteoporosis patients. Intersubject variability was accounted for in the volume of distribution and elimination rate constant terms. The Population PK model was developed in NONMEM V.

The plasma PK data were well represented by the population PK model and individual model predicted steady-state exposure estimates for AUC and C_{trough} were obtained for use in PK/PD model development.

Population PK Model

- One-compartment PK model
- Linear absorption and elimination rates
- Dose-dependent (saturating) bioavailability, expressed on volume term
- Covariates for API (high vs low Surface Area) and Phase I vs Phase II
- Intersubject variation on distribution volume and elimination rate
- Proportional and additive residual error terms
- Model fit to pooled concentration-time data from the Phase IIB study and data from a 3-week PhIB study in postmenopausal women (5, 25, 50, and 100 mg weekly dosing)
- NONMEM V; Estimation method used was FOCE/INT

Population PK Model cont.



$$V_i = V_{i0} * [1 + SL * (Dose - 3)] * EXP(SA * \phi_{SA}) * EXP(Phase * \phi_{Phase})$$

$$SA = \begin{cases} 1 & \text{High Surface Area} \\ 0 & \text{Low Surface Area} \end{cases}$$

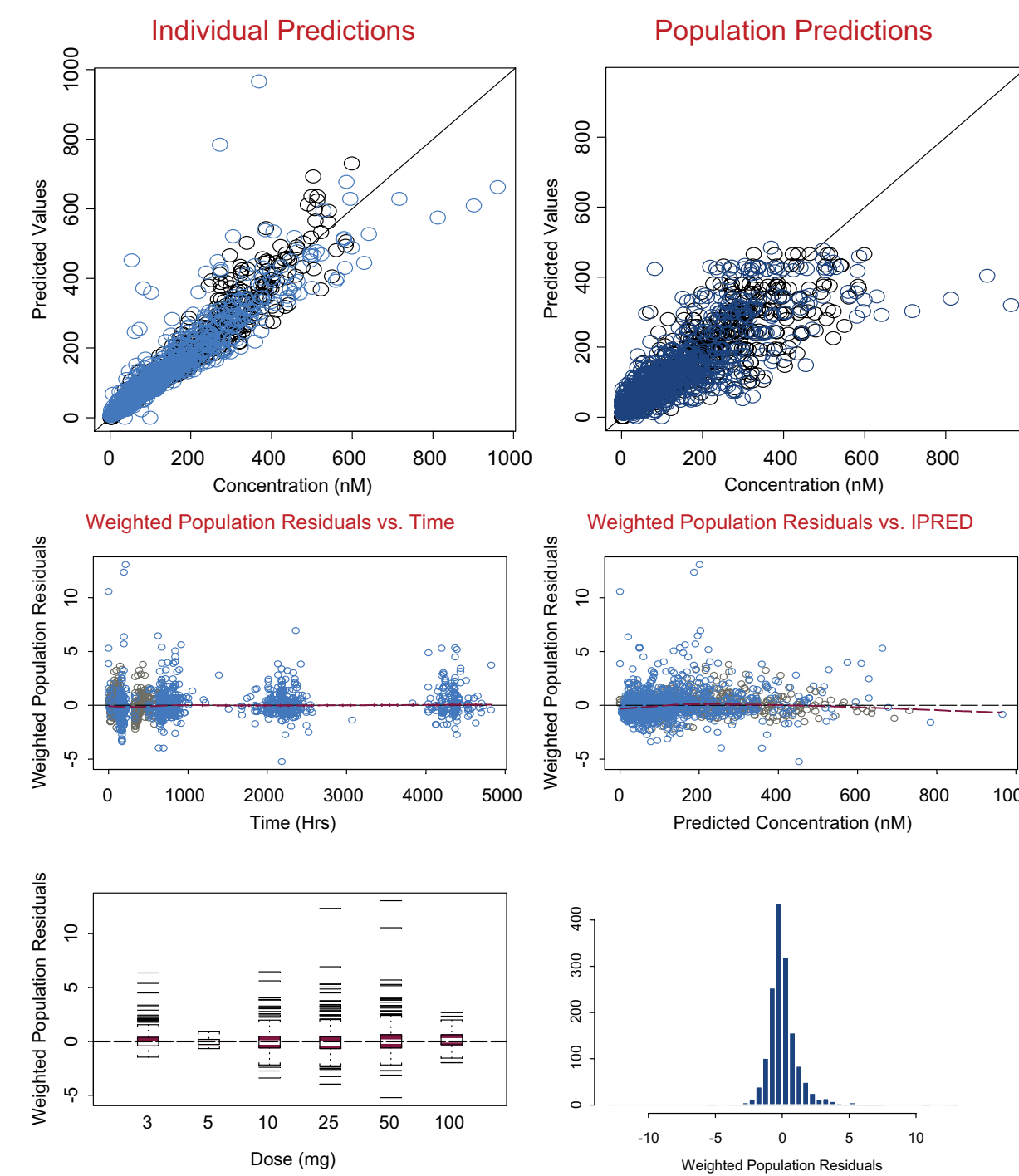
$$Phase = \begin{cases} 1 & \text{Phase II} \\ 0 & \text{Phase I} \end{cases}$$

K_A = absorption rate constant
 K_{10} = elimination rate constant

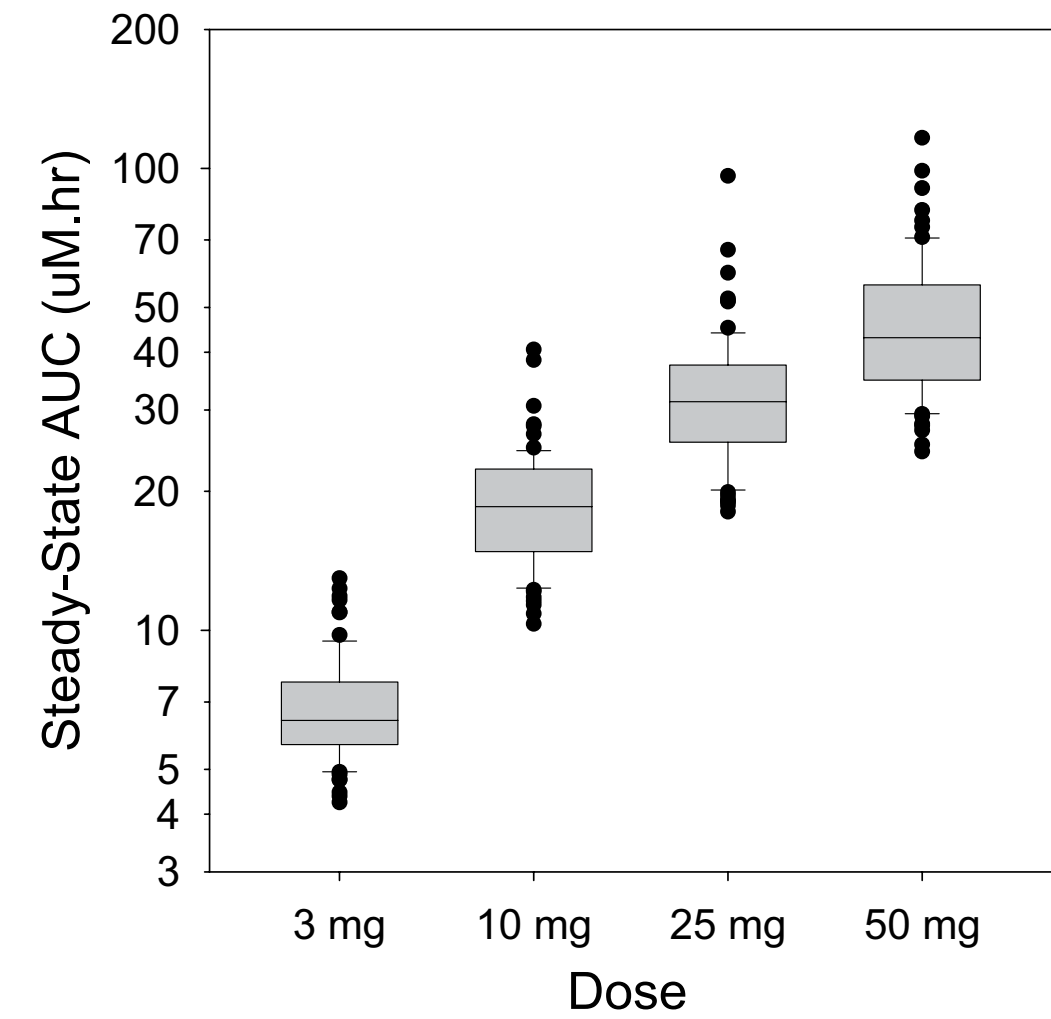
Parameter Values

Parameter	Estimate	SE (% CV)	95% CI
Ka (1/hr)	0.57	0.15 (27)	0.27 - 0.86
Vd (L)	108	8 (7)	- 123
K (1/hr)	9.0×10^{-3}	0.3×10^{-3} (4)	8.4 - 9.6
SL (unitless)	0.03	3×10^{-3} (10)	0.024 - 0.036
API (unitless)	-0.04	0.05 (137)	-0.13 - 0.06
Phase (unitless)	-0.09	0.05 (60)	-0.19 - 0.01
var(η_1) (Vd)	0.12	0.036 (31)	0.04 - 0.18
var(η_2) (K)	0.15	0.03 (20)	0.09 - 0.21
covar(η_1, η_2)	-0.08	0.03 (41)	0.01 - 0.14
σ_1	0.05	0.006 (12)	0.04 - 0.06
σ_2	88	49 (56)	0 - 185

PK Model Diagnostic



Distribution of Model-Predicted Individual AUC0-168HR Values in Phase IIB



Lumbar Spine BMD Model Development

Lumbar spine (L5) BMD PD data out to 12-months were obtained from the Phase IIB study in postmenopausal women with low BMD. The BMD PK/PD model consisted of a power model $[(time)^{\gamma}]$ to represent the time effects, with a simple Emax relationship with area under concentration time curve at steady-state (AUC) to represent drug effects. Intersubject variability was accounted for in the baseline term and a placebo effect was incorporated. The Population BMD PK/PD model was developed in S-Plus. Simulations were conducted and analyzed using Drug Model Explorer (DMX®) and Trial Simulator software.

The relationship between individual LSBMD (% change from baseline) and average steady-state exposure (AUC) in the individual was modeled. The PK measures, C_{max} and C_{trough}, were also investigated, but presented no advantage over AUC. The power model $[(time)^{\gamma}]$ used to represent the time effects, had the fit value ($\gamma=0.62$), since this was <1 this represents a rate of response which is slowing with time. The AUC50 (AUC at which 50% of maximal response is achieved) was estimated as 70 uM.hr. In addition, a modest placebo effect (-0.2%) for BMD decline in the absence of drug was obtained in the model fit.

Lumbar Spine BMD PK/PD Model

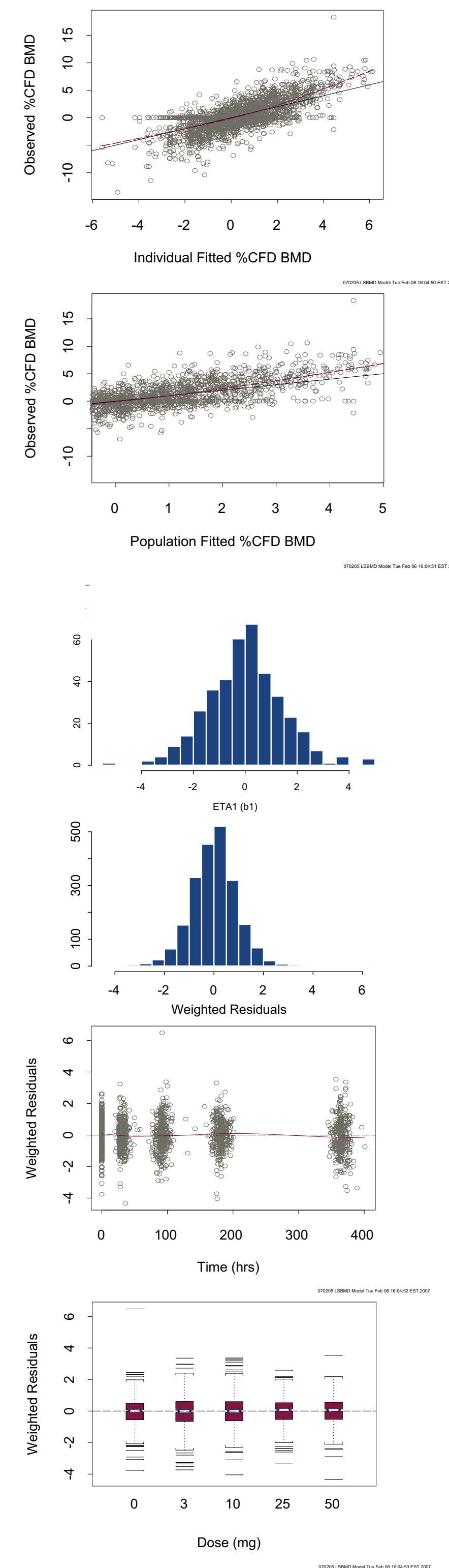
$$\%CFB\ BMD = (BL + \eta_{BL}) + SL * time^{\gamma} * g(AUC) + \epsilon$$

with

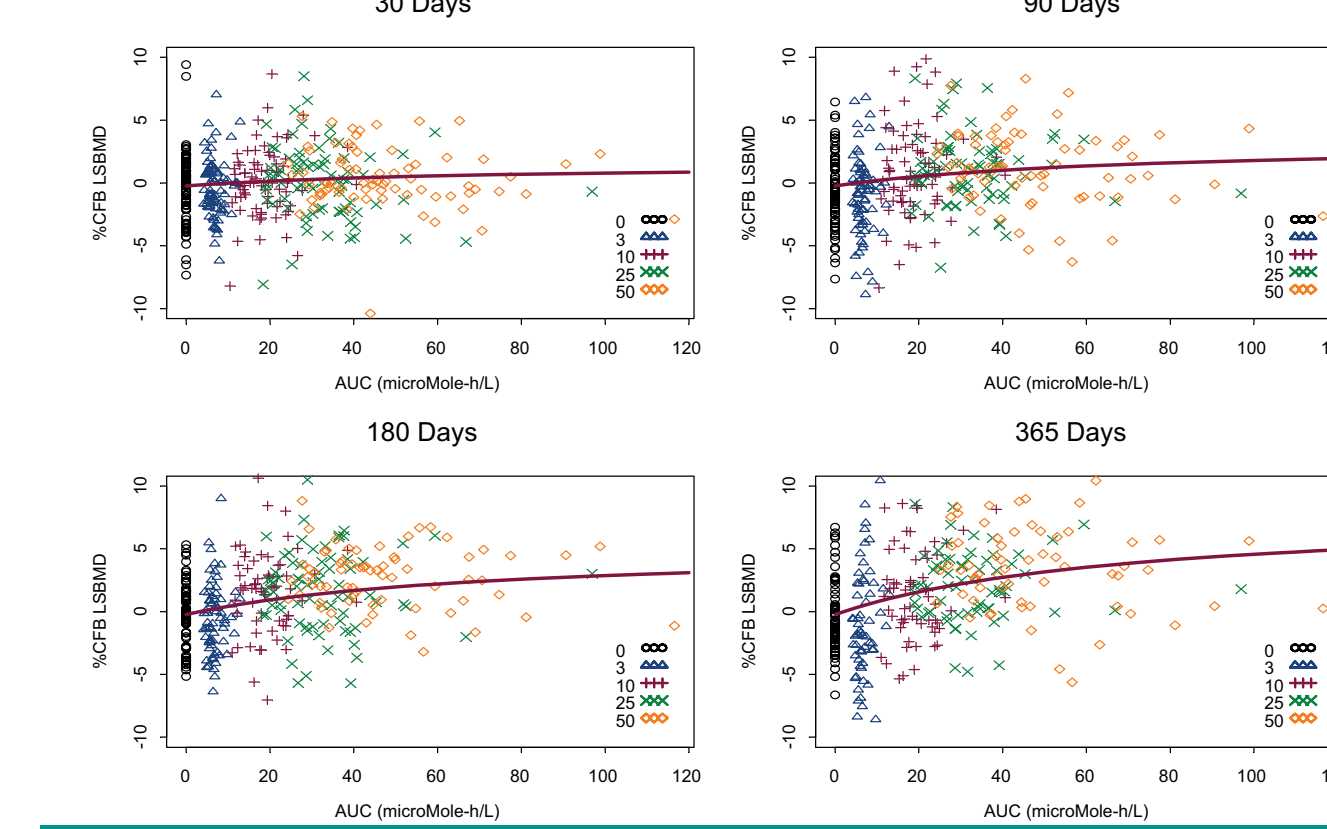
$$g(AUC) = \left(\frac{AUC}{AUC_{50} + AUC} \right)$$

Parameter	Estimate	SE
BL	-0.2	0.1
SL	0.21	0.12
γ	0.62	0.08
AUC ₅₀	70 uMole-h/L	37
η_{BL}	1.6	--
σ^2	2.1	--

BMD PK/PD Model Diagnostics



Best-fit Lines vs. the Observed Data

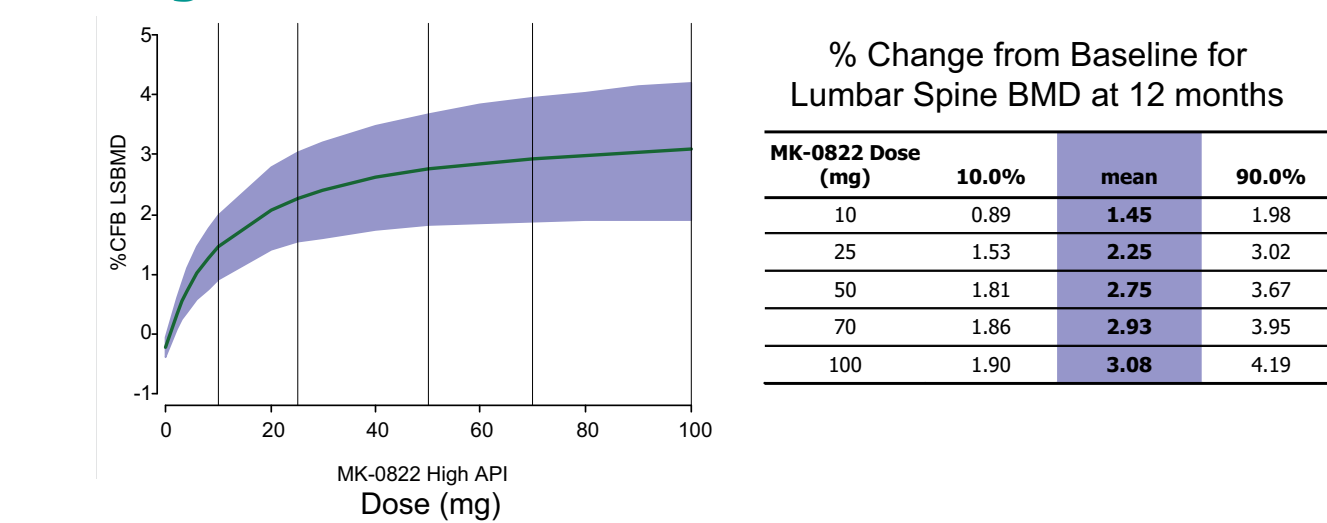


Simulations to Further Evaluate the Dose-Response Relationship

Simulations were conducted and analyzed using Drug Model Explorer (DMX®) and Trial Simulator software.

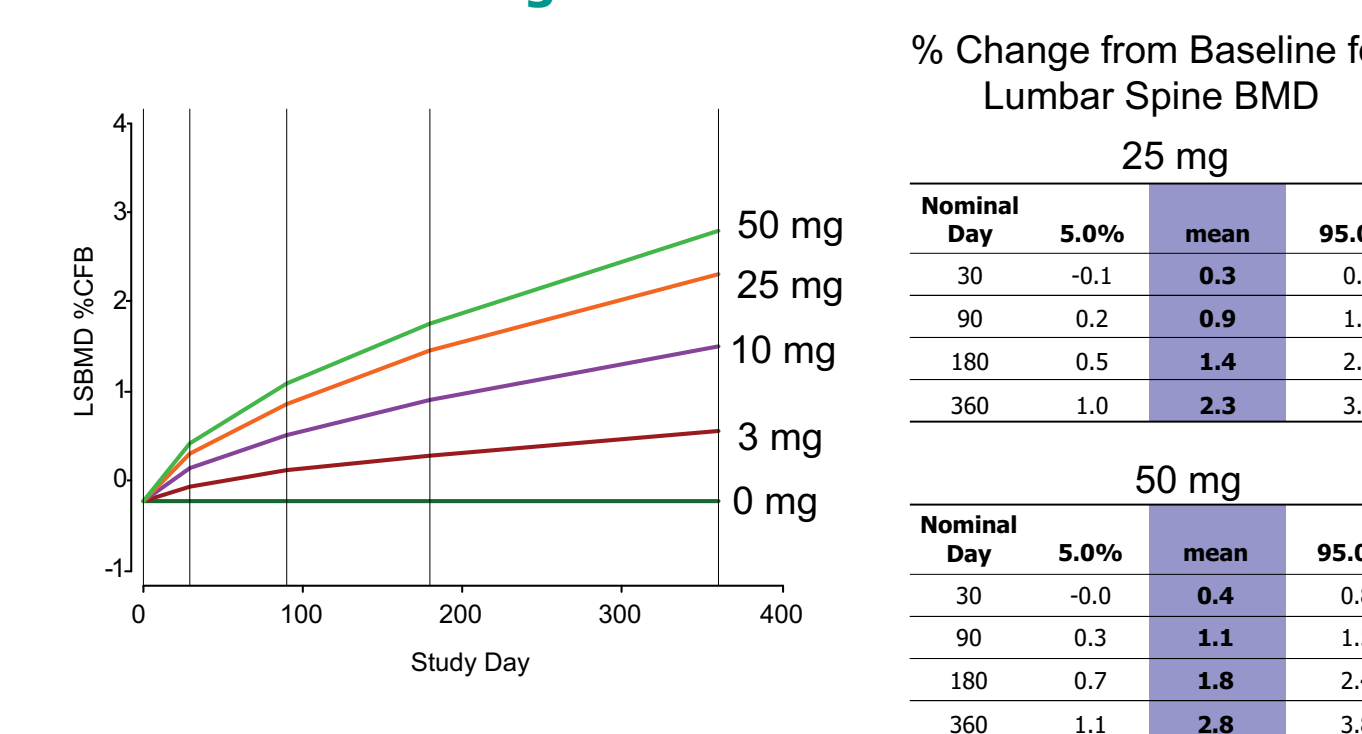
The dose-response relationship for 12-month LSBMD response was simulated in DMX and indicated that the 50 mg dose will likely provide greater BMD efficacy than the 25 mg dose. In further support of a conclusion of reduced efficacy at 25 mg, a sensitivity analysis of the AUC50 parameter indicated that AUC50 value below 40 uM.hr were unlikely. Further simulations of BMD dose-response for doses >50 mg, but ≤100 mg, suggested only very modest gains in pushing to higher doses. A trial simulation of a 500 repeat Phase IIB studies, which included an extra 100 mg arm, suggested that a statistically significant improvement in LSBMD would only be obtained in ~14% of trials.

Predicted Odanacatib Dose-Response for % Change in LSBMD at 12-Months

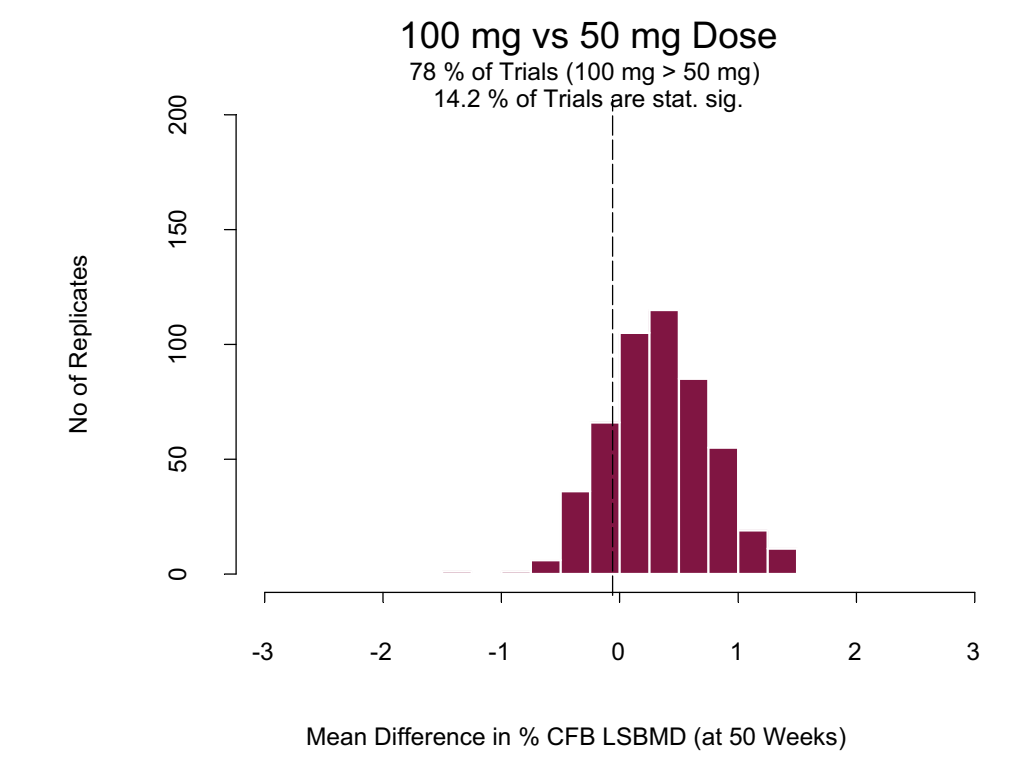


- Mean response and 90% prediction interval on that mean estimate displayed
- High surface area API for simulations

Predicted Mean Odanacatib Dose-Response Versus Time for % Change in LSBMD



Trial Simulation of 50 mg versus 100 mg (14.2% Chance of a Stat Sig Improvement in BMD)



- 500 replicate trials simulated
- Same design as Ph IIB trial except additional arm added for 100 mg once-weekly

Sensitivity Analysis on AUC₅₀ Estimate

AUC ₅₀ Value	log-likelihood	Δ-2LL relative to base model	p-value for significant difference in models
10	-4967.79	34.14	<0.0001
20	-4957.82	14.22	0.0002
30	-4953.84	6.26	0.0124
40	-4952.02	2.62	0.1058
50	-4951.17	0.91	0.3390
60	-4950.81	0.19	0.6607
70	-4950.71	0.00	0.9831

- AUC₅₀ value fixed at various values and model refit as indicated in table.
- Analysis suggests that a true AUC₅₀ value of less than 40 uM.hr (upper range of values at 25 mg) is unlikely.
- Indicates that further gains in efficacy at 50 mg once weekly over 25 mg once weekly are likely to be seen.

Conclusions

- Odanacatib pharmacokinetics in postmenopausal women are well described by a 1-compartment linear model with saturable absorption.
- Lumbar spine BMD response over 12 months is well described by a power model with time and a simple Emax drug effect.
- Model-based simulation suggest that doses greater than 50 mg weekly provide only slight increase in BMD efficacy and that doses less than 50 mg are likely associated with more meaningful reductions in efficacy

Reference

1. H. G. Bone, M. McClung, N. Verbruggen, A. Rybak-Feiglin, C. DaSilva, A. C. Santora, A. Ince, A. Randomized, Double-Blind, Placebo-Controlled Study of a Cathepsin-K Inhibitor in the Treatment of Postmenopausal Women with Low BMD: One Year Results. Oral presentation at ASBMR (September 18, 2007).