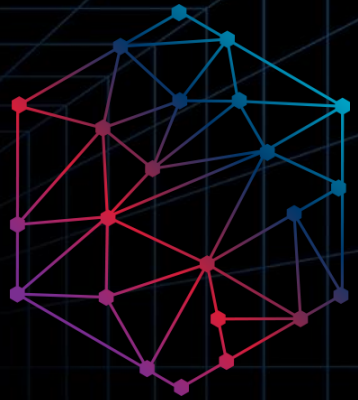
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Semi-mechanistic PK/PD Model of the Effect of Odanacatib (ODN), a Cathepsin K Inhibitor, on Bone Turnover to Characterize Lumbar Spine Bone Mineral Density in Two Phase II Studies of Postmenopausal Women

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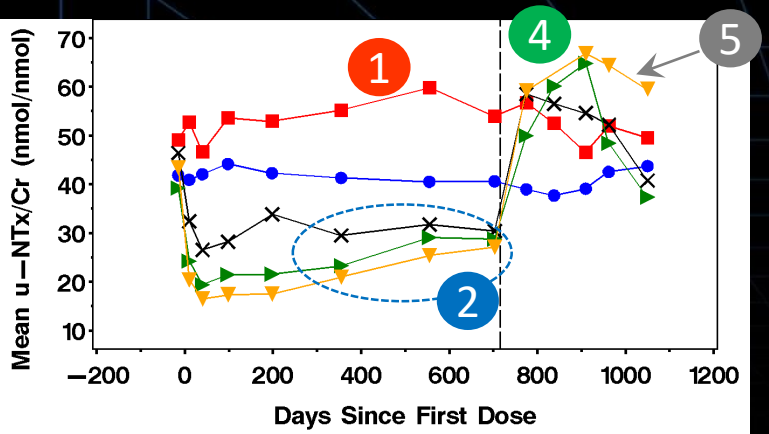
Objectives

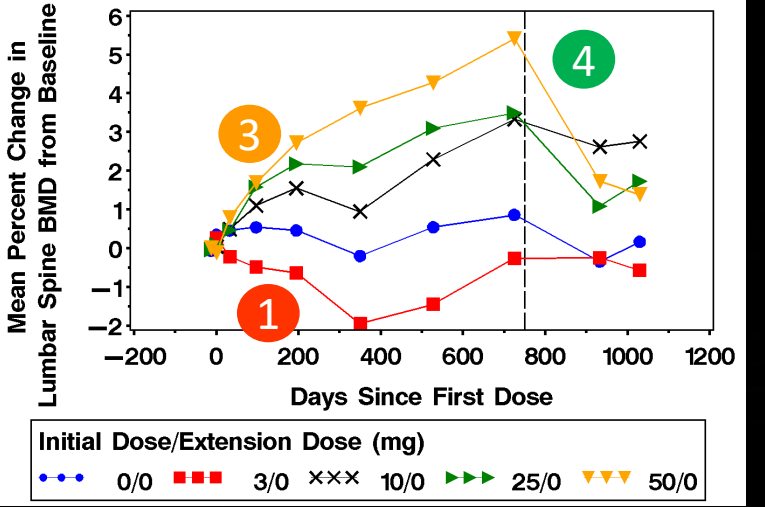
- Develop a semi-mechanistic population PK/PD model to simultaneously characterize the time course of the bone resorption biomarker uNTx (urinary amino-terminal crosslinked telopeptides of Type 1 collagen) and the corresponding lumbar spine BMD response following long-term once-weekly ODN treatment.
- Incorporate relevant mechanistic and empiric model components based on known ODN effects and bone turnover biology to best describe several unique features observed in the dose-concentration-response relationship.

Study Design and Analysis Data

- Data for modeling were collected from a total of 657 postmenopausal women with low bone density enrolled in 2 Phase II trials.
- Dosing regimens: 3, 10, 25, or 50 mg ODN or placebo administered orally once-weekly.
- In one trial (n=391 women), patients who completed 2 years of treatment were re-randomized to either placebo or 50 mg ODN and followed for an additional 1 year.
- ODN plasma concentrations, bone resorption biomarker uNTx (normalized to creatinine), and lumbar spine bone mineral density (measured by DEXA) were collected periodically throughout each study

Mean Biomarker and BMD Response Profiles





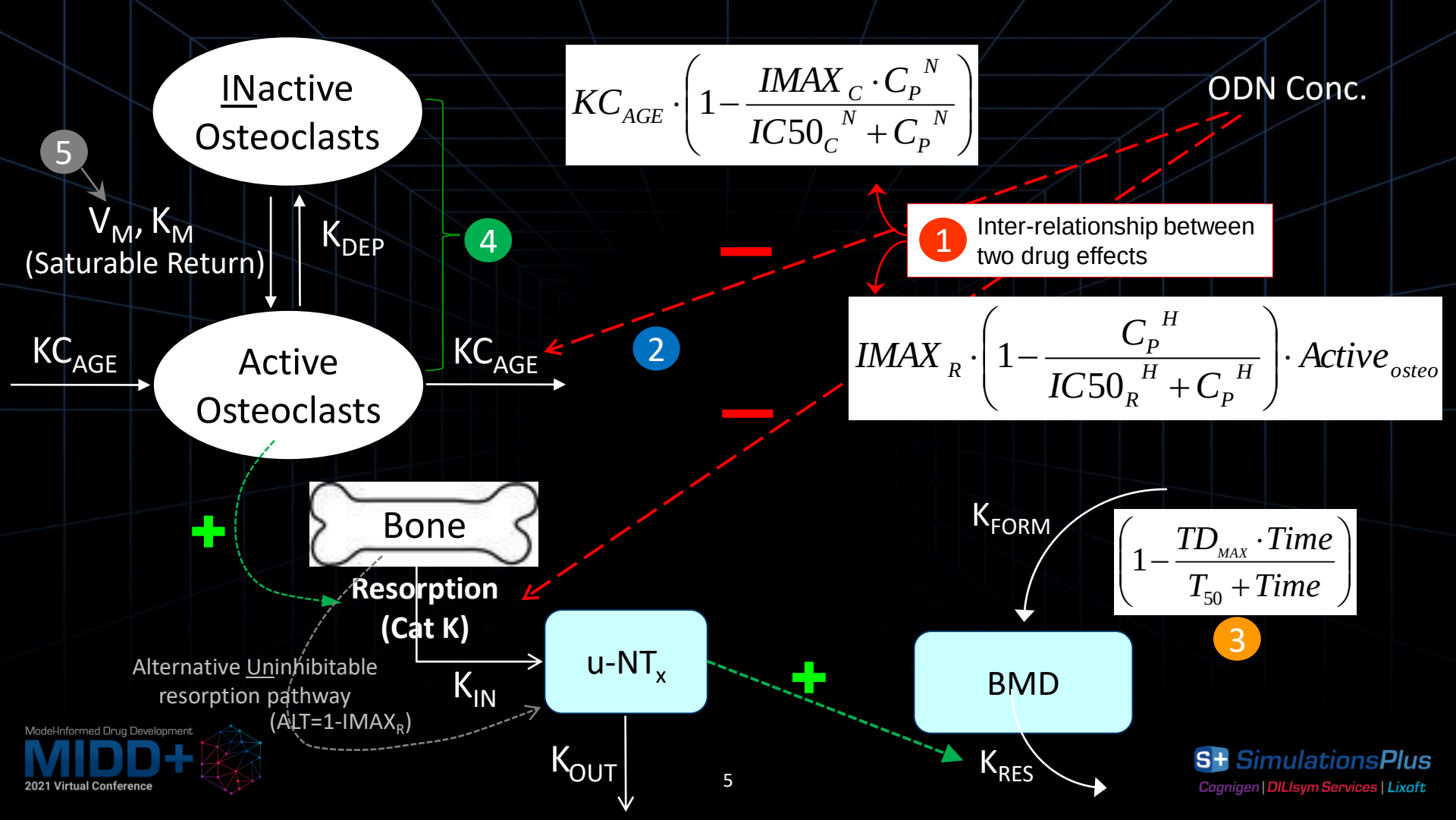
(1) "3-mg Phenomenon":
Non-monotonic dose-response relationship. Lowest dose (red line) yields unwanted increase in biomarker production and resultant lowering of BMD relative to placebo

(2) Time-Dependent Upward Drift:
Consistent (non-artifactual) and slow upward trend in biomarker conc's in response to active Tx

(3) Transient Early 'Burst' in BMD:
Short-term accelerated increase in BMD (observed in both placebo and Tx) likely due to concomitant Ca^{++}/Vit D supplementation

(4) Rapid Post-Tx Rebound in uNTx:
Relatively fast rebound in biomarker conc's above baseline levels after Tx discontinuation. Concurrent rapid decline in BMD in excess of normal bone turnover process.

(5) Resolution of Effects:
Prolonged return of biomarker back to baseline levels


INactive Osteoclasts
5
V_M, K_M (Saturable Return)
K_{DEP}
4
KC_{AGE}
Active Osteoclasts
KC_{AGE}
$KC_{AGE} \cdot \left(1 - \frac{IMAX_C \cdot C_P^N}{IC50_C^N + C_P^N}\right)$
ODN Conc.
1
Inter-relationship between two drug effects
2
$IMAX_R \cdot \left(1 - \frac{C_P^H}{IC50_R^H + C_P^H}\right) \cdot Active_{osteo}$
Bone
Resorption (Cat K)
K_{IN}
Alternative Uninhibitable resorption pathway (ALT=1-$IMAX_R$)
u-NT_x
K_{OUT}
K_{FORM}
$\left(1 - \frac{TD_{MAX} \cdot Time}{T_{50} + Time}\right)$
3
BMD
K_{RES}

Parameter Estimates From the Population PK/PD Model

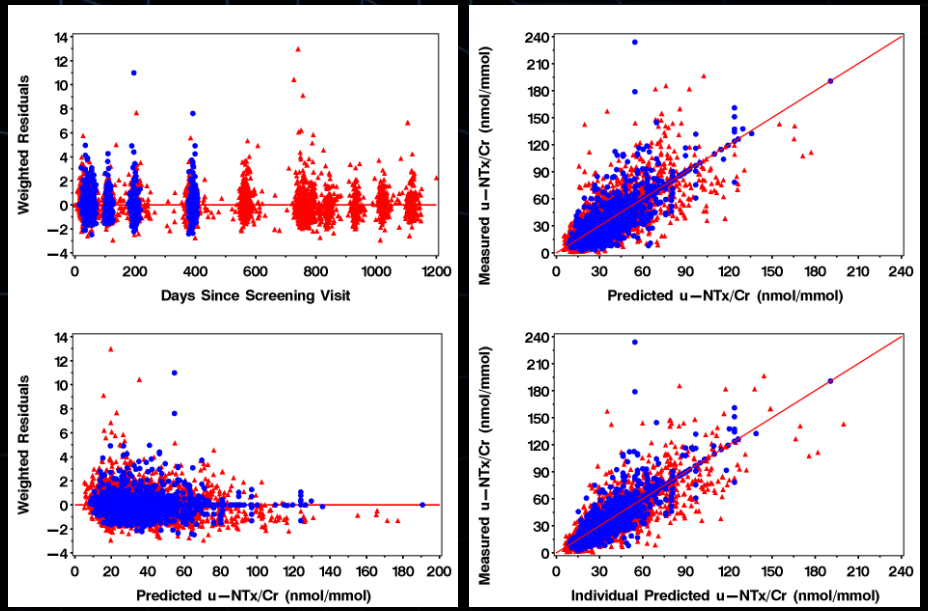
Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
R_{DEP}, ratio of inactive to active osteoclasts	0.050	FIXED	NA	NA
$T5_{CLA}$, osteoclast half-life[a] (days)	28	FIXED		
K_{DEP}, rate of exchange to inactive osteoclast pool (1/day)	0.144	FIXED		
V_M, maximum transfer velocity from inactive to active osteoclast pool[b] (relative osteoclasts/day)	0.304	FIXED		
K_M, relative amount of osteoclasts at 50% V_M	0.0561	13.3	NE	NE
$IMAX_C$, maximum fractional inhibition of osteoclast effects	**0.721**	9.31		
$IC50_C$, concentration at 50% of maximum inhibition of osteoclast effects (nM)	**17.0**	24.6		
N, Hill coefficient for inhibition of osteoclast effects	1.14	36.2		
K_{OUT}, first-order uNTx/Cr removal rate constant (1/day)	1.61	28.9		
$IMAX_R$, maximum fractional inhibition of resorption	**0.680**	4.22	25.9	38.3
$IC50_R$, concentration at 50% $IMAX_R$ (nM)	**38.5**	10.4	70.7	28.5
H, Hill coefficient for inhibition of resorption	1.54	10.7	NE	NE
$K_{ST(FORM)}$, zero-order stationary lsBMD formation rate constant (gm/cm^2/day)	9.16×10^{-5}	7.17	53.4	18.4
$K_{TV(FORM)}$, zero-order time-varying lsBMD formation rate constant (gm/cm^2/day)	5.03×10^{-4}	19.9	237	23.8
K_{RES}, first-order BMD resorption rate constant (1/day)	1.33×10^{-4}	7.65	NE	NE
TD_{MAX}, maximum fractional reduction in $K_{TV(FORM)}$ over time	1.00	FIXED	NA	NA
T_{50}, time at 50% of TD_{MAX} (days)	7.03	18.6	NE	NE
Effect of baseline uNTx/Cr on $IC50_R$ (power)	-0.879	14.0	NA	NA
Ratio of additive/proportional RV components for uNTx/Cr[e] in Study P004 (σ_2/σ_1)	27.1	21.4		
Ratio of additive/proportional RV components for uNTx/Cr[e] in Study P022 (σ_2/σ_1)	12.7	63.2		
Proportional RV component for uNTx/Cr in Study P004 (σ_1)	0.0709	16.6		
Proportional RV component for uNTx/Cr in Study P022 (σ_1)	0.0884	31.7		
RV for BMD in Study P004 (%CV)	2.04	6.06		
RV for BMD in Study P022 (%CV)	1.90	7.95		

[a] The fixed value of $T5_{CLA}$ = 28 days translates into a fixed value for KC_{AGE} = 0.02475 day^{-1}.

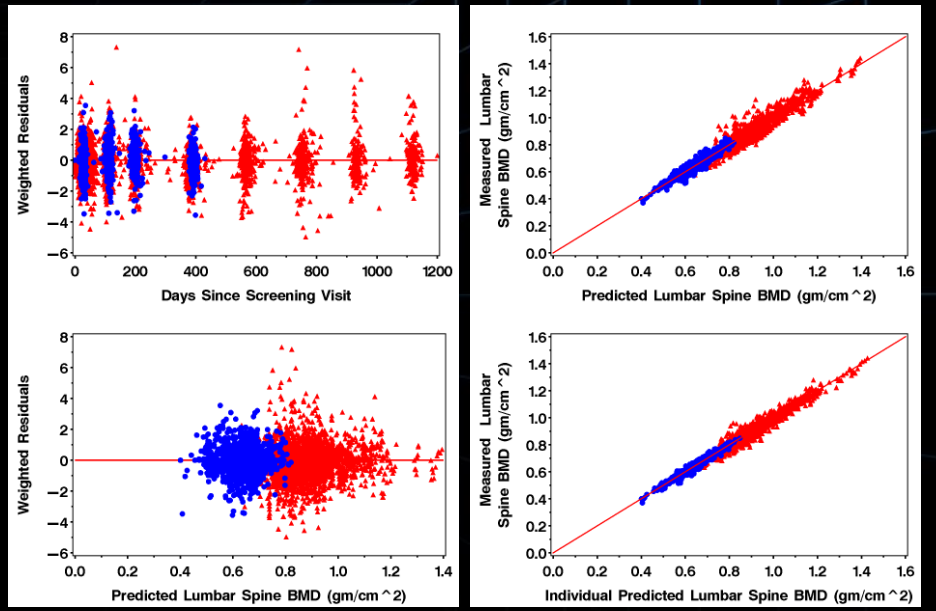
[b] V_M not directly estimated, but calculated via the equation: $V_M = K_{DEP}\times(K_M+R_{DEP})/R_{DEP}$.

Goodness of Fit Plots for the Population PK/PD Model

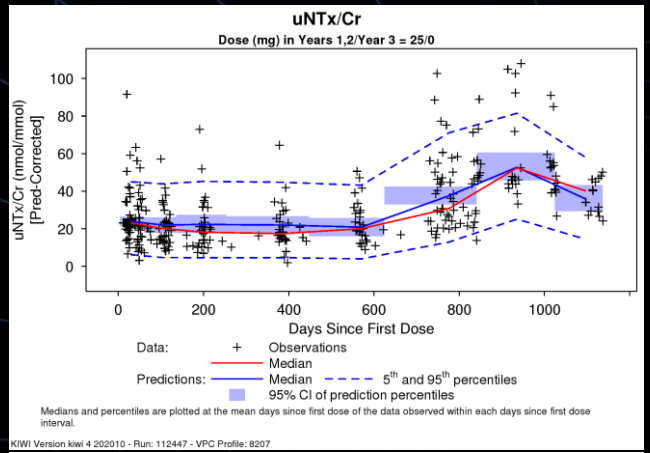
uNTx

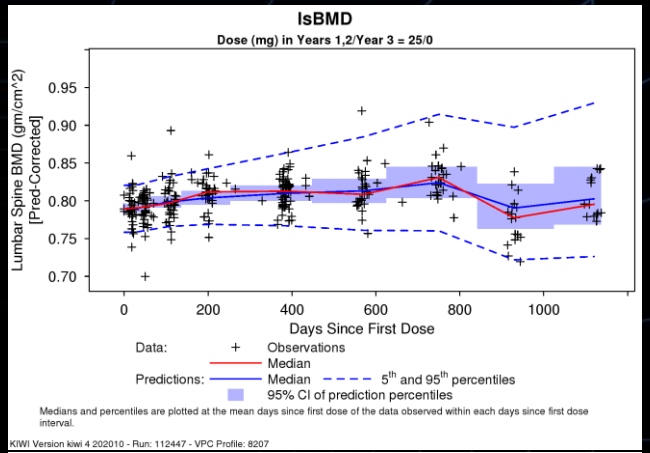


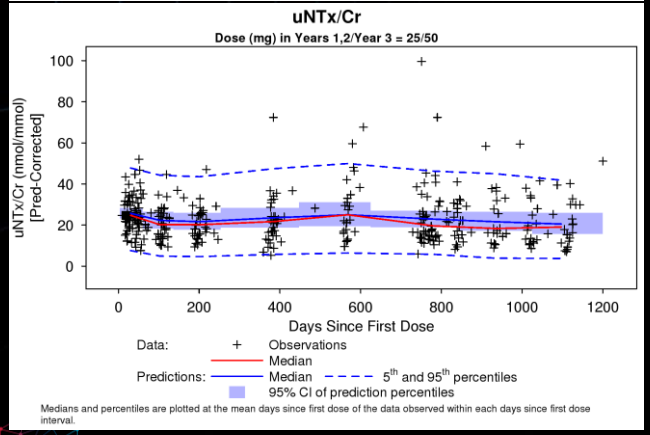
LS-BMD

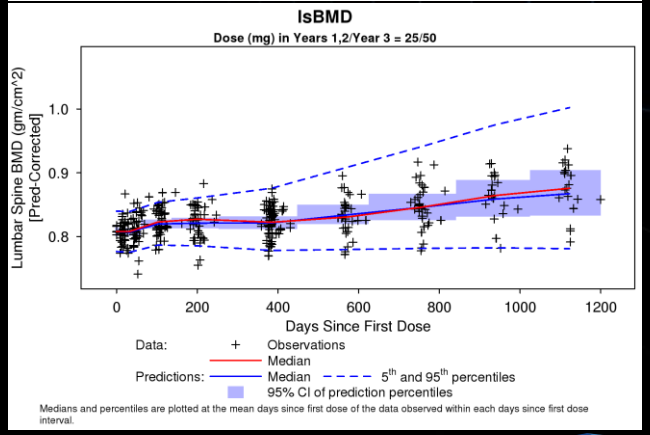


Representative Visual Predictive Checks

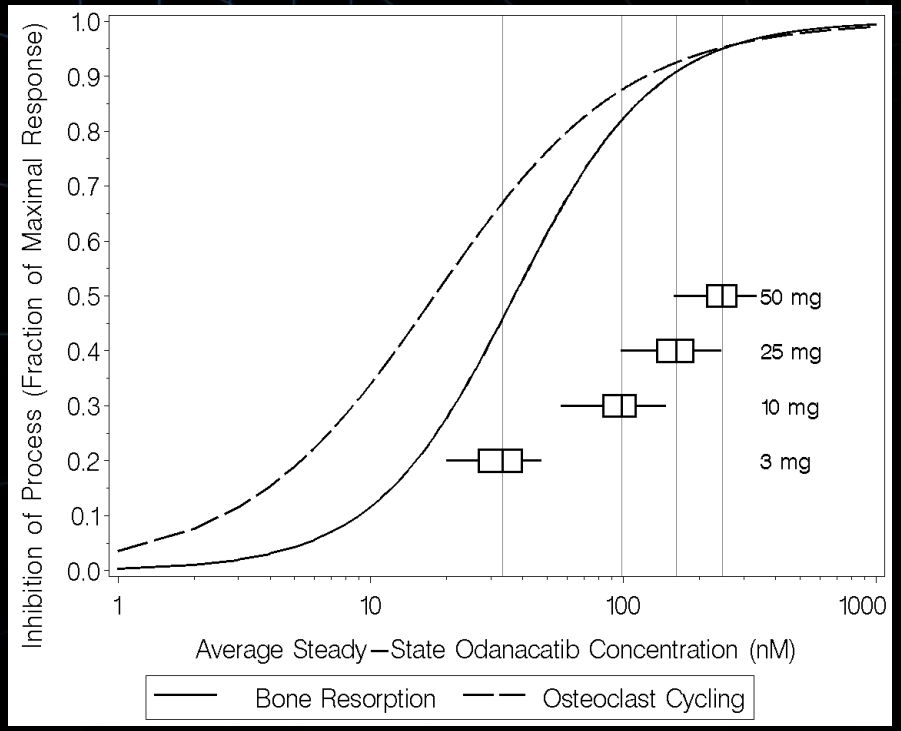


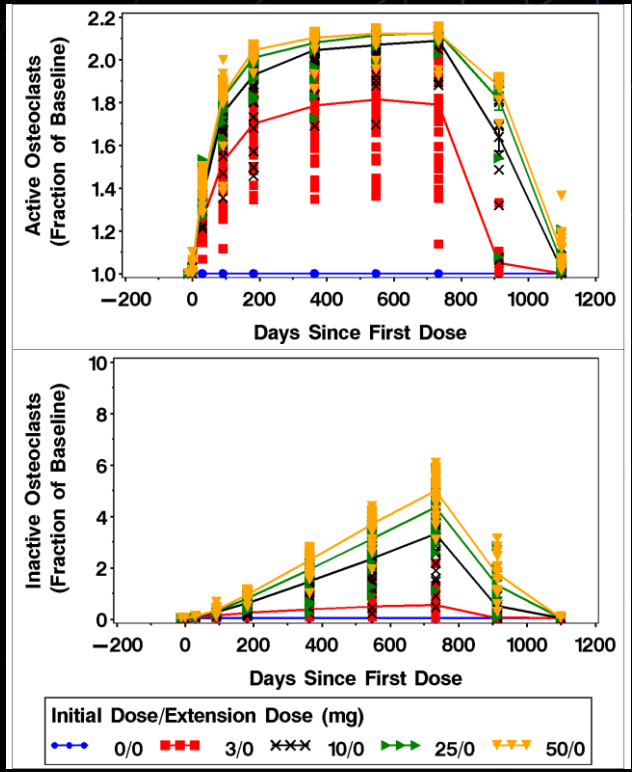




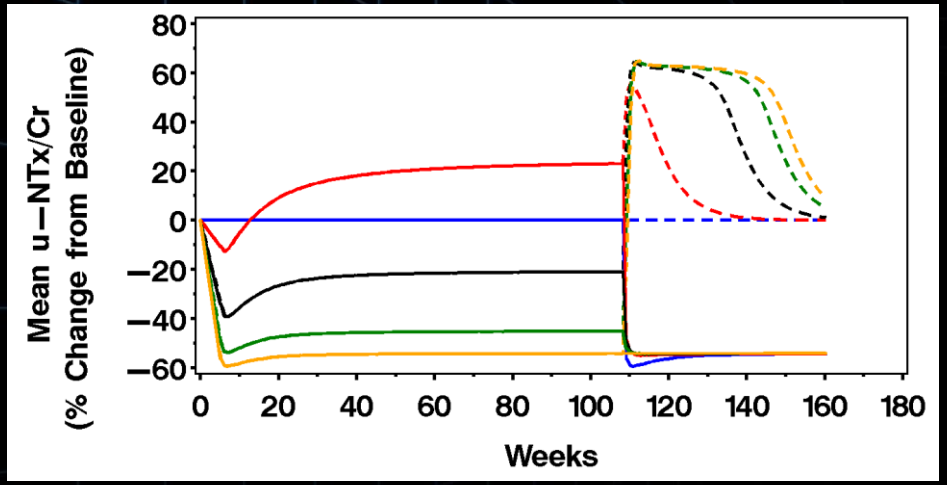


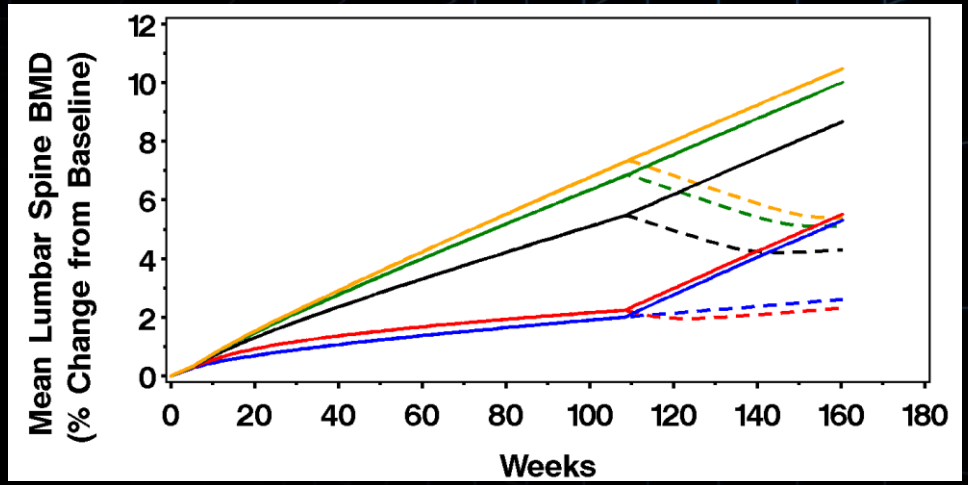
Exposure-Response Profiles for Osteoclast Cycling and Bone Resorption and Corresponding Osteoclast Profiles





Model-Predicted Typical Profiles for uNTx Biomarker and LS-BMD by Dose Regimen





Initial Dose/Extension Dose (mg)

0/0	3/0	10/0	25/0	50/0
0/50	3/50	10/50	25/50	50/50

Conclusions

- A semi-mechanistic population PK/PD model incorporating two inhibitory sigmoid Emax exposure-response relationships (osteoclast effects and resorption inhibition) simultaneously characterized the time-course of the bone resorption biomarker uNTx/Cr and primary efficacy endpoint lsBMD across all doses, including both on-treatment and treatment washout responses.
- The non-monotonic dose-response relationship at the low 3 mg dose derives from a modest difference in the drug potency for the two drug effects (osteoclast effects $IC50_C$ of 17.0 nM and resorption inhibition $IC50_R$ of 38.5 nM).
- The resolution of uNTx/Cr and BMD response after cessation of odanacatib treatment was characterized in the model by a build-up of osteoclast numbers during therapy, which subsequently contribute to the transient rebound effects observed during washout.

Q&A

Questions & Answers

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