Evaluation of Population PK/PD for Osteoporosis during a Vitamin D_3 ($1,25(OH)_2D_3$) Derivative Therapy

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Introduction

Vitamin D_3 ($1,25(OH)_2D_3$) is a hormone that is closely involved with calcium homeostasis in the body by means such as promoting the mobilization of bone minerals, the absorption of Ca from the gut, and Ca reabsorption in the kidney. As it is also involved in osteogenesis and bone loss, it is recognized to be beneficial in increasing bone mass and bone strength in osteoporosis. The drug used in this analysis is a vitamin D_3 ($1,25(OH)_2D_3$) derivative and is in development as an osteoporosis drug. Some clinical trials have already been conducted and the pharmacokinetic linearity of the drug has been assessed at doses ranging from 0.1 μg to 1.0 μg. It was reported that lumbar bone mineral density (BMD) increased about 2.5% from treatment for osteoporosis with the drug (0.75 μg) for 1 year. In addition, the drug showed dose-dependent suppression of bone loss markers (tDPD, CTx, NTx) but no dose response was found for osteogenesis markers (PICP, OC). The primary end point of osteoporosis drug development is to reduce fracture risk. In this analysis, BMD was used as a pharmacodynamics marker because BMD is one factor of bone strength that provides fracture protection.

Objectives

The purpose of this analysis was to characterize the relationship between pharmacokinetics (PK, concentration of vitamin D_3 ($1,25(OH)_2D_3$) derivative) and pharmacodynamics (PD, BMD) in the treatment of osteoporosis with a vitamin D_3 ($1,25(OH)_2D_3$) derivative.

Methods

Data from four clinical studies used in the analysis are as follows:

Study No.	Number of Subjects	Dosage (μg)	Dosing Period	Sampling Point - Drug Concentration (PK) - BMD (PD)
1	12 (healthy volunteer)	0.25	1 day (q.d.) [a]	Pre, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96 h (PK)
2	24 (healthy volunteer)	0.1 0.25 0.5 1.0	15 days (q.d.) [a]	Pre, 2, 4, 6, 8, 12, 24, 72, 120, 168, 216, 264, 288, 312, 336, 337, 338, 339, 340, 342, 344, 348, 360, 384, 408, 432, 456 h (PK)
3	106 (osteoporosis)	0.25 0.5 0.75 1.0	24 weeks (q.d.) [a]	Pre, 8, 16, 24 week (PK) Pre, 24 week (PD)
4 [b]	158 (osteoporosis)	Placebo 0.5 0.75 1.0	48 weeks (q.d.) [a]	Pre, 12, 24, 48 week (PK) Pre, 24, 48 week (PD)

[a] Once daily (quaque die)
[b] All patients in Study No.4 were taking ED-71 or placebo with a vitamin D_3 modular

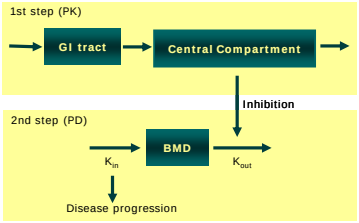
In total, 1397 plasma samples from 300 subjects were obtained for PK analysis from all four studies and 680 BMD data from 264 patients were obtained for PD analysis from two clinical studies where osteoporosis patients were enrolled. The plasma drug concentrations were determined by LC/MS/MS and BMD data were measured by dual energy-X-ray absorptiometry (DXA). This population PK/PD model analysis was performed by sequential methods using NONMEM VI with the FOCE INTER estimation method.

Results

PK/PD Analysis

The final PK/PD model consisted of a one-compartment model with first order absorption and a turnover PD model in which the plasma drug concentration inhibits bone loss (K_{out}). A linear disease progression model including the endogenous vitamin D_3 ($25(OH)D_3$) as a covariate best described the BMD decrease profile.

Figure 1: Population PK and PD Model



Pharmacokinetics

$$\frac{dX_{GI}}{dt} = -K_a \times X_{GI}$$

$$\frac{dX_{central}}{dt} = K_a \times X_{GI} - \frac{CL_{central}}{V_{central}} \times X_{central}$$

Pharmacodynamics

$$C_e = \frac{X_{central}}{V_{central}}$$

$$INH = 1 - \frac{I_{max} \times C_e}{IC_{50} + C_e}$$

$$\frac{dPD_{BMD}}{dt} = K_{in} - K_{out} \times INH \times PD_{BMD} - K_{prog}$$

$$K_{in} = K_{out} \times PD_{BMD}$$

Covariate effects

$$K_{prog} = K_{prog\_base} + K_{prog\_25(OH)D_3}$$

If 25(OH)D$_3$ level is less than 20 ng/mL, $K_{prog\_25(OH)D_3}$ is 0.

Table 1: Parameter Estimates for the PK/PD Model

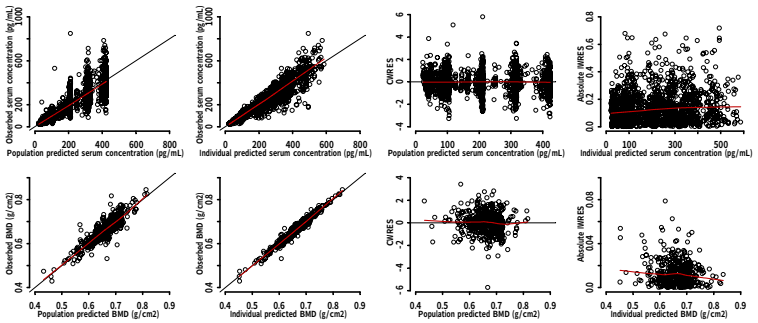
PK Parameters	Unit	Population Mean	SE
Fixed effects			
$CL_{central}$	L/h	0.109	0.00175
$V_{central}$	L	9.50	0.307
K_a	/h	1.06	0.132
Random effects (CV %) [a]			
Inter-individual variability			
IIV $CL_{central}$		25.2	8.68
IIV $V_{central}$		16.1	9.50
IIV K_a		54.9	36.9
Residual error (CV %) [b]		20.8	6.26

[a] Exponential model
[b] Proportional model

PD Parameters	Unit	Population Mean	SE
Fixed effects			
I_{max}		0.0448	0.00794
K_{out}	/h	0.000346	0.0001
IC_{50}	Pg/mL	66.8	20.5
K_{prog_base}	mg/cm²*year	$8.76*10^{-5}$	$1.31*10^{-8}$
$K_{prog\_25(OH)D_3}$	mg/cm²*year	20.5	77.8
Random effects (CV %) [c]			
Inter-individual variability			
IIV I_{max}		55.0	28.8
IIV K_{out}		40.5	40.7
IIV IC_{50}		248	208
IIV K_{prog}		108	62.5
Residual error (CV %) [d]		1.66	0.786

[c] Exponential model
[d] Additive model

Figure 2: Goodness of Fit Plots for the PK/PD Model



Evaluation of the PK/PD Final Model

The PK/PD model was validated both by a visual predictive check and by a numerical predictive check. The percentage of observations above 90% PI and below 90% PI was 7.2% and 5.1%, respectively.

Figure 3: Visual Predictive Check with 90% PI

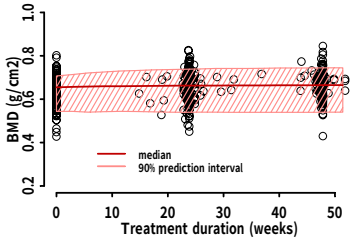


Table 2: Numerical Predictive Check

		Observations (%)
Median	Above	53.2
	Below	46.8
50% PI	Above	27.4
	Below	25.1
90% PI	Above	7.2
	Below	5.1

Simulation for Long-Term Administration

The median of the percentage change in BMD in the treatment of osteoporosis with the drug (0.75 μg) for 3 years was predicted to be 2.2%. BMD was predicted to decrease 0.67% without the treatment due to disease progression. The percentage change in BMD increased rapidly up to almost 1 year and was maintained at the same level after that at all doses.

Figure 4: Simulated BMD Change Profiles at Doses of 0.75 μg for 3 Years

a) Median of predicted efficacy without disease progression, predicted efficacy and predicted disease progression

b) Median of predicted efficacy with 90 % PI

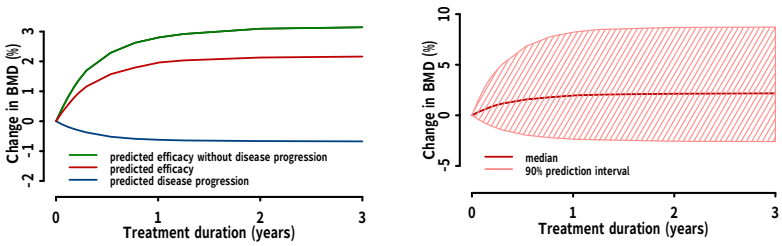


Table 3: Comparison of Observed Data and Simulation Data

Dosage (μg)	Median of Observed Data (90% CI)		Median of Simulation Data (90% PI)	
	After 1-year Treatment	After 3-year Treatment	After 1-year Treatment	After 3-year Treatment
0.25	-	-	1.0% (-3.3% ~ 7.1%)	1.1% (-3.7 ~ 7.5%)
0.5	2.4% (-5.2% ~ 10.1%)	-	1.5% (-3.9% ~ 7.6%)	1.7% (-4.6 ~ 8.2%)
0.75	2.3% (-2.5% ~ 10.7%)	(available soon)	2.0% (-2.4% ~ 8.5%)	2.2% (-2.6 ~ 8.7%)
1.0	2.3% (-1.0% ~ 10.0%)	-	2.0% (-3.3% ~ 8.4%)	2.1% (-3.7 ~ 9.0%)

Conclusions

A PK/PD model has been developed which shows linear disease progression during 1 year of treatment with a vitamin D_3 ($1,25(OH)_2D_3$) derivative. The model is likely to be useful for predicting the percentage change in BMD after administration of a vitamin D_3 ($1,25(OH)_2D_3$) derivative. The model needs further estimation using the data of a long-term clinical study to be available next year.