Population pharmacokinetics of balicatib, a cathepsin K inhibitor

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Abstract

Background: Cathepsin K is a key enzyme for the breakdown of collagen during bone resorption. Balicatib inhibits cathepsin K and has been shown to reduce bone turnover.

Methods: Pharmacokinetic data after oral dosing of healthy subjects and patients with post-menopausal osteoporosis were obtained in Caucasians and Orientals during Phase 1 and Phase 2A of the clinical development of balicatib. Single doses of 5 to 400 mg and multiple daily doses of 5 to 50 mg up to 12 weeks were administered with intensive sampling on day 1 and at steady state. A mixed effects pharmacokinetic model for balicatib and a metabolite AEE325 was developed using NONMEM Version V Release 1.1.

Results: A two compartment disposition model with zero-order input and first-order elimination described plasma balicatib concentrations. Lag time with between occasion variability and between subject variability in extent improved the fit. An unexpected finding was a dose dependent decrease in the apparent volume of distribution of the peripheral compartment. Metabolite formation was very rapid and was well defined by assuming instantaneous conversion in a fixed ratio to the predicted parent concentration (population median 0.11; apparent CV 46%). Parameters were scaled allometrically using body weight. Renal clearance was predicted by assuming a linear relationship to predicted creatinine clearance (CLcr) and accounted for 13% of total clearance. The variability in balicatib total clearance was unexpectedly small for a CYP3A substrate (apparent CV 12.2%).

Objectives

The first objective was to develop a model for the time course of balicatib and a major metabolite.

The second objective was to identify covariates which could predict differences in balicatib exposure for pharmacokinetic-pharmacodynamic model development and clinical simulation studies.

Patients

Healthy subjects (N=56)
Postmenopausal women with reduced bone mineral density (N=675)
Postmenopausal women with normal bone mineral density (N=191)

Models

Two compartment model with zero-order input and lag time.
First-order elimination of balicatib and its metabolite (AEE325).
Instantaneous conversion of balicatib to its metabolite (Equation 1).
Parameters scaled with total body weight using allometric theory (Equation 2).
Renal clearance assumed to be a linear function of renal function (Equation 3)
Renal function calculated from predicted creatinine clearance relative to standard of 6 L/h/70kg.
Covariate effects of age, race, formulation, concomitant ketoconazole use and dose (Equations 4-8).
Between subject and between occasion parameter variability.
Individual residual error variability.

Model Equations

$$C_{AEE325} = F2M \cdot C_{balicatib}$$ Equation 1

$$FSZV = \frac{Wt}{Wt_{STD}}$$ Equation 2

$$FSZCL = FSZV^{\hat{}}$$

$$CL = (CL_{NR\,STD} + CL_{R\,STD} \cdot RF) \cdot FCOV$$ Equation 3

FCOV=FSZCLFAGEFRACE FFORM FKETO FDOSE

$$FAGE = e^{KCLAGE \cdot (AGE - AGE_{STD})}$$ Equation 4

if (RACE.EQ.3) then ;Oriental Equation 5
FRACE = FCLORI
else
FRACE = 1 ; Caucasian
endif

if (STAB.EQ. 0) then ;Capsule Equation 6
FFORM = FCAP
else
FFORM = 1 ; Tablet
endif

if (KETO.EQ.1) then ;Ketoconazole treatment Equation 7
FDRUG = FF1KET
else
FDRUG = 1 ; Without ketoconazole
endif

$$FDOSE = 1 + DELTA \cdot DOSE/(D50 + DOSE)$$ Equation 8

Computation

NONMEM Version V Release 1.1
FOCE with INTERACTION
SIGDIG=6
Source code patched and qualified with NMQUAL Version 4
Compaq Visual Fortran Version 6.6 Update C. Compiler options /fltconsistency /optimize:4 /fast.
Windows Server 2000, AMD Athlon MP2000

Discussion

The absorption of balicatib is rapid. A major metabolite, AEE325, is formed quickly, probably during absorption. The elimination appears to be formation-rate limited.

The between subject variability in clearance was 12.2%. This estimate was not appreciably changed by inclusion of covariates. Approximately 13% of balicatib clearance is attributable to renal elimination when the predicted creatinine clearance is 6L/h/70kg.

An unexpected finding was a decrease in peripheral compartment volume of distribution for balicatib with increasing dose.

The effect of ketoconazole treatment on bioavailability of AAE581 was more on bioavailability than effect on clearance. This is in line with ketoconazole inhibition of CYP3A4 in the gut wall as well as in the liver.

Conclusions

The PK model describes both the central shape and the variability in time course of balicatib and a major metabolite after the first dose and over 12 weeks of treatment.

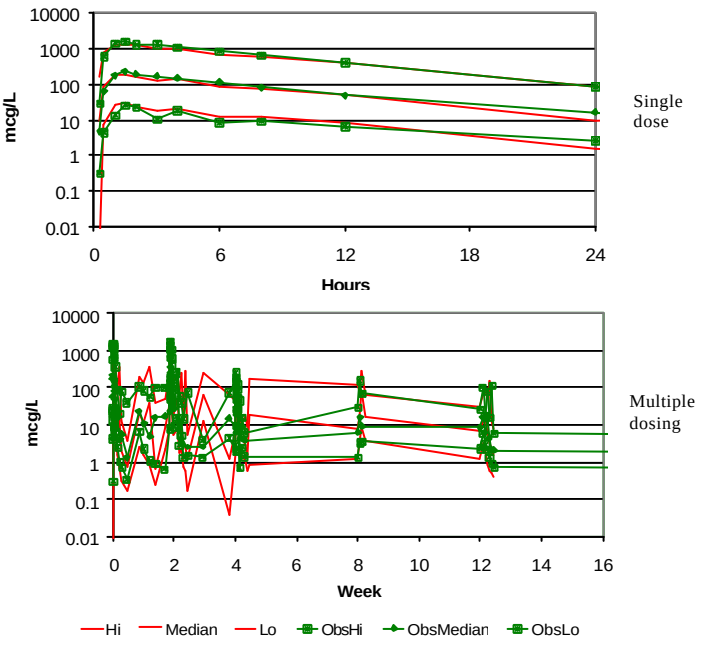
The main covariates identified by NONMEM which predict between subject differences are weight and dose (volume of distribution), weight and renal function (clearance) and ketoconazole (bioavailability).

Pharmacokinetic Parameter Estimates for Balicatib

Description	Units	Estimate	PPV	BOV
Renal clearance (CLcr=6L/h/70kg)	L/h/70kg	4.19		
Non-renal clearance	L/h/70kg	27.6	0.122*	
Central volume	L/70kg	304	0.215	
Inter-compartmental clearance	L/h/70kg	5.56	0.531	
Peripheral volume	L/70kg	390	0.113	
Duration of zero-order input	h	0.55		
Absorption lag-time	h	0.224		0.499
Nominal bioavailability	-	1 FIXED	0.214	
Fractional max decrease in Vp	-	0.9		
Balicatib dose at 50% of VPMIN	mg	17.3		
Fractional clearance change in Orientals	-	1.14		
Fractional bioavailability change with ketoconazole	-	2.97		
Fractional clearance change per year of age	y^{-1}	-0.002		
Proportional residual error	-	0.188		
Additive residual error	mcg/L	0.00805		
Between subject variability in residual error	-	0.349		

*=PPV for both renal (CLR) and non-renal (CLNR) clearance
PPV=population parameter variability (SQRT(OMEGA))
BOV=between occasion variability (SQRT(OMEGA))

Visual Predictive Check
90% Prediction and Observation Intervals



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