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 was explained by high plasma 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 a linear relationship to plasma 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 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%).

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

Healthy subjects (N=56) Postmenopausal women with reduced bone mineral density (N=675)
Postmenopausal women with normal bone mineral density (N=931)

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

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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).

\[ \text{Fractional clearance change per year of age} \times y \]

\[ \text{Absolute residual error mcg/L} = 0.00805 \]

\[ \text{Proportional residual error} = -0.188 \]

\[ \text{Fractional clearance change in Orientals} \times 1.14 \]

\[ \text{Fractional bioavailability change with ketoconazole} \times 2.37 \]

\[ \text{Fractional clearance change per year of age} \times 0.002 \]

\[ \text{Proportional residual error} \times 0.188 \]

\[ \text{Additive residual error mcg/L} \times 0.00805 \]

\[ \text{Between subject variability in residual error} \times 0.349 \]

*PPV=population parameter variability (SQRT(OMEGA))
BOV=between occasion variability (SQRT(OMEGA))

Pharmacokinetic Parameter Estimates for Balicatib

<table>
<thead>
<tr>
<th>Description</th>
<th>Units</th>
<th>Estimate</th>
<th>PPV</th>
<th>BOV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal clearance (CLcr=6L/h/70kg)</td>
<td>L/h/70kg</td>
<td>4.13</td>
<td>0.0122</td>
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<tr>
<td>Non-renal clearance</td>
<td>L/h/70kg</td>
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<td>Central volume</td>
<td>L/70kg</td>
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<td>Inter-compartmental clearance</td>
<td>L/h/70kg</td>
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<td>0.031</td>
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<tr>
<td>Peripheral volume</td>
<td>L/70kg</td>
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<tr>
<td>Duration of zero-order input</td>
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<tr>
<td>Absorption lag time</td>
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<tr>
<td>Nominal bioavailability</td>
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<tr>
<td>Fractional max decrease in Vp</td>
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<tr>
<td>Maximal dose of 50% of CLcr</td>
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<tr>
<td>Fractional clearance change in orientals</td>
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<td>1.14</td>
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<td></td>
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<td></td>
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<tr>
<td>Fractional clearance change per year of age</td>
<td>y</td>
<td>0.002</td>
<td></td>
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<td>-</td>
<td>0.188</td>
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Acknowledgments:
The authors gratefully acknowledge Aurelie Gautier and Vincent Buchheit for their programming skills.

Visual Predictive Check 90% Prediction and Observation Intervals

Conclusions

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

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