Population pharmacokinetics of ripretinib in patients with advanced malignancies

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INTRODUCTION

Ripretinib is a multi-targeted kinase inhibitor approved for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib. The magnitude of increased ripretinib exposures in females or with high body mass index (BMI) were comparable in simulation results. The PK of DP was described by a 1-compartment model with linear elimination.

RESULTS

The PK of ripretinib 150 mg BID were comparable to values in patients with renal function category in NCT02571036 (CLm/F) at the 150 mg QD dose for patients with mild hepatic impairment based on the National Cancer Institute hepatic dysfunction classification. The PK of DP was described by a 1-compartment model with linear elimination.

METHODS

Table 1. Clinical studies included in the analysis

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study design, no.</th>
<th>Drug dose and schedule</th>
<th>Phase PK sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02571036</td>
<td>A multicenter, single-center, open-label study to evaluate PK in patients with advanced malignancies</td>
<td>28 day cycles</td>
<td>Escalation Phase: Cycle 1: Day 1 and Day 8; Cycle 2: Day 1 and Day 8; Cycle 3: Day 1 and Day 8; Cycle 4: Day 1 and Day 8; Cycle 5: Day 1 and Day 8; Cycle 6: Day 1 and Day 8; Cycle 7: Day 1 and Day 8; Cycle 8: Day 1 and Day 8; Cycle 9: Day 1 and Day 8; Cycle 10: Day 1 and Day 8. Intermittent dose escalation was performed.</td>
</tr>
<tr>
<td>GEVALIT CLIN-313 (WANTUS)</td>
<td>A phase 1, open-label study to evaluate PK in patients with advanced malignancies treated with a fat meal following a 150 mg QD dose for patients with moderate renal impairment were comparable to values in patients with mild hepatic impairment or patients with mild hepatic impairment.</td>
<td>100 mg QD or matching placebo (P); 64 days</td>
<td>Escalation Phase: Cycle 1: Day 1; Cycle 2: Day 1; Cycle 3: Day 1; Cycle 4: Day 1; Cycle 5: Day 1; Cycle 6: Day 1; Cycle 7: Day 1; Cycle 8: Day 1; Cycle 9: Day 1; Cycle 10: Day 1; Cycle 11: Day 1; Cycle 12: Day 1; Cycle 13: Day 1; Cycle 14: Day 1; Cycle 15: Day 1; Cycle 16: Day 1; Cycle 17: Day 1; Cycle 18: Day 1; Cycle 19: Day 1; Cycle 20: Day 1; Cycle 21: Day 1; Cycle 22: Day 1; Cycle 23: Day 1; Cycle 24: Day 1; Cycle 25: Day 1; Cycle 26: Day 1; Cycle 27: Day 1; Cycle 28: Day 1; Cycle 29: Day 1; Cycle 30: Day 1; Cycle 31: Day 1; Cycle 32: Day 1; Cycle 33: Day 1; Cycle 34: Day 1; Cycle 35: Day 1; Cycle 36: Day 1; Cycle 37: Day 1; Cycle 38: Day 1; Cycle 39: Day 1; Cycle 40: Day 1; Cycle 41: Day 1; Cycle 42: Day 1; Cycle 43: Day 1; Cycle 44: Day 1; Cycle 45: Day 1; Cycle 46: Day 1; Cycle 47: Day 1; Cycle 48: Day 1; Cycle 49: Day 1; Cycle 50: Day 1; Cycle 51: Day 1; Cycle 52: Day 1; Cycle 53: Day 1; Cycle 54: Day 1; Cycle 55: Day 1; Cycle 56: Day 1; Cycle 57: Day 1; Cycle 58: Day 1; Cycle 59: Day 1; Cycle 60: Day 1. Intermittent dose escalation was performed.</td>
</tr>
</tbody>
</table>

Figure 1. Steady-state ripretinib AUC relative to reference

Table 2. Final population PK estimates for ripretinib

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fixed effect estimate</th>
<th>95% CI</th>
<th>Standard error</th>
<th>Relative standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F</td>
<td>6.17 L/hr</td>
<td>5.31, 7.12</td>
<td>0.58</td>
<td>0.32</td>
</tr>
<tr>
<td>V/F</td>
<td>206 L</td>
<td>159, 258</td>
<td>48.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Ka</td>
<td>1.82 hr</td>
<td>1.22, 2.87</td>
<td>0.32</td>
<td>0.01</td>
</tr>
<tr>
<td>fD</td>
<td>0.07</td>
<td>0.06, 0.08</td>
<td>0.002</td>
<td>0.005</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Ripretinib oral PK was well described by a 2-compartment model and had a modest, linear dose-dependent decrease in relative bioavailability by linear elimination.

REFERENCES