CYP450 INHIBITION, INDUCTION, METABOLISM, AND ROUTES OF ELIMINATION OF SNS-595, A NOVEL CELL CYCLE INHIBITOR IN PHASE 1 CLINICAL TRIALS

Ute Hoch, Marc J. Evcanlı, Jeffrey A. Silverman, Sunesis Pharmaceuticals, Inc. South San Francisco, CA 94080

ABSTRACT

Background: SNS-595 is a novel naphthyridine analog that acts during the S phase of the cell cycle to induce apoptosis and antitumor activity. SNS-595 has been shown to induce apoptosis and antitumor activity in vivo and in vitro in a range of human tumor cell lines through both the intrinsic and extrinsic pathways of apoptosis. The mechanism of SNS-595 has been shown to affect multiple cellular targets, including cell cycle arrest, CHK1 and CHK2 inhibition, and the activation of caspases.

Methods: In vitro metabolic stability of SNS-595 was evaluated following incubation with rat and human liver microsomes in the presence of NADPH or UDPGA for up to 60 min; the percentage of parent remaining was determined by LC-MS/MS. The pharmacokinetic properties, including the terminal half-life. Metabolites detected after incubations with liver microsomes, were detected and identified by using LC-MS/MS. Chemically synthesized authentic standards.

Results: SNS-595 was minimally metabolized in rat and human liver microsomes, with more than 99% of the parent compound remaining after 60 min. The major metabolites identified in vitro are the glucuronide metabolite, and two des-methyl metabolites are detected.

Conclusion: In vitro and in vivo studies demonstrate that SNS-595 is minimally metabolized and does not inhibit or induce the CYP3A4 enzyme system; therefore, SNS-595 has a low potential for clinically relevant drug-drug interactions and for non-linear pharmacokinetics in humans. A major route of excretion is through the bile, where unchanged SNS-595, a glucuronide metabolite, and two demethyl metabolites are detected.

LIVER MICROSOMAL STABILITY

The metabolic stability of SNS-595 was determined after incubation with rat and human liver microsomes in the presence of NADPH or UDPGA for up to 60 min; the percentage of parent remaining was determined by LC-MS/MS. The pharmacokinetic properties, including the terminal half-life. Metabolites detected after incubations with liver microsomes, were detected and identified by using LC-MS/MS. Chemically synthesized authentic standards.

CONCLUSIONS

- SNS-595 has low potential for drug-drug interactions when administered in combination with other drugs
- SNS-595 is not readily metabolized by the major P450 isoforms
- SNS-595 is not an inhibitor of the major P450 isoforms
- SNS-595 does not show the ability to induce the major P450 isoforms

SNS-595 is predicted to show excellent human pharmacokinetic behavior (see abstract by Advani et al.)

- Tight inter-individual pharmacokinetics in all animal species
- Low to medium CL and long T½ seen in all species
- Dose linear PK in all species
- Similar in vitro and in vivo metabolism in rats

PHARMACOKINETICS

IV Pharmacokinetics Parameters for Mouse, Rat, and Monkey

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg)</th>
<th>T½ (h)</th>
<th>Vd (L/kg)</th>
<th>CL (mL/min/kg)</th>
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</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>53</td>
<td>22.5</td>
<td>7.3</td>
<td>0.26</td>
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<tr>
<td>Rat</td>
<td>75</td>
<td>25</td>
<td>7.6</td>
<td>0.28</td>
</tr>
<tr>
<td>Monkey</td>
<td>12.5</td>
<td>27.5</td>
<td>4.7</td>
<td>0.31</td>
</tr>
</tbody>
</table>

SNS-595 shows linear increase in mice (•) and rats (•).

Metabolites observed in vitro also observed in vivo in rats.

Routes of excretion include bile and urine.

 baket

low to medium clearance and long terminal half-life across species.

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