Preclinical Characterization of SCH 900518, A Novel Mechanism-Based Inhibitor of HCV NS3 Protease


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Background: Sustained response hepatitis C virus (HCV) monotherapy with protease inhibitors have shown clinical activity in combination as well as in combination with pegylated interferon, and viral clinical benefit. However, clinical efficacy can be limited by pegylated interferon drug exposure and development of antiviral resistance. Inhibitory targets of proteases and pharmacokinetic properties offer opportunities for evaluation such limitations and to further increase DAAs.

Methods: Inhibitors of HCV NS3 protease were screened using a single-cell NS3-4A protease assay. The antiviral effect and resistance study of protease inhibitors were evaluated using genotypes 1b NS3 replicon cells.

Results: Continuous Spectrophotometry Assay

• Replication activity of SCH 900518 was evaluated in the HCV replicon system.

• Kinetic parameters for SCH 900518 were determined using an inhibitor dilution protocol.

Resistance Studies

• Inhibitory concentrations of replicon clones recovered from SCH 900518 do not show resistance studies identified mutations at 2 different nucleotide sites (100 and 101) for the protease domain (Table 1) – other nucleotide sites (A156V/G) were also observed. Fewer mutations were seen in the IFN alfa-2b combination; whereas, the proteasome activity and IC90 for SCH 900518 was decreased to approximately 1.5-fold over the projected baseline in cyclic threshold (ΔCT).

• Resistance colony, %

• SCH 900518 was cross-resistant to mutations raised against boceprevir.

Conclusions

• The emergence of resistance to SCH 900518 was associated with increased IC90 values for SCH 900518 with IC50 of 20 nM and 130 nM.

• Replication cells resistant to SCH 900518 remained sensitive to IFN alfa-2b.

• The emergence of resistance to SCH 900518 was associated with increased resistance colony (Table 1). The resistance colony was observed in the SCH 900518-resistant cell line at 4× IC90 dose, which conferred a higher level of resistance to the compound.

• SCH 900518 was shown to be more potent in combination with other protease inhibitors.

• The combination of SCH 900518 with IFN alfa-2b resulted in a lower fold change in IC90 values for SCH 900518 with IC50 of 20 nM and 130 nM.

• Inhibitions of HCV NS3/4A Protease In Mte

• When treated with SCH 900518, cells were inhibited by SCH 900518 when IC90 for SCH 900518 = 50 nM; for boceprevir = 180 nM.

• In the absence of NS3 protease, there was a dose-dependent, inhibitor-sensitive inhibition of virus RNA.

• Combination studies with interferon alfa-2b

• SCH 900518 was cross-resistant to mutations raised against boceprevir and telaprevir, but retained more activity on many of the mutants as a result of its higher intrinsic antiviral activity.

• Resistance colony was observed at approximately the 0.13% level.

• Culturing of replicon-bearing cells in the presence of 3× IC90 SCH 900518 showed minimal effects on cell viability in a variety of human cell lines and primary cell cultures using standard MTS (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyltetrazolium bromide) enzyme plaques.

• The results demonstrated a potential for clinical use of SCH 900518 in combination with pegylated interferon alfa-2b.

• The replicon assay, SCH 900518 alone.

• When interferon (IFN) alfa-2b was coadministered with SCH 900518, there was a dose-dependent increase in antiviral activity.

• The replicon assay, SCH 900518 with IFN alfa-2b (30 IU/mL; approximately 10× IC90 SCH 900518).

Figure 1. Inhibition of HCV genotype 1b NS3/4A protease by SCH 900518.

Figure 2. Replicon assay of SCH 900518.

Table 1. Resistance Mutations Selected by SCH 900518

<table>
<thead>
<tr>
<th>Replicon</th>
<th>Resistance Colony, %</th>
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<tbody>
<tr>
<td>SCH 900518 alone</td>
<td>0.13</td>
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<tr>
<td>SCH 900518 with IFN alfa-2b (30 IU/mL)</td>
<td>0.13</td>
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</tbody>
</table>

Table 2. Enzyme Activity of SCH 900518 Against Mutations Conferring Resistance to Boceprevir

<table>
<thead>
<tr>
<th>Mutation</th>
<th>IC50 (µM) a</th>
<th>IC90 (µM) a</th>
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<tbody>
<tr>
<td>A156S</td>
<td>5.0 ± 1.0</td>
<td>16.0 ± 1.0</td>
</tr>
<tr>
<td>A156T</td>
<td>5.0 ± 1.0</td>
<td>16.0 ± 1.0</td>
</tr>
<tr>
<td>A156V</td>
<td>5.0 ± 1.0</td>
<td>16.0 ± 1.0</td>
</tr>
<tr>
<td>A156G</td>
<td>5.0 ± 1.0</td>
<td>16.0 ± 1.0</td>
</tr>
</tbody>
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Note: IC50 and IC90 values represent the concentration of SCH 900518 that resulted in an increase of 1 over the projected baseline in cyclic threshold (ΔCT).

References


3. Schiff E et al. 43rd Annual Meeting of the European Association for the Study of the Liver; April 23-27, 2008; Milan, Italy.


Disclosures

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