IDX184, A Liver-Targeted Nucleotide HCV Polymerase Inhibitor: Results of a First-in-Man Safety and Pharmacokinetic Study

Idenix Pharmaceuticals, Inc., Cambridge, MA, USA

BACKGROUND

The safety and antiviral activity of investigational, first-generation nucleoside analog inhibitors of HCV NS5B may be limited by wide systemic distribution and inefficient conversion to the monophosphate, which limits production of active triphosphate (TP) species in the liver.

As previously reported, IDX184 is a liver-targeted nucleotide prodrug designed to enhance formation of its active TP in the liver, while minimizing systemic exposure to the parent drug and the nucleoside metabolite (NM). Figure 1. IDX184 is a potent and selective inhibitor of HCV in vitro and demonstrated multifold viral load reductions in HCV-infected chimpanzees receiving 10 mg/kg for 4 days.1,2

OBJECTIVES

• To evaluate the safety and tolerability of IDX184 at single oral doses from 5 to 100 mg in healthy adult male and female subjects.
• To evaluate the plasma and urine PK of IDX184 and the NM at single oral doses.
• To guide dose selection for subsequent Phase Ib/Ila studies in HCV-infected patients.

METHODS

Subjects and Study Design

Randomized, blinded, placebo-controlled, sequential cohort, single-dose escalation study

Healthy male and female volunteers (N=48) between 19 and 65 years participated in this study.

Eight subjects per dose were randomized to a single dose of IDX184 (5, 10, 25, 50, 75, or 100 mg) or matching placebo. Subjects observed a fasting period of approximately 10 hr prior to dosing and an additional 4 hr post dosing.

Safety data were reviewed at the end of each dosing cohort, prior to escalation to the next sequential dose.

PK Sampling and Analysis

Plasma and urine PK of IDX184 and the NM were evaluated prior to dosing on Day 1 through a period of 120 hr (Day 6).

Plasma and urine concentrations of IDX184 and the NM were quantified using validated LC/MS-MS methodologies.

Plasma PK parameters, obtained using standard non-compartmental analysis, include Cmax, Tmax, AUC to t last, and terminal elimination half-life (T1/2)

Statistical Analysis

Summary statistics were used for PK parameters.

• Dose proportionality was assessed with respect to drug exposure parameters (AUC and Cmax) by fitting a regression line and was to be concluded if the 95% CI for the slope ranged from 0.70 to 1.30.

RESULTS

Demographics

Table 1: Demographic Characteristics of Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5 mg</th>
<th>10 mg</th>
<th>25 mg</th>
<th>50 mg</th>
<th>75 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), yrs</td>
<td>35.0 (15.10)</td>
<td>27.8 (6.43)</td>
<td>33.7 (17.59)</td>
<td>28.8 (6.37)</td>
<td>37.0 (14.82)</td>
<td>24.3 (2.58)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>6 (50.0)</td>
<td>4 (66.7)</td>
<td>5 (83.3)</td>
<td>5 (83.3)</td>
<td>3 (50.0)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Caucasian</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Body weight (SD), kg</td>
<td>73.5 (11.93)</td>
<td>80.5 (23.36)</td>
<td>79.6 (7.21)</td>
<td>79.9 (11.83)</td>
<td>76.9 (10.09)</td>
<td>78.5 (16.08)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plasma PK Parameters of IDX184 and the Nucleoside (NM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5 mg</th>
<th>10 mg</th>
<th>25 mg</th>
<th>50 mg</th>
<th>75 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean plasma conc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax, hr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0-12h, ng*hr/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0-24h, ng*hr/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetics

Figure 2: Mean (±SD) Plasma Concentrations Versus Time of IDX184 and the Nucleoside (NM)

IDX184 was rapidly absorbed with higher exposure as doses increased from 25 mg.

Steady-state is estimated at 5-7 days.3

Pharmacokinetic parameters (AUC, Cmax) were derived from plasma concentrations at 24 hr post dosing (C24h) and can be used to calculate molar ratios:

\[ \text{Molar ratio} = \left( \frac{\text{NM} \times \text{C24h}}{\text{IDX184} \times \text{Cmax}} \right) \]

The mean molar ratio of NM/C0 increased from 3.04±0.52 at 5 mg to 11.98±3.08 at 100 mg in a dose-proportional manner.

• IDX184 was rapidly absorbed with higher exposure as doses increased from 25 mg.

Cumulative amount of the NM excreted in urine was higher than IDX184, representing 12 to 20% of administered doses (% molar ratio).

DISCUSSION AND CONCLUSIONS

• IDX184 appeared to be safe and well tolerated in healthy subjects at single doses up to 100 mg.

Pharmacokinetics of IDX184 and the nucleoside metabolite (NM) are consistent with a liver-targeting approach based on:

• Low systemic exposures
• Plasma NM: of NM approximating the intracellular T1/2 of NM-TP in hepatocytes

The predicted plasma trough levels of the NM after daily dosing of IDX184 at 25, 50, 75 and 100 mg ranged from 1.2 to 7.1 ng/mL, after three doses and from 1.0 to 10.3 ng/mL at steady-state.

The favorable safety and PK profiles warrant further clinical development of IDX184.

References


Acknowledgments

We thank Teresa Dahman for assistance with the poster preparation.

Disclosures

B. Belanger is a former employee of and B. Kuca is a former consultant to Idenix Pharmaceuticals, Inc. All other authors are current employees of Idenix Pharmaceuticals, Inc.