Antiviral Activity of the Liver-Targeted Nucleotide HCV Polymerase Inhibitor IDX184 Correlates with Trough Serum Levels of the Nucleoside Metabolite in HCV-infected Chimpanzees

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Disclosure

• Robert Lanford is an employee of Southwest Foundation for Biomedical Research, San Antonio, TX, USA. The Southwest Foundation for Biomedical Research has received compensation from Idenix for conducting preclinical studies of IDX184.

• All other authors are current employees of Idenix Pharmaceuticals, Inc., Cambridge, MA USA
Future of HCV Treatment: Combination of Direct-Acting Antivirals

Nucleoside/tide and protease inhibitors should be preferred double combination due to distinct modes of action, complementary resistance profiles and pan-genotypic activity; Potent non-nucleosides as third component of STAT-C cocktail may replace interferon(s).

Idenix HCV Cocktail Combination Strategy

**Comprehensive HCV Pipeline**

- **Nucleoside/tide Polymerase Inhibitor IDX184**
  - Potent antiviral activity *in vitro* and *in vivo*
  - Liver-targeted with low systemic exposure
  - Phase I/II in HCV-1 patients ongoing (QD)
  - See Poster #966

- **Non-Nucleoside Polymerase Inhibitor IDX375**
  - Low nanomolar potency
  - Favorable early PK profile (BID,QD)
  - IND planned for 2009
  - See Poster #323

- **Protease Inhibitor IDX316**
  - Single nanomolar potency
  - Favorable early PK profile (BID,QD)
  - IND planned for 2009
  - See Poster #344
IDX184: HCV Liver-Targeted Nucleoside/tide Polymerase Inhibitor Program Overview

• IDX184 is a potent and selective inhibitor of HCV in vitro
  • Fully active against HCV genotypes 1, 2, 3 and 4
  • Additive to synergistic with PI, NNI, IFN or RBV

• Liver-targeted
  • >95% of absorbed IDX184 is extracted by the liver in vivo
  • Preferentially activated in human primary hepatocytes vs. human cell lines
  • Low systemic exposure of parent drug and nucleoside metabolite with high levels of nucleoside-triphosphate (TP) in liver
    – May limit off-target toxicities/increase anti-HCV activity

• Potent antiviral activity in HCV genotype-1 infected chimpanzees (up to $3.8 \log_{10}$ HCV RNA reduction over 4 days)
Advantages of Liver-Targeted HCV Nucleotides

*Nucleoside Triphosphate Inhibits Viral Replication*

**Nucleosides**
- No PK/PD relationship observed for nucleoside and nucleoside analogues in general.

**Liver-Targeted Nucleotide Prodrugs**
- Nucleoside metabolite (NM) is generated by hydrolysis of nucleotides in hepatocytes.

IDX184
IDX184 Study in HCV-Infected Chimpanzees

• **Objective**
  - To investigate any PK/PD relationship between trough levels of parent drug or the nucleoside metabolite and viral load reductions

• **Methods**
  - Six HCV genotype-1 infected chimpanzees received IDX184 (10 mg/kg/day) by oral gavage with sedation for 4 days
  - Serum drug/metabolite levels and viral RNA were measured at trough (24 h post dose)
    - 24 samples during a 4-day dosing period
    - 6 samples at day 7
  - IDX184 and NM levels were determined by LC/MS/MS
  - PK/PD relationships were assessed by regression analyses
Viral Load Reductions and NM Trough Levels after Oral Administration of 10 mg/kg of IDX184 in HCV-Infected Chimpanzees

- NM trough levels were 2-8 ng/mL during 4-day dosing period
- These NM levels were low, consistent with a liver-targeted drug
Serum trough NM levels of >2 ng/mL were associated with
>1 log₁₀ HCV viral load reductions.

PK/PD Relationship Between Viral Load
Reduction and Serum Nucleoside Metabolite
Levels in HCV-Infected Chimpanzees

Day 7 data
(post-dosing)

Chimp 1
Chimp 2
Chimp 3
Chimp 4
Chimp 5
Chimp 6
Linear
95% CI

Dose: 10 mg/kg of IDX184

$R^2 = 0.42$
$P < 0.001$
No PK/PD Relationship Between Viral Load Reduction and IDX184 Trough Levels

- IDX184 trough levels were low (<1.4 ng/mL), with many samples undetectable (9/24).

\[ R^2 = 0.004 \]
Resistance Profile of IDX184

• Resistance to IDX184 emerges slowly in the HCV replicon system as compared to NNIs and PIs
• S282T is the only known resistance mutation for IDX184
• S282T mutant HCV replicons replicate at 5% of wild-type capacity
• No evidence for emergence of resistance (S282T) by population or clonal sequencing (20 clones per sample) in chimpanzees showing weak antiviral response or viral rebound
IDX184 Phase I Dose-Escalation Study

- **Design**
  - Single rising doses of 5, 10, 25, 50, 75, 100 mg IDX184 with 8 healthy subjects randomized 6:2 (active:placebo) for a total N=48
  - Primary endpoint: safety and tolerability
  - Secondary endpoints: plasma and urine IDX184 and NM intensive PK

- **Results**
  - IDX184 was safe and well tolerated
  - Pharmacokinetics of IDX184 and NM were consistent with a liver-targeted drug
  - For details, see Poster #966
Trough Plasma Levels of Nucleoside Metabolite after IDX184 QD Dosing

- NM levels measured at 24 h in the Phase I single-dose study were used to model (non-compartmental superposition) NM trough levels after three daily doses of IDX184 and at steady state (5-7 days).

<table>
<thead>
<tr>
<th>IDX184 Dose (mg)</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; dose (actual)</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; dose (predicted)</th>
<th>Steady state (predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0.582</td>
<td>1.230</td>
<td>1.776</td>
</tr>
<tr>
<td>50</td>
<td>2.880</td>
<td>5.847</td>
<td>8.722</td>
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<tr>
<td>75</td>
<td>2.311</td>
<td>5.640</td>
<td>7.478</td>
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<tr>
<td>100</td>
<td>2.228</td>
<td>7.406</td>
<td>10.266</td>
</tr>
</tbody>
</table>

- These predicted values suggest that administration of 50 to 100 mg/day of IDX184 in HCV-infected patients should lead to NM trough levels associated with >1 \( \log_{10} \) HCV RNA reduction in HCV-infected chimpanzees.
IDX184 Phase I/II Proof-of-Concept Study

- Multi-center, international, randomized, double-blind, placebo-controlled, sequential cohort, dose-escalation study in treatment-naïve HCV genotype-1 patients
- Objectives: safety and tolerability, antiviral activity
- Subjects randomized 8:2 (active:placebo)
- Initiated December 2008; anticipated completion mid-2009

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Dose</th>
<th>Drug Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>25 mg</td>
<td>1 x 25 mg capsule (or placebo) QD for 3 days</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>50 mg</td>
<td>2 x 25 mg capsules (or placebo) QD for 3 days</td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td>75 mg</td>
<td>3 x 25 mg capsules (or placebo) QD for 3 days</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>100 mg</td>
<td>4 x 25 mg capsules (or placebo) QD for 3 days</td>
</tr>
</tbody>
</table>
Animal Model

- Mean serum trough levels of IDX184 and the nucleoside metabolite (NM) were low, consistent with a liver-targeted drug
- A significant PK/PD relationship was demonstrated between NM trough level and HCV RNA reduction
- No such relationship was observed with IDX184
- No evidence for emergence of resistance (S282T)
IDX184 Conclusions (2)

Clinical

- IDX184 was safe and well tolerated in a Phase I study
- Mean plasma levels of IDX184 and NM were low (<20 ng/ml)
- Predicted NM trough levels after repeated QD administration of 50 to 100 mg of IDX184 in HCV-infected patients are in the range of those associated with antiviral effects (>1 log₁₀ viral load reduction) in HCV-infected chimpanzees
- A 3-day POC study in HCV-1 treatment-naïve patients is ongoing