Samatasvir (IDX719), a Potent Pan-Genotypic NS5A Inhibitor, for the Treatment of Hepatitis C Virus (HCV) Infection

Douglas Mayers, MD
December 11, 2013
Idenix: Advancing All-Oral, Pan-Genotypic Combination HCV Regimens

- **Samatasvir (IDX719)** – phase II NS5A inhibitor
  - Favorable safety and potent pan-genotypic activity of samatasvir demonstrated in HCV-infected patients
  - Ongoing all-oral phase II 2-DAA HELIX-1 trial in combination with Janssen’s simeprevir
  - Ongoing all-oral phase II 3-DAA HELIX-2 trial with Janssen’s simeprevir and ritonavir-boosted non-nucleoside inhibitor (TMC647055)
  - All-oral phase II combination study of samatasvir and nucleotide in 2014

- **IDX21437** – phase I/II nucleotide prodrug inhibitor candidate
  - Single-dose escalation in Healthy Volunteers and HCV-infected subjects is ongoing

- **Multiple, earlier-stage nucleotide prodrug candidates**
Samatasvir: Best-in-Class Profile Among HCV NS5A Inhibitors

- Strong preclinical profile
- Granted FDA fast track designation
- 3-Day proof-of-concept phase I/II clinical trial in 64 GT1-4 HCV-infected patients demonstrated safety and pan-genotypic activity
- Two 12-week phase II all-oral DAA combination HELIX clinical trials in collaboration with Janssen Pharmaceuticals, Inc.
Samatasvir: NS5A Inhibitor
Promising Profile for Combination Therapy

- Clean preclinical safety profile
- Potential for low mg doses and QD dosing in humans
- No \textit{in vitro} interaction with 7 human CYP 450 enzymes at 10 µM (well above physiologic concentrations)
- No significant interaction with human transporters at physiologic concentrations
- Additive antiviral effects with other HCV DAAs
- No \textit{in vitro} DDIs with common HBV and HIV therapeutic agents
Samatasvir
Strong Preclinical Profile

- Potent activity against genotypes 1a, 1b, 2a, 3a, 4a and 5a with high selectivity indices *in vitro*
  - 2-24 pM activity overall
Samatasvir Phase I/II Clinical Trial
*Potent and Pan-genotypic in 3-Day Proof-of-Concept Study*

- Three-day proof-of-concept clinical trial in 64 HCV-infected patients
  - GT 1 patients: placebo, 25 mg QD, 50 mg QD, 50 mg BID or 100 mg QD
  - GT 2, 3 or 4 patients: placebo, 50 mg BID or 100 mg QD
- Well-tolerated with no treatment-emergent serious adverse events reported and no safety-related discontinuations
- Potent antiviral activity across genotypes GT1-4 in HCV-infected patients with mean maximal viral load reductions up to ~4.0 log₁₀ IU/mL

<table>
<thead>
<tr>
<th>Dose</th>
<th>GT1a n=23</th>
<th>GT1b n=5</th>
<th>GT2 n=8</th>
<th>GT3 n=8</th>
<th>GT4 n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg QD</td>
<td>3.3 log₁₀</td>
<td>3.0 log₁₀</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>50 mg QD</td>
<td>3.6 log₁₀</td>
<td>4.3 log₁₀</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>50 mg BID</td>
<td>3.2 log₁₀</td>
<td>--</td>
<td>2.0 log₁₀</td>
<td>3.3 log₁₀</td>
<td>3.9 log₁₀</td>
</tr>
<tr>
<td>100 mg QD</td>
<td>3.5 log₁₀</td>
<td>--</td>
<td>2.0 log₁₀</td>
<td>3.4 log₁₀</td>
<td>3.6 log₁₀</td>
</tr>
</tbody>
</table>
Samatasvir Phase I/II Clinical Trial
3-Day Proof-of-Concept Antiviral Activity in GT 1-4 HCV-Infected Patients

Genotype 1A

Genotype 1B

Genotype 2

Genotype 3

Genotype 4

Mean Change from Baseline HCV RNA (log10 IU/mL)

Time (hrs)

1: Placebo
2: IDX719 25 mg QD
3: IDX719 50 mg QD
4: IDX719 50 mg BID
5: IDX719 100 mg QD

Building a Leading Antiviral Franchise
Individual antiviral activity in genotype 2 HCV-infected subjects

- M31 NS5A Polymorphism was associated with reduced antiviral responses in GT 2 but not GT 4-infected subjects
HELIX-1 Clinical Trial Design
All-oral 12-week 2-DAA Combination Regimen

<table>
<thead>
<tr>
<th>Part A</th>
<th>Study weeks</th>
<th>Week 12 (EOT)</th>
<th>Week 16 (SVR4)</th>
<th>Week 24 (SVR 12)</th>
<th>Week 36 (SVR 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=~20</td>
<td>Treatment naïve, GT 1b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg samatasvir + 150 mg simeprevir + RBV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=~20</td>
<td>Treatment naïve, GT 1b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg samatasvir + 150 mg simeprevir + RBV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=~20</td>
<td>Treatment naïve, GT 1b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg samatasvir + 150 mg simeprevir + RBV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Part B is currently enrolling exploratory arms designed to evaluate safety and antiviral activity of simeprevir and ribavirin combined with:
  - 25 mg dose of samatasvir in GT 1b-infected patients
  - 100 mg dose of samatasvir in GT 6-infected patients
  - 100 mg dose of samatasvir in additional GT 1b-infected patients

- Objectives: safety and tolerability, efficacy (primary SVR$_4$ with supportive SVR$_{12}$ and SVR$_{24}$), pharmacokinetics and pharmacodynamics, emergence of resistance
HELIX-2 Clinical Trial Design

All-oral 12-week 3-DAA Combination Regimen

- Treatment naïve or relapsers, GT 1
  - 50 mg samatasvir + 75 mg simeprevir + 450 mg TMC647055/r + RBV

- Additional exploratory arms may be added to evaluate safety and antiviral activity

- Objectives: safety and tolerability, efficacy (primary SVR₄ with supportive SVR₁₂ and SVR₂₄), pharmacokinetics and pharmacodynamics, emergence of resistance

- Week 12 (EOT) - Week 24 (SVR 12) - Week 36 (SVR 24)
Novel Nucleotide Prodrug Discovery Program

- Identify promising compounds *in vitro* and in mouse and monkey
  - Triphosphate production, kinetics of metabolism, favorable safety, cytotoxicity
  - Levels of TP in the liver after oral administration *in vivo*

- Explored diverse spectrum of nucleotides
  - Purines and pyrimidines, known and novel prodrugs, and 2’ Me sugars and some novel sugars

- Strong intellectual property position
  - Covering diverse range of candidate compounds in R&D pipeline

- NUC discovery capability also can be applied to non-HCV therapeutic areas
  - External interest in screening library
  - Restructured Novartis agreement allows flexibility to explore other indications
IDX21437: Next-Generation Uridine Nucleotide Prodrug
Phase I/II clinical trial ongoing

- Single-dose escalation in Healthy Volunteers and HCV-infected subjects ongoing

- Potent, pan-genotypic activity *in vitro*; high liver triphosphate levels generated *in vivo*
  - Potential for high potency at low once-daily doses in the clinic
  - Suitable for fixed-dose combination with samatasvir and other DAAs

- Favorable preclinical safety profile
  - Preclinical toxicology profile to date provides good safety margins for anticipated clinical doses
  - Clean genotoxicity and cardiac safety assessments to date
IDX21437: Phase I/II Clinical Trial Design

- A phase I/II study assessing single and multiple doses of IDX21437 in healthy volunteers and HCV-infected patients

Single Dose

- Healthy Volunteers
  - IDX21437 monotherapy

- Treatment naïve, GT 1
  - IDX21437 monotherapy

- Treatment naïve, GT 1, Cirrhotic
  - IDX21437 monotherapy (1 dose)

Multiple Dose (7-day)

- Healthy Volunteers
  - IDX21437 monotherapy (1 dose)

- Treatment naïve, GT 1
  - IDX21437 monotherapy

- Treatment naïve, GT 2-6
  - IDX21437 monotherapy

- Treatment naïve, GT 1, Cirrhotic
  - IDX21437 monotherapy (1 dose)
Summary/Conclusions

- Samatasvir has been safe and well tolerated after single and multiple doses of up to 150 mg in healthy volunteers up to 14 days duration, and in HCV-infected patients up to 12 weeks duration.

- Samatasvir proof-of-concept study in HCV GT 1 – 4-infected patients showed potent, pan-genotypic activity with mean maximal viral load reductions up to approximately \(4.0 \log_{10} \text{ IU/mL}\).

- *In vitro* results for samatasvir were predictive of *in vivo* antiviral activity.

- All-oral 12-week phase II combination studies including samatasvir in collaboration with Janssen ongoing.

- Initiation of 12-week combination studies of samatasvir and IDX21437 planned in 2014.
Acknowledgments

- **Idenix Montpellier**
  - Medicinal Chemistry team
  - Clinical team

- **Idenix Cambridge**
  - Clinical team
  - Biology team
  - DMPK team
  - CMC team

- With special thanks to all of our investigators and patients who participated in our clinical trials of samatasvir