Building a Leading Antiviral Franchise

Combination DAA Therapy for Hepatitis C

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Berlin, Germany, October 18-20, 2012
170 million individuals carry chronic HCV infection worldwide which represents a global prevalence of 2.35%\(^1\)

Less than 2% of HCV-positive patients in US, EU and Japan are currently being treated\(^2\)

**Idenix has a potential pan-genotypic regimen for HCV**

\(^{1}\)Kershenobich 2011 (US); \(^{2}\)Decision Resources 2009
Historical data from HIV combination drug studies suggest that:

- Combinations of drugs with different mechanisms of action and non-overlapping resistance patterns result in optimal responses
- Virus must be completely suppressed by drug combinations or viral rebound will occur
- A critical level of potency is required for the regimen to be durably effective
- Drug combinations with good safety and tolerability are critical to maintain compliance needed for durable viral suppression
- Nucleosides/tides are the backbone of HIV drug combinations
- Unlike HIV, HCV can be cured
Combination Therapy with Direct-Acting HCV Drugs

Optimal DAA regimens should combine agents with multi-genotypic coverage, distinct modes of action and non-overlapping resistance profiles.
The Most Profound *In Vitro* Synergy is Achieved With Triple Combination of HCV DAA with Different Mechanisms of Action

Two-drug and three-drug combinations tested at equivalent concentrations (EC$_{50}$s) in the HCV replicon model
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IDX184*</th>
<th>IDX719</th>
<th>IDX19368**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Class</td>
<td>Nucleotide Inhibitor</td>
<td>NS5A Inhibitor</td>
<td>Nucleotide Inhibitor</td>
</tr>
<tr>
<td>Phase</td>
<td>IIb</td>
<td>Ib/IIa</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Genotype coverage</td>
<td>Pan-genotypic</td>
<td>Pan-genotypic</td>
<td>Pan-genotypic</td>
</tr>
<tr>
<td>Barrier to resistance</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Efficacy</td>
<td>cEVR = 93%; Initial SVR4= 100% (100 mg 12+12 group)</td>
<td>Up to - 3.9 log_{10} (3-day POC)</td>
<td>NA</td>
</tr>
<tr>
<td>Safety</td>
<td>Well tolerated</td>
<td>Well tolerated</td>
<td>NA</td>
</tr>
<tr>
<td>DAA combination properties</td>
<td>Additive/low potential for DDIs</td>
<td>Additive/low potential for DDIs</td>
<td>Additive/low potential for DDIs</td>
</tr>
<tr>
<td>Dosing</td>
<td>100 mg QD</td>
<td>50 -100 mg QD</td>
<td>&lt;= 50 mg QD</td>
</tr>
</tbody>
</table>

*In August 2012, IDX184 was placed on partial clinical hold by the FDA
**In August 2012, IDX19368 was placed on clinical hold by the FDA
IDX184: Liver-Targeted Nucleotide HCV Polymerase Inhibitor Background

- IDX184 demonstrated potent, pan-genotypic inhibition of HCV \textit{in vitro} \cite{Cretton-Scott_2008}.

- IDX184 is a liver-targeted nucleotide prodrug
  - >95\% of absorbed IDX184 is extracted by the liver (portal/systemic ratio >20 in monkey)
  - Low systemic levels of IDX184 & 2'-MeG; high levels of active 2'-MeGTP in the liver

- High barrier to resistance
  - No S282T or other resistance mutation has been detected in any of the clinical programs

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{chiral.png}
\caption{2'-C-methylguanosine monophosphate prodrug}
\end{figure}

Advantages of Liver-targeted HCV Nucleotides

*Nucleoside(●) Triphosphate(●●●) Inhibits Viral Replication*

2'-methylguanosine (2'-MeG) is generated by hydrolysis of 2'-methylguanosine nucleotides in hepatocytes.

Liver-targeted Nucleotide Prodrugs

IDX184
IDX184: Efficient Liver Targeting

- Rat: high liver concentrations of total radioactivity (G label) obtained following a single oral dose at 100 mg/kg

<table>
<thead>
<tr>
<th>Time point (hr)</th>
<th>µg equiv/g</th>
<th>µM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5.09</td>
<td>10.6</td>
</tr>
<tr>
<td>6</td>
<td>10.3</td>
<td>21.8</td>
</tr>
<tr>
<td>24</td>
<td>4.08</td>
<td>8.6</td>
</tr>
</tbody>
</table>

* Calculated using rat hepatocellularity of 117 million cells/g liver and cell volume of 6.44 pL per hepatocyte

- Rat liver-to-plasma concentration ratios 8-10, AUC ratio: 10
- Extensive (>95%) hepatic extraction of IDX184 in the monkey**
IDX184: Phase IIb 12-Week PegIFN/RBV Study Overview

- **Study design**
  - 12-week, randomized, double-blind, parallel groups
  - Treatment-naïve genotype 1 HCV-infected patients; stratified by IL28B
    - 50 mg IDX184 with PegIFN/RBV
    - 100 mg IDX184 with PegIFN/RBV
  - Response-guided PegIFN/RBV extension for 12 or 36 weeks
  - Endpoints: safety and tolerability; antiviral activity
  - 67 patients have been enrolled

- **Phase IIb study status**
  - In July 2012, DSMB confirmed no safety or efficacy concerns; side effect profile remains consistent with known safety profile of PegIFN/RBV alone
  - No patients are receiving IDX184. Patients currently on PegIFN/RBV extension
  - IDX184 was placed on partial clinical hold by FDA in August 2012 due to serious cardiac-related adverse events seen with BMS-094
  - Complete SVR data in 2013
### IDX184* Interim Antiviral Activity and Safety Summary - First Cohort

#### Phase IIb 12-Week PegIFN/RBV Study

- **Safety:**
  - Safety observed to date consistent with known safety profile of PegIFN/RBV alone

- **Antiviral activity:**

<table>
<thead>
<tr>
<th>Dose</th>
<th>n</th>
<th>Median Time to &lt;25 IU/mL</th>
<th>HCV RNA &lt;25 IU/mL at Week 4 (RVR)</th>
<th>HCV RNA &lt;25 IU/mL at Week 12 (cEVR, ITT)</th>
<th>SVR4† (12+12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg IDX184 + Peg/RBV</td>
<td>16</td>
<td>22 days</td>
<td>10/16 (63%)</td>
<td>13/16 (81%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>100 mg IDX184 + Peg/RBV</td>
<td>15</td>
<td>15 days</td>
<td>11/15 (73%)</td>
<td>14/15 (93%)</td>
<td>4/4 (100%)</td>
</tr>
</tbody>
</table>

† Interim analysis of 9 patients who achieved eRVR and were randomized to stop treatment after an additional 12 weeks of PegIFN/RBV.

- Majority of patients had normal ALT levels by Week 12

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*In August 2012, IDX184 was placed on partial clinical hold by the FDA*
IDX184 and IDX19368 Update

- In August 2012, FDA placed IDX184 on partial clinical hold and IDX19368 on clinical hold due to serious cardiac-related adverse events seen with BMS-094 (formerly INX-189)
- Idenix is working with FDA and BMS to resolve the clinical holds
- Idenix received formal FDA letter related to IDX184
  1. Clinical: majority of requested data has been collected; external cardiology expert review planned
     - Echocardiograms, ECGs and cardiac biomarkers, including NT pro-BNP’s, CK, and ultra sensitive troponins
  2. Non-clinical: certain requested data have been submitted, further testing is underway
     - *In vitro* cytotoxicity studies, including human cardiomyocytes
     - Cardiac safety assessments in ongoing IDX184 in vivo studies
  3. Risk management plan for cardiac monitoring for future clinical trials requested
- Idenix received formal FDA letter related to IDX19368
  1. Additional toxicology and metabolism preclinical studies requested
Structure of IDX184 Compared to BMS-094

- Structural similarities:
  - Both produce 2’-methyl guanosine triphosphate as the active species in the liver

- Structural differences:
  - Very different prodrugs - SATE for IDX184, McGuigan for BMS-094
  - These prodrugs generate distinct metabolites
  - They have clearly distinguishable liver targeting profiles
  - Modification of the natural guanosine in IDX184 with a methoxy group in BMS-094

Source: BMS-094 structure from Kolykhalov et al., Poster #1888 AASLD (2010)
IDX719: NS5A Inhibitor

**Strong Preclinical Profile**

- Potent broad genotypic activity across multiple genotypes with high selectivity indices *in vitro* (2-24 pM activity overall)
- Clean preclinical safety profile to date
- Low potential for drug-drug interactions
IDX719: Phase I/II Study

Potent and Pan-genotypic in 3-Day Proof-of-Concept Study

- Three-day proof-of-concept clinical trial in 64 HCV-infected patients completed
  - GT 1 patients randomized to receive placebo, 25 mg QD, 50 mg QD, 50 mg BID or 100 mg QD for three days
  - GT 2, 3 or 4 patients randomized to receive placebo, 50 mg BID or 100 mg QD for three days

- Well tolerated with no treatment-emergent serious adverse events reported

- Potent antiviral activity across genotypes in HCV-infected patients:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean Maximum Viral Load Reduction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>GT1 n=28</td>
</tr>
<tr>
<td></td>
<td>GT2 n=8</td>
</tr>
<tr>
<td></td>
<td>GT3 n=8</td>
</tr>
<tr>
<td></td>
<td>GT4 n=7</td>
</tr>
<tr>
<td>25 mg QD</td>
<td>3.2 log_{10}</td>
</tr>
<tr>
<td>50 mg QD</td>
<td>3.7 log_{10}</td>
</tr>
<tr>
<td>50 mg BID</td>
<td>3.2 log_{10} 2.0 log_{10} 3.3 log_{10} 3.9 log_{10}</td>
</tr>
<tr>
<td>100 mg QD</td>
<td>3.5 log_{10} 2.0 log_{10} 3.4 log_{10} 3.4 log_{10}</td>
</tr>
</tbody>
</table>

- Plan to move IDX719 into 3 month study in early 2013
IDX719: Competitive Potency in HCV NS5A Landscape

<table>
<thead>
<tr>
<th>Drug Candidate</th>
<th>Viral Load Reduction (GT1)</th>
<th>Patient Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDX719</td>
<td>2.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50 mg</td>
</tr>
<tr>
<td>BMS-790052</td>
<td>3.2</td>
<td>10 mg</td>
</tr>
<tr>
<td>BMS-790052</td>
<td>3.3</td>
<td>100 mg</td>
</tr>
<tr>
<td>IDX719</td>
<td>3.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 mg</td>
</tr>
<tr>
<td>IDX719</td>
<td>3.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100 mg</td>
</tr>
<tr>
<td>IDX719</td>
<td>3.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 mg</td>
</tr>
<tr>
<td>ABT-267</td>
<td>2.89 – 3.10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5-200 mg QD</td>
</tr>
<tr>
<td>PPI-461</td>
<td>3.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50 mg QD</td>
</tr>
<tr>
<td>GS-5885</td>
<td>3.1 - 3.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 - 30 mg QD</td>
</tr>
<tr>
<td>PPI-461</td>
<td>3.65&lt;sup&gt;c&lt;/sup&gt;</td>
<td>100 mg QD</td>
</tr>
<tr>
<td>ACH-2928</td>
<td>3.68&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60 mg QD</td>
</tr>
<tr>
<td>IDX719</td>
<td>3.2-3.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25-100 mg QD</td>
</tr>
</tbody>
</table>

<sup>a</sup> = mean maximal reduction, <sup>b</sup> = median maximal reduction, <sup>c</sup> = mean maximal reduction, GT 1a
Novel Nucleotide Prodrug Discovery Program

- Robust synthetic and screening efforts ongoing
- Diverse spectrum of nucleotides
  - Purines and pyrimidines
  - Known prodrugs and novel prodrugs
  - 2’ Me sugars and some novel sugars
- Identify promising compounds \textit{in vitro} and in mouse and monkey
  - Level of triphosphate (TP) production, kinetics of metabolism, cytotoxicity, etc
  - Levels of TP in the liver after oral administration \textit{in vivo}
- Many new potential clinical candidates currently being evaluated
  - Exploring diverse spectrum of nucleotides with different and novel bases, prodrugs and sugars
  - Additional INDs expected to be filed in 2013 for non-2’Methyl G compounds
Idenix Novel Nucleotide Prodrugs: Program Scope and Scale

>140 Different Nucleoside Analogues

>1900 Nucleotide Prodrugs

>660 Individual Prodrug Diastereomers Separated

Liver TP levels in vivo for:
>160 prodrugs in mouse
>10 prodrugs in monkey

>20 Different Prodrug Types
In Vivo Levels of Liver TP from Different Prodrugs

- New prodrug approaches have led to compounds that generate robust dose normalized TP levels in vivo

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The HCV Treatment Paradigm is Rapidly Evolving

Characteristics of the Optimal DAA Regimen to Cure HCV

- **Pan-genotypic**
  - Can be used in any genotype

- **Potent**
  - >80% SVR
  - Nulls, relapsers, cirrhotics
  - High barrier to resistance

- **Safe**
  - Low toxicity
  - High tolerability
  - Minimal AEs

- **Convenient**
  - Once- or twice-daily
  - Low dosage

- **All Oral**
  - PegIFN-free
  - RBV still a question

- **Ease of Administration**
  - ≤ 12 weeks duration
  - Simple stopping rules

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Acknowledgements

- 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 IDX184 and IDX719