Paris Hepatitis Conference

New Therapeutic Strategies
Second Generation Protease inhibitors

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Outline

• HCV protease structure and drug targeting
  – First generation PIs
    – Major step forward
    – Major limitations
  – PIs in development
    – Second wave
    – Second generation
• Clinical trial data
  – IFN-containing PI regimens
  – IFN-free PI-containing regimens
• Timelines and treatment paradigms
NS3 protease targeting

TARGETING
- Substrate- and product analogs
- Tri-peptides
- Serine-trap inhibitors
- Ketoamides (boceprevir, telaprevir)
- Macrocyclic inhibitors (e.g. Simeprevir, Danoprevir, Vaniprevir, etc.)
- NS4A inhibitors

Lorenz et al., Nature 2006
Kronenberger et al., Clin Liver Dis 2008
Welsch et al. Gut in press
A Major Step Forward: First Generation PIs

<table>
<thead>
<tr>
<th>Group</th>
<th>PegIFN/RBV</th>
<th>BOC or TVR + pegIFN/RBV</th>
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<tbody>
<tr>
<td>Naive</td>
<td>38-44</td>
<td>63-75</td>
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<td>Relapsers</td>
<td>24-29</td>
<td>69-83</td>
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<td>Partial</td>
<td>7-15</td>
<td>40-59</td>
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<tr>
<td>Null</td>
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<td>29-40</td>
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Limitations of First Generation PI-Based Therapy

- **Efficacy**
  - Very dependent on the IFN response
  - Limited to gen 1 (1b>1a)

- **Low genetic barrier to resistance**

- **Tolerability**
  - Additional AEs beyond pegIFN/RBV

- **Regimens**
  - Complicated (lead-in, RGT)/pill burden
  - TID regimens (food required with TVR)

- **DDIs**
  - Many with both agents to common drugs (CYP3A4)
Protease Inhibitors in Active Phase 2/3 Development

- Second Wave (better dosing, improved tolerability, broader genotype coverage)
  - Asunaprevir (BMS)
  - Faldaprevir (Boehringer)
  - Simeprevir (Janssen/Tibotec)
  - Sovaprevir, (Achillion)
  - Danoprevir/r (Roche)
  - Vaniprevir (Merck)
  - ABT-450/r (Abbott)
  - GS-9451 (Gilead)

- Second generation (pan-genotype, high barrier to resistance)
  - MK-5172 (Merck)
  - ACH-2684 (Achillion)
Antiviral Activity of NS3 Protease-Inhibitors

Protease-Inhibitor Monotherapy Data for 3–14 days in HCV genotype 1 patients (no head-to-head studies)

Mean or median HCV RNA decline (log_{10} IU/mL)

Adapted from Sarrazin et al., *J Hepatol* 2012 suppl
Expanded genotype activity of next generation HCV protease inhibitors

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### Improved genetic barrier to resistance for next generation protease inhibitors

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<th>V36A/M</th>
<th>T54S/A</th>
<th>V55A</th>
<th>Q80R/K</th>
<th>R155K/T/Q</th>
<th>A156S</th>
<th>A156T/V</th>
<th>D168A/E/G/H/T/V/Y</th>
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- **mutations associated with resistance in patients**
- **mutations associated with resistance in vitro**
- ***no viral break-through during 7 days monotherapy***

Adapted from Sarrazin et al., *J Hepatol* 2012 suppl
**ACH-2684**

Potency against GT 1-6 and Activity Against Common 1\textsuperscript{st}-Gen PI Resistant Mutations

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>R155Q</th>
<th>R155K</th>
<th>A156S</th>
<th>A156T</th>
<th>D168A</th>
<th>D168V</th>
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<td><strong>Incivek</strong></td>
<td>370</td>
<td>500</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>33</td>
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<td><strong>ACH-2684</strong></td>
<td>1.6</td>
<td>2.1</td>
<td>0.21</td>
<td>1.6</td>
<td>2.4</td>
<td>7.5</td>
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Data on File, Achillion Pharmaceuticals, Inc.
MK-5172 has activities against RAVs elicited by the 1st generation PIs
### Summary: Protease Inhibitor Profiles

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<tr>
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<th>DAA</th>
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<td></td>
<td>NS3¹</td>
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<td>Resistance profile</td>
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<td>Pan-genotypic efficacy</td>
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<td>Efficacy</td>
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<td>Adverse events</td>
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- **Good profile**
- **Average profile**
- **Least favorable profile**

1: 1\(^{st}\) generation  
2: 2\(^{nd}\) wave  
3: 2\(^{nd}\) generation
Investigational HCV Regimens with PIs in Phase III Clinical Trials

**Regimens With 1 DAA + PegIFN alfa/RBV**
- Faldaprevir (BI 201335)
- Simeprevir (TMC-435)
- Vaniprevir (MK-7009)

**Regimens With 2 DAAs + PegIFN alfa/RBV**
- Daclatasvir + Asunaprevir

**IFN-Free Regimens**
- Daclatasvir + asunaprevir
- ABT-450/RTV + ABT-267 ± ABT-333 ± RBV
- Faldaprevir + BI 207127 + RBV
TMC 435 (PI) + PEG-IFN/RBV in Treatment Naïve and Experienced Patients

SVR 12 of MK-5172 for 12 Weeks in Combination With Pegylated Interferon Alfa-2b and Ribavirin for 24 Weeks in HCV Genotype 1 Treatment-Naïve, Noncirrhotic Patients (Vanguard Cohort Analysis)

Dose-dependent transaminase levels in 400 mg and 800 mg dosing in the course of therapy.
Asunaprevir (PI) + Daclatasvir (NS5A)

Pts: Gen1b, non-cirrhotic

Among pts with breakthrough (7%) or relapse (9%), low plasma concentrations of DAC and ASU.
AVIATOR: SVR12 Rates With ABT-450/ RTV, ABT-267, ABT-333, and RBV

**Treatment-Naive Patients**

- **ABT-450**: Protease/RTV QD
- **ABT-267**: NS5A QD
- **ABT-333**: NNI BID

**Observed data (above bar)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>8 wks</th>
<th>12 wks</th>
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<td>ABT-450</td>
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<td>ABT-267</td>
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<td>ABT-333</td>
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<tr>
<td>RBV</td>
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- 86% 96%
- 82% 100%
- 88% 100%
- 88% 100%
- 98% 100%

**ITT (within bar)**

- 84% 96%
- 79% 100%
- 85% 100%
- 83% 96%
- 86% 100%
- 81% 100%

**Null Responders**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>12 wks</th>
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<tr>
<td>ABT-450</td>
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<td>ABT-333</td>
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<tr>
<td>RBV</td>
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- 81% 100%
- 81% 100%
- 89% 100%

First All Oral HCV Regimens Likely Available In The US in 2014-2015

Options for PI-Based Regimens

Nucleoside-based regimens

• Sofosbuvir + RBV (G2/3, select G1)
• Sofosbuvir + Daclatasvir (off-label)
• **Sofosbuvir + PI (TMC 435, TVR, BOC, etc)** (off-label)
• Sofosbuvir + GS-5885 + RBV (pan-genotype)

Other regimens

• **Asunaprevir** + Daclatasvir (G1b)
• **ABT-450/r** + ABT-333 + ABT-267 + RBV (G1)
• **Faldaprevir** + BI-207127 + RBV (G1b)
Conclusions: Future therapy options for PI

The second wave of PIs

- Better tolerability, safety profile
- Improved dosing
- Broader genotype coverage for some
- Improved DDI profile

Second generation of PIs

- Higher efficacy
- Pan-genotypic
- High barrier to resistance