Creating Small Molecule Drugs for Viral Infections and Liver Diseases

Jefferies 2016 Healthcare Conference
June 8, 2016
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Virology & liver disease-focused biotech company

- Royalties from 1st HCV Protease Inhib. (PI): paritaprevir (AbbVie partner)
- Second HCV PI program in Ph3: ABT-493 (AbbVie partner)
- Wholly-owned clinical stage HCV compounds
  - Cyclophilin inhibitor (Ph1) EDP-494
  - NS5A inhibitor (POC) EDP-239
- NASH program Ph1 start in 2H 2016 EDP-305
- New programs in HBV and RSV
- Strong balance sheet with approx. $246M cash at March 31, 2016
- Resources to fund clinical programs and to explore new disease areas
Expanding Beyond HCV

- Leverage our core strength in HCV to become a leader in Viral and Liver diseases
- Multiple therapeutic areas with goal of building multiple approaches in each
## Broad Virology and Liver Disease Portfolio

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclin</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV Wave 1</strong></td>
<td>Paritaprevir (Protease Inhibitor) in <strong>3-DAA Regimen</strong> in US &amp; EU <em>(AbbVie)</em></td>
<td></td>
<td></td>
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<tr>
<td><strong>HCV Wave 2</strong></td>
<td>Paritaprevir in <strong>2-DAA Regimen</strong> in US, EU &amp; Japan <em>(AbbVie)</em></td>
<td></td>
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<tr>
<td><strong>HCV Wave 3</strong></td>
<td>ABT-493 (Protease Inhibitor) <strong>2-DAA Regimen</strong> <em>(AbbVie)</em></td>
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<tr>
<td><strong>HCV Wave 4</strong></td>
<td>EDP-239 (NS5A Inhibitor)</td>
<td></td>
<td>EDP-494 (Cyclophilin Inhib)</td>
<td></td>
<td></td>
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<tr>
<td><strong>HBV</strong></td>
<td>Core Inhibitor</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>RSV</strong></td>
<td>Non-fusion Inhibitor</td>
<td></td>
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<tr>
<td><strong>NASH &amp; PBC</strong></td>
<td>EDP-305 FXR Agonist</td>
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</tbody>
</table>
HCV Market

• Market for HCV therapies:
  - Estimated > $18B in 2015
  - Major market in U.S. & E.U. is genotype 1
    • Represents approx. 74% of all HCV infections

• Prevalence
  - CDC recently estimated 2.7M people in U.S. are chronically infected
  - In Europe, an estimated 9M people are infected*
  - In Japan, an estimated 1.5M to 2M people are infected; high prevalence of GT1b**


Source: www.cdc.gov
## Four Waves of HCV Opportunity

<table>
<thead>
<tr>
<th>Wave</th>
<th>Regimen</th>
<th>Enanta Asset</th>
<th>Economics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wave 1</td>
<td>3-DAA (ABBV)</td>
<td>paritaprevir (PI)</td>
<td>Double-digit royalty on 30% of net sales</td>
</tr>
<tr>
<td>Wave 2</td>
<td>2-DAA (ABBV)</td>
<td>paritaprevir (PI)</td>
<td>Double-digit royalty on 45% of net sales</td>
</tr>
<tr>
<td>Wave 3</td>
<td>2-DAA (ABBV)</td>
<td>ABT-493 (PI)</td>
<td>Double-digit royalty on 50% of net sales</td>
</tr>
<tr>
<td>Wave 4</td>
<td>Wholly-owned</td>
<td>EDP-494 (Cyclophilin Inh.) EDP-239 (NS5A Inhibitor)</td>
<td>Wholly-owned</td>
</tr>
</tbody>
</table>
Paritaprevir-Containing 3D and 2D Regimens

Wave #1: 3D (3-DAA) regimen
- BID dosing, w/wo RBV
- 3QD (once-daily) co-formulated version approval expected in U.S. 2H16

Wave #2: 2D (2-DAA) regimen
- QD dosing
- GT4 with RBV
Wave #3   New 2-DAA regimen: ABT-493 (PI) and ABT-530* (NS5A)

- Once-daily
- Fixed dose combination
- RBV-free
- Broad genotype profile
- Excellent activity against key resistance mutants

<table>
<thead>
<tr>
<th>HCV Replicon</th>
<th>Mean EC₅₀, nM</th>
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<tbody>
<tr>
<td>GT 1a</td>
<td>0.85 ± 0.15</td>
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<tr>
<td>GT 1b</td>
<td>0.94 ± 0.35</td>
</tr>
<tr>
<td>GT 2a</td>
<td>2.7 ± 1.1</td>
</tr>
<tr>
<td>GT 3a</td>
<td>1.6 ± 0.49</td>
</tr>
<tr>
<td>GT 4a</td>
<td>2.8 ± 0.41</td>
</tr>
<tr>
<td>GT 6a</td>
<td>0.86 ± 0.11</td>
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</table>

*AbbVie's new NS5A inhibitor

Ng, et.al, CROI, Mar. 4, 2014
<table>
<thead>
<tr>
<th>Patient Profile/Study</th>
<th>Treatment Duration</th>
<th>SVR\textsubscript{12} Rates ITT</th>
<th>Virologic Failure</th>
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<tbody>
<tr>
<td>GT1 Non-cirrhotic SURVEYOR-1</td>
<td>8 weeks</td>
<td>97% (n=33/34)</td>
<td>None</td>
</tr>
<tr>
<td>GT2 Non-cirrhotic SURVEYOR-2</td>
<td>8 weeks</td>
<td>98% (n=53/54)</td>
<td>None</td>
</tr>
<tr>
<td>GT3 Non-cirrhotic SURVEYOR-2</td>
<td>8 weeks</td>
<td>97% (n=28/29)</td>
<td>None</td>
</tr>
<tr>
<td>GT3 Cirrhotic (Child-Pugh A) SURVEYOR-2</td>
<td>12 weeks</td>
<td>100% (n=24/24)</td>
<td>None</td>
</tr>
<tr>
<td>GT3 Cirrhotic (Child-Pugh A) SURVEYOR-2</td>
<td>12 weeks w/RBV</td>
<td>100% (n=24/24)</td>
<td>None</td>
</tr>
<tr>
<td>GT 4,5,6 Non-cirrhotic SURVEYOR-1</td>
<td>12 weeks</td>
<td>100% GT4 (n=22/22) GT5 (n=1/1)</td>
<td>None</td>
</tr>
</tbody>
</table>

SURVEYOR 1 & 2 Results  (EASL April 2016)
ABT-493 (300mg) + ABT-530 (120mg) once daily
## ABT-493: Phase 3 & Expanded Phase 2 Trials Underway

- Enrollment >2,000 patients
- Phase 3 dose ABT-493 (300mg) + ABT-530 (120/mg) fixed dose combination, once daily
- Durations of 8 and/or 12 weeks being explored in most trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>ENDURANCE-1</td>
<td>Non-cirrhotic GT1</td>
</tr>
<tr>
<td>ENDURANCE-2</td>
<td>Non-cirrhotic GT2</td>
</tr>
<tr>
<td>ENDURANCE-3</td>
<td>Non-cirrhotic GT3</td>
</tr>
<tr>
<td>ENDURANCE-4</td>
<td>Non-cirrhotic GT4,5,6</td>
</tr>
<tr>
<td>SURVEYOR-2</td>
<td>Cirrhotic* GT3</td>
</tr>
<tr>
<td>EXPEDITION-1</td>
<td>Cirrhotic* GT1,2,4-6</td>
</tr>
<tr>
<td>EXPEDITION-2</td>
<td>HCV/HIV GT1-6</td>
</tr>
<tr>
<td>EXPEDITION-4</td>
<td>Renal Impair. GT1-6</td>
</tr>
<tr>
<td>CERTAIN-1</td>
<td>GT1-6 (Japan)</td>
</tr>
<tr>
<td>CERTAIN-2</td>
<td>GT2 (Japan)</td>
</tr>
<tr>
<td>MAGELLAN-1</td>
<td>Prior DAA failures</td>
</tr>
<tr>
<td>MAGELLAN-2</td>
<td>Liver/Kidney transplant</td>
</tr>
</tbody>
</table>

*Child Pugh A cirrhotic patients
Goal: Create combo using high resistance barrier HCV agents and target RAVs, DAA failures, and other hard-to-treat virus / patient populations

• Initial focus: cyclophilin / nuc polymerase inhibitor combo
  - high resistance barrier mechanisms make both classes attractive

• Most expedient path is to complete Ph1 and single agent POC with cyclophilin inhibitor EDP-494, then seek external development-stage Nuc for combination studies

• Add NS5A EDP-239, if needed, for additional antiviral pressure
Cyclophilin Inhibitor EDP-494 is Uniformly Active Against **NS5A RAVs**

- Also uniformly active against NS5B RAVs (Nuc and Non-Nuc) and NS3 RAVs
• Host Targeted Antiviral (HTA) with high barrier to resistance

• Pan-genotypic activity
  - Excellent nM potency against GT1-6 replicons
  - Maintains potency against DAA RAVs (NS5A, NS5B, and PI RAVs)
  - Additive to synergistic with DAAs (NS5A, NS5B, and PI inhibitors)

• Low potential for DDI via CYP450 inhibition and induction

• QD dosing potential

• Next steps:
  - Complete Ph1
  - Initiate single agent POC in GT1 & GT3
Virology & Liver Disease Focus Areas

- HCV
- NASH /PBC
- HBV
- RSV
Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH)

- Number one cause of liver disease in Western Countries
- NAFLD: excessive fat (triglyceride) accumulation in the liver (steatosis)
- A subgroup of NAFLD patients has liver cell injury and inflammation in addition to excessive fat (steatohepatitis), i.e. NASH
- NASH is associated with the metabolic syndrome – diseases related to type 2 diabetes, insulin resistance, obesity, hyperlipidemia, and hypertension
- While NAFLD does not correlate with short-term morbidity or mortality, progression to NASH dramatically increases risks of cirrhosis, liver failure, and hepatocellular carcinoma

Stages of Liver Injury (NIDDK)

- Fatty liver: Deposits of fat cause liver enlargement.
- Liver fibrosis: Scar tissue forms. More liver cell injury occurs.
- Cirrhosis: Scar tissue makes liver hard and unable to work properly.
Primary Biliary Cholangitis (PBC)

- Bile is a digestive liquid made in the liver that travels through bile ducts to the small intestine, where it helps in digestion.

- PBC is a chronic inflammatory liver disease that slowly destroys bile ducts, causing bile to remain in the liver, leading to liver cell damage and cirrhosis.

- As cirrhosis progresses and liver scar tissue increases, the liver loses its ability to function, leading to potential liver failure, liver transplantation, or hepatocellular carcinoma.
**NASH and PBC Potential Markets**

**NASH**
- Currently no approved therapies
- US prevalence estimated to be 3%-5% (~9 to 15 million)
  - 20% of whom likely to develop cirrhosis (Rinella, Hepatology, 2011)
- Patient pool size may rival HCV
- Prevalence of NASH likely to increase due to increase in underlying causes, e.g. obesity

**PBC**
- One approved PBC therapy (ursadiol); only 50% effective
- Estimated US incidence: 4.5 cases for women and 0.7 cases for men per 100,000 population
- Significant potential add-on value beyond NASH
Enanta’s Approach to NASH and PBC—Agonists of Farnesoid X Receptor (FXR)

- FXR is a nuclear receptor and main regulator of bile acid levels in liver and small intestine
- FXR responds to bile acids by regulating transcription of key enzymes and transporters
- FXR agonists have ameliorated a number of the pathologies in NASH and PBC, including an effect on fibrosis
- Clinical validation has been achieved in NASH and PBC with the FXR agonist 6-ECDCA (OCA)

Matsubara *Mol Cell Endocrinol* 2013

Goal: Initiate clinical studies in 2H 2016
EDP-305 is a Potent and Selective FXR Agonist

Chimeric FXR activation (CHO cells)

<table>
<thead>
<tr>
<th></th>
<th>EDP-305</th>
<th>OCA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC50</td>
<td>24 nM</td>
<td>530 nM</td>
</tr>
<tr>
<td>Efficacy</td>
<td>312%</td>
<td>279%</td>
</tr>
</tbody>
</table>

* OCA: Obeticholic acid

EDP-305 Nuclear Receptor Selectivity

TGR5 (bile acid receptor) | EDP-305
---|---
EC50 | 4,300 nM
Efficacy | 20%
FXR-mediated Regulation of Bile Acid Synthesis & Lipid Metabolism

Modica S. et al., Nuclear Receptor Signaling (2010), 8, 1-28
EDP-305 Shows a Stronger Effect than OCA on FXR-Dependent Gene Expression in Human Hepatocytes

Induces the small heterodimer partner (SHP) expression

Represses cytochrome P450 7A1 (CYP7A1) expression

* Indicates a statistically difference from OCA
EDP-305 Effects on FXR-dependent Gene Expression Translate into Potent \textit{In Vivo} Activity

Induces Shp expression

![Graph showing induced Shp expression with EDP-305 at different doses compared to control and OCA.](image1)

Represses Cyp7a1 expression

![Graph showing repressed Cyp7a1 expression with EDP-305 at different doses compared to control and OCA.](image2)

Signature gene expression in mouse liver (q.d. dosing x 5 days)

* Indicates a statistical difference from OCA
# Indicates a statistical difference from control
**STAM™ Mouse Model for NASH**

**1st hit**
(low dose STZ injection)

STZ: streptozotocin

<table>
<thead>
<tr>
<th>STAM mouse model</th>
<th>0 w</th>
<th>Low dose STZ injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 – 10 w</td>
<td>High fat diet</td>
</tr>
<tr>
<td></td>
<td>5 w</td>
<td>Fatty liver evident</td>
</tr>
<tr>
<td></td>
<td>7 w</td>
<td>NASH evident</td>
</tr>
<tr>
<td></td>
<td>9 w</td>
<td>Fibrosis evident</td>
</tr>
<tr>
<td></td>
<td>10 w</td>
<td>End pt, NAS score</td>
</tr>
</tbody>
</table>

**Continuous 2nd hit**
(High Fat Diet, HFD)

- **HFD + Vehicle**
  - 4 weeks

- **HFD + EDP-305**
  - 3 mg/kg/day
  - 4 weeks

- **HFD + EDP-305**
  - 10 mg/kg/day
  - 4 weeks

- **HFD + OCA**
  - 10 mg/kg/day
  - 4 weeks

**NAS**
(NAFLD Activity Score)
## EDP-305 vs OCA in STAM™ Mouse Model

<table>
<thead>
<tr>
<th>Drug</th>
<th>mg/kg/d</th>
<th>n</th>
<th>Hepatocyte Ballooning Score</th>
<th>NAFLD Activity Score (NAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>* p&lt;0.05</td>
<td>* p&lt;0.05</td>
</tr>
<tr>
<td>Control</td>
<td>--</td>
<td>7</td>
<td>1.9</td>
<td>5.3</td>
</tr>
<tr>
<td>EDP-305</td>
<td>3</td>
<td>7</td>
<td>1.1</td>
<td>3.7*</td>
</tr>
<tr>
<td>EDP-305</td>
<td>10</td>
<td>8</td>
<td>0.75*</td>
<td>3.8*</td>
</tr>
<tr>
<td>OCA</td>
<td>10</td>
<td>8</td>
<td>1.1</td>
<td>4.3</td>
</tr>
</tbody>
</table>

**Graphs:**
- **Hepatocyte Ballooning Score:**
  - Control: n.s.
  - EDP-305 low: p<0.05
  - EDP-305 high: n.s.
  - OCA: n.s.

- **NAFLD Activity Score (NAS):**
  - Control: n.s.
  - EDP-305 low: p<0.05
  - EDP-305 high: n.s.
  - OCA: p<0.05
FXR Agonist EDP-305: Summary

- Potent FXR receptor agonist activity vs OCA
- Highly selective for FXR vs other nuclear receptors and vs TGR5 receptor
- Potent and differentiated effects on FXR-dependent gene expression vs OCA
  - human hepatocytes
  - *in vivo* mouse model
- Improvement in hepatocyte ballooning and overall NAFLD Activity Score vs OCA in *in vivo* NASH model
- EDP-305 nominated as a development candidate
- On track to initiate clinical trials in 2H 2016

* Source: AbbVie
Virology & Liver Disease Focus Areas

- HCV
- NASH/PBC
- HBV
- RSV
HBV Background

- Potentially life-threatening liver infection caused by the hepatitis B virus
- Current treatments rarely give true cures
  - **Interferon** gives better results (~10%), but with side effects
  - **RT inhibitors** very effective at reducing viral load, but offer very low cure rates (1% or lower) and must be taken for life to improve cirrhosis or HCC outcomes
- Prevalence estimates
  - US: ~550,000 - 2 million
  - US + Japan + major EU populations: ~4.9 million
  - Worldwide: ~240 million
- Estimated 15-25% of patients with chronic HBV infection will develop chronic liver diseases including cirrhosis, HCC, or liver decompensation

Sources: WHO, CDC, Datamonitor
Respiratory Syncytial Virus (RSV)

- Negative-sense, single-stranded RNA virus of family Paramyxoviridae
- Most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children <1 year old in the U.S.
- Each year, 75,000 to 125,000 children in this age group are hospitalized due to RSV infection (most < 6 months old)
- Almost all children have had an RSV infection by age 2
- When infants/children are exposed to RSV for first time, 25% to 40% have signs or symptoms of bronchiolitis or pneumonia
- Adults with compromised immune systems and those age 65+ are also at increased risk of severe disease
- No safe and effective treatments

Source: CDC
HBV & RSV Programs: Update

• HBV: Initial focus on Core Inhibitors
  - Clinical validation (Novira)
  - Exploring additional mechanisms with goal of a functional cure

• RSV: Initial focus on Non-Fusion Inhibitors
  - Potential to be effective at later stage of infection

• Pre-clinical leads and IP activity in both programs

• GOAL: Initiate clinical studies with at least one program in 2017
# Financial Highlights

<table>
<thead>
<tr>
<th></th>
<th>Fiscal Year Ended Sept. 30, 2015</th>
<th>Fiscal 2Q16</th>
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</thead>
<tbody>
<tr>
<td><strong>Total Revenues</strong></td>
<td>160.9*</td>
<td>$13.0</td>
</tr>
<tr>
<td><strong>R&amp;D Expenses</strong></td>
<td>$23.2</td>
<td>$9.1</td>
</tr>
<tr>
<td><strong>G&amp;A Expenses</strong></td>
<td>$13.5</td>
<td>$4.4</td>
</tr>
<tr>
<td><strong>Net Income (loss)</strong></td>
<td>$79.0</td>
<td>$(1.6)</td>
</tr>
<tr>
<td><strong>EPS (per diluted share)</strong></td>
<td>$4.09</td>
<td>$(0.09)</td>
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**Balance Sheet**

<table>
<thead>
<tr>
<th></th>
<th>Fiscal Year Ended Sept. 30, 2015</th>
<th>Fiscal 2Q16</th>
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</thead>
<tbody>
<tr>
<td><strong>Cash and Cash Equivalents</strong></td>
<td>$209.4</td>
<td>$245.6</td>
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</table>

* Includes $125M in payment earned from AbbVie for U.S. and EU commercialization regulatory approvals.
Financial Summary

• Cash as of March 31, 2016: Approx. $246M, no debt
• Double-digit royalties on allocated paritaprevir sales
• Financial opportunity from ABT-493
  - targeted approval 2017*
  - up to $80M in regulatory approval milestone payments
  - additional double-digit royalty opportunity

* Source: AbbVie
Key 2016 Catalysts

• **Paritaprevir**: Ongoing royalties from Viekira®, Viekirax™, and Technivie® *(AbbVie)*

• **ABT-493**: Data from Ph3 trials on pan-genotypic HCV program starting in 4Q16, targeting 2017 approval *(AbbVie)*

• **Cyclophilin inhib. EDP-494**: Complete Ph1 and initiate POC clinical studies in GT1 & GT3 *(3Q16)*

• **FXR agonist EDP-305 for NASH / PBC**: Initiate Ph1 *(2H16)*

• **HBV and RSV programs**: Advance leads with goal of 2017 Ph1 start in at least one program