Proof of concept: pradefovir is a liver-targeting antiviral with potent activity against HBV

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Proof-of-Concept
Pradefovir Is a Liver-targeting Antiviral with Potent Activity against HBV

Zhi Hong, Ph.D.
HepDart 2005
Valeant R & D, Costa Mesa, CA
Current & Future HBV Therapies

- **Immunomodulators**
  - IFN/Peg-IFN (Schering/Roche)

- **Nucleos(t)ides**
  - Lamivudine-like
    - Lamivudine/Epivir\textsuperscript{TM}-HBV (GSK)
    - Entecavir/Baraclude\textsuperscript{TM} (BMS)
    - Telbivudine (Novartis/Idenix) – Phase 3
    - Clevudine (Bukwang) – Phase 3
  - Adefovir-like
    - Adefovir Dipivoxil/Hepsera\textsuperscript{TM} (Gilead)
    - Tenofovir Disoproxil Fumarate/Viread\textsuperscript{TM} (Gilead) – Phase 3
    - Pradefovir Mesylate (Valeant) – Phase 2
Two Distinct Drug Resistant Patterns

ADV: 1) equally active against LAM\(^R\) and wt viruses in vitro
2) equally active in clinical studies
Hepsera® Product Profile

- Esterase-based prodrug of PMEA (adefovir)
- Once a day oral dosing
- Complete conversion across GI
- Active against Lamivudine-resistant HBV
- Higher threshold against resistance development
- Dose-limiting nephrotoxicity: Suboptimal Efficacy
The HepDirect Concept

Liver (Hepatocyte)

PMEA-PP

Prodrug

Kinases

Kidney

PMEA-PP

Prodrug

PMEA

CYP3A4

Liver (Hepatocyte)

PMEA

Kinases

PMEA-PP

Kidney

Prodrug

PMEA

Blood

Esterases

GI Wall

Hepsera® (Adefovir Dipivoxil)

Pradefovir

Pradefovir
CYP3A4 Tissue Distribution in Human

- Liver: 5490 nmol
- Intestine: 71 nmol
### Whole Body Autoradiography

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Remofovir (R)</th>
<th>Adefovir Dipivoxil</th>
<th>R/AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>14012</td>
<td>889</td>
<td>15.76</td>
</tr>
<tr>
<td>Kidney Cortex</td>
<td>3783</td>
<td>10264</td>
<td>0.37</td>
</tr>
<tr>
<td>Liver/Kidney Cortex</td>
<td>3.7</td>
<td>0.087</td>
<td>42.80</td>
</tr>
</tbody>
</table>
PMEA Actives in Rat Liver & Kidney

**Kidney**
- Pradefovir: 6.47 mg/g
- Adefovir: 39.2 mg/g

**Liver**
- Pradefovir: 17.5 mg/g
- Adefovir: 5.73 mg/g
Open-label Phase 2 Design

24 week Interim Analysis

Final 24 Weeks of Treatment
(48 Weeks Total on Treatment)

Randomization

- Pradefovir 5 mg QD (N=47)
- Pradefovir 10 mg QD (N=49)
- Pradefovir 20 mg QD (N=48)
- Pradefovir 30 mg QD (N=48)
- Adefovir Dipivoxil 10 mg QD (N=50)

21 sites
- Taiwan: 11
- Singapore: 2
- Korea: 6
- US: 2

(N=244)
### Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Pradefovir</th>
<th>Adefovir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>85.1 (N=47)</td>
<td>75.5 (N=49)</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>37 (9)</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Median</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Range</td>
<td>18-59</td>
<td>22-58</td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>68 (11)</td>
<td>68 (11)</td>
</tr>
<tr>
<td>Median</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Range</td>
<td>47-94</td>
<td>47-89</td>
</tr>
</tbody>
</table>
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pradefovir</th>
<th>Adefovir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg (N=47)</td>
<td>10 mg (N=49)</td>
</tr>
<tr>
<td><strong>HBeAg (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>70.2</td>
<td>67.3</td>
</tr>
<tr>
<td>Negative</td>
<td>31.9</td>
<td>34.7</td>
</tr>
<tr>
<td><strong>Genotype (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>31.9</td>
<td>36.7</td>
</tr>
<tr>
<td>C</td>
<td>68.1</td>
<td>63.3</td>
</tr>
<tr>
<td><strong>HBV DNA (log&lt;sub&gt;10&lt;/sub&gt; c/mL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Median</td>
<td>8.1</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>ALT (xULN)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.6 (1.4)</td>
<td>2.8 (2.1)</td>
</tr>
<tr>
<td>Median</td>
<td>2.3</td>
<td>2.0</td>
</tr>
<tr>
<td>Previously Treated</td>
<td>22 (47%)</td>
<td>29 (59%)</td>
</tr>
</tbody>
</table>
Mean Change from Baseline in HBV DNA

Assay: Roche Cobas TaqMan®

P value vs ADV Control
-3.39 log_{10} (p=0.262)
-3.66 log_{10}
-4.22 log_{10} (p=0.012)
-4.33 log_{10} (p=0.004)
-5.02 log_{10} (p<0.001)

Lim SG et al AASLD 2005
Serum PMEA AUC\textsubscript{0-24h}  

24 week HBV DNA Reduction from Baseline

-3.39 (N=47)
-4.22 (N=49)
-4.33 (N=48)
-5.02 (N=48)
-3.66 (N=50)

PK groups consist of subsets of patients from each cohort
### Serum PMEA AUC0-24h

**Treatment Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>PMEA AUC0-24hr (ng.h/mL)</th>
<th>24 week HBV DNA Reduction from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDV 1</td>
<td>-3.39 (N=47)</td>
<td>-3.39 (N=47)</td>
</tr>
<tr>
<td>PDV 2</td>
<td>-4.22 (N=49)</td>
<td>-4.22 (N=49)</td>
</tr>
<tr>
<td>PDV 3</td>
<td>-5.02 (N=48)</td>
<td>-4.33 (N=48)</td>
</tr>
<tr>
<td>ADV 1</td>
<td>-3.66 (N=50)</td>
<td>-5.02 (N=50)</td>
</tr>
</tbody>
</table>

PK groups consist of subsets of patients from each cohort.
Comparison of Antiviral Response

All Patients (ITT)

< 2.0 log$_{10}$ reduction in serum HBV DNA from baseline

% patients with < 2 log$_{10}$ reduction

Treatment week

4 12 24

PDV (5 mg) PDV (10 mg) PDV (20 mg) PDV (30 mg) ADV (10 mg)
Comparison of Antiviral Response

HBeAg-Positive

< 2.0 log₁₀ reduction in serum HBV DNA from baseline

<table>
<thead>
<tr>
<th>Treatment week</th>
<th>PDV (5 mg)</th>
<th>PDV (10 mg)</th>
<th>PDV (20 mg)</th>
<th>PDV (30 mg)</th>
<th>ADV (10 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>24</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

p < 0.05
Comparison of Antiviral Response

HBeAg-Negative

< 2.0 log_{10} reduction in serum HBV DNA from baseline

% patients with < 2 log_{10} reduction

PDV (5 mg)
PDV (10 mg)
PDV (20 mg)
PDV (30 mg)
ADV (10 mg)

Treatment week

0% 20% 40% 60%

< 2.0 log_{10} reduction in serum HBV DNA from baseline
Pradefovir is a highly active anti-HBV antiviral
- Significantly more active than Hepsera®

Pradefovir, at daily oral doses of 5, 10, 20 and 30 mg per day, is well tolerated

No major safety concerns to date
- No indication of renal toxicity

The 30mg dose selected for phase III studies
Mean $\text{Log}_{10}$ Reduction from Baseline

- Entecavir: $-6.9/9.6$ at wk 48
- Telbivudine: $-6.5/9.5$ at wk 52
- Pegasys/Lamivudine: $-7.1/10$ at wk 48
- Pradefovir: $-5.0/8.2$ at wk 24
Remaining Virus Titers

- Good marker for efficacy
  - Good measurement of treatment success
  - Correlative with replication status
  - Correlation with clinical benefits

- More reliable comparison between trials
Comparison of Antiviral Efficacy

Legend: blue dots represent HBeAg+ and green dots represent HBeAg- Patients. Open circles represent results at week 24 & solid circles represent week 48/52 data or projections at week 48.

Summary on Pradefovir

- May have maximum potency
  - Equivalent to Entecavir & Telbivudine

- May have best activity in Lamivudine-refractory patients

- May have best safety profiles
# Acknowledgement

**Valeant R & D**

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