Focus on Hepatitis C

Key Takeaways from our Expert Panel Discussion on Hepatitis C

- On Wednesday, we hosted our first “Panel with the Experts” discussion by inviting three distinguished clinicians: Dr. David Clain (Beth Israel), Dr. Douglas Dieterich (Mount Sinai), and Dr. Paul Gaglio (Columbia-Presbyterian). Key highlights are as follows:

- **HCV Standard of Care** – Dr. Clain reviewed the current therapy, which consists of PEG-IFN-alpha (qw) and ribavirin (qd). Data comparing PEG-IFN-α-2a and PEG-IFN-α-2b were also discussed.

- **Experimental Therapies** – Dr. Dieterich discussed ribavirin analogues, protease inhibitors, polymerase inhibitors, and the immunomodulator class of drugs. Enthusiasm was expressed for HGSi’s Albuferon, which could potentially support every 2 or 4 week dosing regimens instead of weekly dosing visits required with PEG-IFNs. For VRX’s viramidine, Dr. Dieterich noted that in the VISER1 study, response rates with the drug were lower than with ribavirin (38% vs. 52%), however, viramidine did cause fewer incidences of anemia (5% vs. 24%) compared to ribavirin. Similar results were observed in the VISER2 study. In his view, viramidine was likely underdosed and if the dose had been doubled (at least based on VISER1 exposure data), then SVR would likely have approached 62% with an anemia rate of 10% (well below the ~30% anemia rate associated with ribavirin). VRTX’s VX-950 received little support as a monotherapy option due to resistance. However, as a combination therapy with PEG-IFN and ribavirin, the 5.5 log reduction in HCV RNA at day 14, observed in VRTX’s Phase 1b trial, was viewed as very impressive, and unlike the monotherapy trial, all patients experienced HCV RNA declines. IDIX’s NM283 was viewed as generally less susceptible to resistance. NM283’s GI side effects, which lead to the FDA requesting a dose reduction last March, have been, in the panel’s opinion, overly-exaggerated. In Dr. Dieterich’s experience, the nausea effects were easily preventable with antiemetic agents, such as, for example, Reglan®. In addition, despite the lowered NM283 dose, it was not believed that this would lead to an appreciable loss of antiviral activity. Patient enrollment for the ribavirin/NM283 interaction study, according to Dr. Dieterich, will begin on Monday. In addition, immunomodulators, such as COLY’s CPG10101 (Actilon™), that activate toll-like receptors, in his view, could prove to be synergistic in combination with conventional therapy.

- **AASLD Abstract Preview (Oct. 27-31)** – We do not expect any surprises at the meeting in Boston over the next few days. Dr. Gaglio discussed the following abstracts: 1136 and 1141 for albuferon, 1133 for viramidine; 927, 1142, and 89 for incremental data on VX-950; 93 for NM283, and 96 for CPG10101 (Actilon™). For a detailed schedule of HCV relevant abstracts, please refer to our October 25, 2006, published note.

- “Panel Discussion with Experts” archived webcast information can be obtained by contacting your salesperson or the authors of this report.
Focus on Hepatitis C
Key Takeaways from our Expert Panel Meeting on Hepatitis C

- **HCV Standard of Care** – Dr. Clain reviewed the current therapy, which, for genotype 1 patients, comprises treatment with PEG-IFN-α-2a (Pegasys; Roche) administered at a dose of 180 µg subcutaneously once weekly and ribavirin (Rebetol, Schering-Plough; or Copegus, Roche) taken orally at a dose of 800-1200 mg (weight-based; daily at 1,000 mg if ≤ 75 kg or 1,200 mg daily if > 75 kg). Sustained viral response rates at 24 weeks post-therapy (defined as negative serum HCV RNA) range between 40-50% for genotype 1 infected patients (Table 1). Data comparing PEG-IFN-α-2a and PEG-IFN-α-2b were also discussed, however, it was agreed that it was difficult to make direct comparisons of the two studies (Fried et al. *NEJM.* 2002;347: 975-982 vs. Manns et al. *Lancet.* 2001;358: 958-965).

Table 1. PEG-IFN α-2a, as compared to IFN α-2b, plus RBV for the treatment of chronic hepatitis C virus infection

<table>
<thead>
<tr>
<th></th>
<th>Peginterferon α-2a plus ribavirin (N = 453)</th>
<th>Interferon α-2b plus ribavirin (N = 444)</th>
<th>Peginterferon α-2a plus placebo (N = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>255/453 (56)</td>
<td>197/444 (44)</td>
<td>66/224 (29)</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>138/298 (46)</td>
<td>103/285 (36)</td>
<td>30/145 (21)</td>
</tr>
<tr>
<td>Genotype 2/3</td>
<td>106/140 (76)</td>
<td>88/145 (61)</td>
<td>31/69 (45)</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>10/13 (77)</td>
<td>4/11 (36)</td>
<td>4/9 (44)</td>
</tr>
</tbody>
</table>

*No./total no. (%)*

*aA sustained virologic response was defined as no detectable hepatitis C virus (HCV) RNA 24 weeks after the cessation of therapy.

*bSix patients had other genotypes


- **Experimental Therapies** – Dr. Dieterich discussed numerous experimental drugs having mechanisms of action generally falling into the ribavirin analogue, protease inhibitor, polymerase inhibitor, and immunomodulator class. In our view, some of the salient points were as follows:

  o Enthusiasm was expressed for Human Genome Sciences’ (HGSI) Albuferon, a modified protein consisting of IFN-α fused to human serum albumin, which has an extended half-life of 6 days, which may support every 2 or 4 week dosing regimens instead of weekly dosing required with PEG-IFNs.

  o For Valeant Pharmaceuticals’ (VRX) ribavirin analogue, viramidine, Dr. Dieterich noted that in the VISER1 study (combination with IFN-α-2b; Peg-Intron) response rates with the drug were lower than with ribavirin (38% vs. 52% in the overall population), however viramidine did cause fewer incidences of anemia (5% vs. 24%) compared to ribavirin. Similar results were observed in the VISER2 study which, except for use of the type of IFN (alpha-2b vs. alpha-2a), was similar in design to VISER1. Dr. Dieterich noted that, in his view, viramidine was likely underdosed and if the dose had been doubled (at least based on VISER1 exposure data), then SVR would likely have approached 62% with anemia rate of 10% (still below the 30% rate seen with ribavirin).

  o Vertex’s (VRTX) VX-950, an NS3 protease inhibitor, received little support as a monotherapy option due to emergence of resistance as early as 7-days post-therapy and rebound or plateau observed in 4/8 patients (Reesink HW, et al. 41st EASL. 2006. Abst 737). However, as a combination therapy with PEG-IFN and ribavirin, the 5.5 log reduction in HCV RNA at day 14, observed in VRTX’s Phase 1b and reported at EASL in April, was viewed as very impressive, and unlike the monotherapy trial, all patients experienced HCV RNA declines.
NM283 (valopicitabine), the NS5B polymerase inhibitor of Idenix Pharmaceuticals (IDIX) was viewed as generally less susceptible to resistance than the protease inhibitor class of drugs. Concerns regarding the gastrointestinal side effects, which culminated in the FDA requesting a dose reduction to 200-400 mg from 800, are, in the panel’s opinion, exaggerated. Dr. Dietrich also pointed out that the nausea effects were easily preventable with antiemetics agents, such as, for example, Reglan®. In addition, despite the lowering of the dose, it was not believed that it would lead to an appreciable loss of antiviral activity since there was convergence of HCV RNA titer reductions by 12 weeks (see Fig. 1). In addition, according to Dr. Dieterich, patient enrollment for the ribavirin/NM283 interaction study will begin on Monday.

Fig. 1. NM-283 in HCV-1 Treatment-Naïve Patients

There was surprising enthusiasm for immunomodulators, such as Coley Pharmaceutical Group’s (COLY) CPG10101 (Actilon™), which activate toll-like receptors. These agents, in theory, target both the innate and adaptive immune responses and could prove to be synergistic in combination with conventional therapy.

**AASLD Abstract Preview** – We do not believe that there will be any big surprises coming out of the meeting over the next few days. Dr. Gaglio discussed the following abstracts: 1136 and 1141 for albuferon, 1133 for viramidine; 927, 1142, and 89 for incremental data on VX-950; 93 for NM283, and 96 for CPG10101 (Actilon™). Investors may also refer to our October 25, 2006, note for a detailed schedule of HCV relevant abstracts.

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