



## Telaprevir's Exciting Hep C Potential

### Strong Efficacy May Improve Overall Treatment Paradigm

#### Companies

Vertex Pharmaceuticals (VRTX)  
Schering Plough (SGP)  
Novartis (NVS)  
Human Genome Sciences (HGSI)  
Roche (Swiss: ROG)  
Astellas (Frankfurt Exchange: YPH)  
Chugai Pharma (Private)  
Enzon Pharmaceuticals (ENZN)

#### Products

Telaprevir (VRTX)  
Boceprevir (SGP)  
Zalbin (Albupheron; HGSI, NVS)  
Intron-A (SGP, YPH)  
Pegasys (Chuagi)  
Pegintron (SGP)  
Ribavirin (SGP, ENZN)

#### About the Expert

**Dr. Jules Dienstag, M.D.** is the Dean of Medical Education at Harvard Medical School and the Principal Investigator for the Hepatitis C Antiviral Long-term Treatment against Cirrhosis ("HALT-C") trial. He is also an attending physician at Massachusetts General Hospital in Boston, MA. Dr. Dienstag is well published on Hepatitis C and his work is highly regarded by the medical community.

- Dr. Jules Dienstag spoke for *inThought*'s expert discussion series on Tuesday, where he highlighted the limitations of current hepatitis C virus (HCV) treatments.
- Two developmental drugs in phase III - Vertex's (VRTX) telaprevir and Schering Plough's (SGP) boceprevir - are likely to increase efficacy and acceptability of treatment. **Telaprevir appears more efficacious than boceprevir**, as it clears virus in less time and with fewer adversities.
- Dr. Dienstag believes that **adding telaprevir will become standard of care nearly immediately after FDA approval**, and that it will be used to treat the typical HCV population as well as a subpopulation of patients who have not responded to the current treatments.
- **We estimate that the U.S. hepatitis C market will grow from \$1.4 billion today to about \$5 billion in 2018 due to the more effective and tolerable treatments.**
- Contact *inThought* for details on our probability of approval models for telaprevir and boceprevir, and on our revenue models for seven marketed and developmental HCV agents.

## Real World Diagnosis and Treatment

The *Annals of Internal Medicine* estimates that the prevalence of HCV infection in the United States is 1.6% of the population, or approximately 4.7 million infected people [“The Prevalence of Hepatitis C Virus Infection in the United States, 1999 through 2002,” Armstrong, et al, *Annals of Internal Medicine*. Volume 144. Issue 10. Pages 705-714]. Nearly 75% are chronically infected. Dr. Dienstag estimates that less than one third of infected people are diagnosed and even fewer get treated. Patients are most often diagnosed by blood banks or life insurance companies, not in a traditional medical setting.

Current standard of care is interferon therapy, most often a long acting interferon that is injected weekly, plus ribavirin, a daily antiviral. This regimen has unpleasant side effects: Interferons can cause flu like symptoms, fatigue, low blood counts, depression, anxiety, and autoimmune disorders such as thyroiditis. Ribavirin used in conjunction with interferons can cause anemia and other issues. Dr. Dienstag believes that improved approaches to treatment are critical.

Three drugs are in phase III development in the U.S. - Vertex’s telaprevir, Schering Plough’s boceprevir, and Human Genome Sciences’ Zalbin. Dr. Dienstag believes that the two that will be used most by the medical community are telaprevir and boceprevir, as they increase “cure rates” and potentially shorten treatment regimens. Telaprevir and boceprevir are each used in conjunction with the current treatment of interferon plus ribavirin.

Although these new drugs do not lessen side effects of HCV treatment, they are likely to improve efficacy. Telaprevir may indirectly improve overall treatment-related adversity by shortening the duration of interferon treatment, leading to better patient adherence to the treatment regimen. According to Dr. Dienstag, the current treatments have a “cure rate” of about 45% to 50%, but the upcoming treatments, including telaprevir and boceprevir, increase the cure rate to at least 65%. By “cure rate,” it is meant that the viral load becomes undetectable in blood tests, but that the virus could return at some point in the future.

## Telaprevir vs. Boceprevir Efficacy and Safety

Phase II trials suggest that telaprevir, interferon, plus ribavirin makes a six-month treatment duration possible, while boceprevir’s addition typically yields a one-year treatment duration. Some early boceprevir responders may be able to stop treatment after six months.

The most impressive aspect of telaprevir, according to Dr. Dienstag, is its efficacy. Telaprevir quickly reduces the level of HCV virus to undetectable. It will drop the level of virus in >80% of patients in the first 4 weeks.

The downside to telaprevir is a rash that occurs at a median of eight weeks into treatment (telaprevir is used with interferons and ribavirin for 12 weeks and then only interferons and ribavirin are used for the remaining three months). This rash was considered to be severe in 7% of patients in the phase II study. The rash is red, raised, itchy, and quite uncomfortable. It is typically treated with corticosteroid creams.

Boceprevir’s phase II trial showed a 55% response rate at 6 months and a 65% rate at one year (a full treatment). Boceprevir’s one-year efficacy was similar to telaprevir’s six month response rate. Both drugs are demonstrating response rates better than the current standard of care, which yields 40% to 45%.

About 50% of boceprevir recipients experience anemia. Dr. Dienstag expects telaprevir to be preferred over boceprevir as a first-line agent because of efficacy, adversity, and duration of treatment advantages, becoming a new standard of care shortly after its approval.

## Zalbin

Zalbin is a long-acting interferon alpha in phase III trials for the treatment of HCV. Dr. Dienstag does not see Zalbin having a significant impact on HCV treatment. Zalbin has to date shown non-inferiority to currently available interferons, but concerning adversity and toxicity profiles. Adversities include shortness of breath, cough, and pulmonary complications.

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## Changing Treatment Paradigms

Once approved, telaprevir is likely to change current treatment paradigms from two drugs to triple drug therapy, but it may also shorten treatment time to six months from at least a year.

Some have speculated that telaprevir could be used as a monotherapy. Dr. Dienstag does not see telaprevir monotherapy as a possibility because the hepatitis C virus replicates very quickly, making more than one antiviral necessary. He does think that there is a possibility that telaprevir with only ribavirin could be a viable treatment. Dual therapy without interferon could be more tolerable than traditional triple drug therapy, leading to an increase in the percent of people treated as well as adherence to treatment. In Australia, Intermune's phase II protease inhibitor, ITMN-191, and Pharmasset's nucleoside polymerase, R7128, were used as dual therapy for two weeks without interferons, suggesting that significant viral load reduction is possible even without interferon injections.

Shorter duration of therapy with a telaprevir background is also possible. Dr. Dienstag predicts that three months of triple drug therapy using telaprevir + peginterferon + ribavirin would be efficacious, but that six months will be better.

## Impact on the HCV Market

With an estimated 4.7 million infected people in the United States, we believe that only around 1.5 million know they are infected, and only around 25% of the diagnosed seek treatment. With shortened therapy, the percent treated is likely to increase. The overall percent treated increases from 8% today to 12% by 2018 in our model. The potential to use new therapies without interferons, which cause side effects like flu like symptoms and fatigue, could increase treatment rates even more.

Telaprevir has additional upside due to potential use in infected people who have not responded to current therapies. Nearly half of patients do not respond to the current therapy. This large population could be immediate adopters of the triple drug therapy.

Dr. Dienstag believes that 40% of non-responders can effectively be treated with telaprevir. At the American Association for the Study of Liver Diseases

(AASLD) meeting October 30 to November 4, an abstract titled, "PROVE3 Final Results and 1-Year Durability of SVR with Telaprevir-Based Regimen in Hepatitis C Genotype 1-Infected Patients with Prior Non-response, Viral Breakthrough or Relapse to Peginterferon-Alfa-2a/b and Ribavirin Therapy" by McHutchison et al shows that viral response rates in patients receiving telaprevir + peginterferon + ribavirin were significantly higher than with patients receiving peginterferon + ribavirin for 48 weeks. The trial showed that patients who failed prior peginterferon + ribavirin therapy can successfully be treated with a telaprevir-based regimen and maintain viral response one year after the end of treatment.

Similarly, boceprevir in prior non-responders showed good results in the abstracts for the liver meeting. An abstract titled, "Clonal analysis of mutations selected in the HCV NS3 protease domain of genotype 1 non-responders sequentially treated with boceprevir (SCH503034) and/or pegylated interferon alfa-2b (PEG-IFN  $\alpha$ -2b)," by Vermehren et al showed that non-responders who were subsequently treated with boceprevir + peginterferon + ribavirin showed a consistent viral decline.

## HCV Pipeline

Two classes of HCV drugs are being developed: protease inhibitors, such as telaprevir and boceprevir, and non-nucleoside polymerase inhibitors.

Of the protease inhibitors, Dr. Dienstag believes that **Boehringer Ingelheim's BI 201335** is most interesting. It is in phase II in Europe. Phase I showed no patients discontinuing monotherapy, indicating that it is well tolerated. The drug was administered as monotherapy for two weeks followed by peginterferon + ribavirin for two more weeks. The trial showed a strong and rapid antiviral response compared to placebo. The liver meeting abstracts show that BI 201335 with peginterferon + ribavirin demonstrated rapid, potent antiviral activity with virologic responses at weeks 4 and 12 in the abstract titled, "Early antiviral activity and safety of BI 201335 combined with peginterferon alfa-2a and ribavirin in treatment-naïve patients with chronic genotype 1 HCV infection," by Sulkowski et al.

**ITMN-191** is Intermune and Roche's orally available protease inhibitor. It is in phase II trials in the U.S. Like the other protease inhibitors, it is typically

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used with peginterferon and ribavirin. Early studies show that this combination is generally safe and well tolerated. An abstract from the liver meeting showed that among 40 patients receiving ITMN-191 monotherapy, 14 patients experienced virologic rebound. This study indicates the possibility of getting a strong response using only monotherapy.

**TMC-435** was called out by Dr. Dienstag. It is a protease inhibitor being developed by Tibotec (a subsidiary of Johnson & Johnson) as an oral treatment to be used in combination with peginterferon and ribavirin. In April, Tibotec released positive efficacy and tolerability data after 28 days of triple therapy. No data are expected at the liver meeting.

**ANA 598** is a phase II drug being studied by Anadys Pharmaceuticals. This small molecule, non-nucleoside, polymerase inhibitor is being studied as

a monotherapy. It has been shown to be well tolerated. No data are expected AASLD.

Vertex is in phase I with its oral small-molecule, non-nucleoside inhibitor called **VCH 222**. Dr. Dienstag found this drug interesting, as it could be used as a single therapy. In March, Vertex announced that in patients receiving 750mg twice daily demonstrated the most significant viral load reductions for polymerase inhibitors seen to date after only three days of single therapy. Results were consistent from patient to patient.

**IDX 184** is a once-daily oral nucleotide polymerase inhibitor being developed by Idenix Pharmaceuticals. Early studies have shown a significant reduction in viral load after only days of therapy. Dr. Dienstag finds this to also be an interesting drug candidate.

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