Pipeline Report: Hep C to Meet Its Maker

By year's end, a new crop of interferon-free hepatitis C combination therapies will likely hit the market, more or less signing the virus's death warrant. But at what financial cost?

May 19, 2014 By Benjamin Ryan

Since Gilead Sciences' Sovaldi (sofosbuvir) hit the market in December 2013, a whirlwind of excitement has surged over its phenomenal results: The drug typically cures 85 to 95 percent of those with hepatitis C virus (HCV) in just 12 to 24 weeks. Amid a widespread uproar over the drug's $1,000-a-pill price tag, people living with the virus who have long been holding out for the release of more effective therapies have sought out the drug in droves. Gilead sold $2.3 billion worth of Sovaldi in the first quarter of 2014, shattering the record for any drug's entire first year on the market.

The Sovaldi debut, however, amounts to only the opening act for an even grander pharmaceutical spectacle that is now waiting in the wings.

"It's mind-boggling how good they are," says Douglas Dieterich, MD, a professor of medicine at Mount Sinai School of Medicine, of the heady crop of new, even more effective combination hep C therapies that are currently waiting for U.S. Food And Drug Administration (FDA) approval. "It's really spectacular."

By the end of 2014, near-perfect cure rates will start to become the norm in the hep C treatment paradigm. In addition, interferon will finally get the pink slip, along with the injectable drug's miserable flu-like side effects. And in many cases ribavirin may be jettisoned as well.

In February, Gilead filed for FDA approval for the treatment considered the one to beat: a once-a-day, single-tablet, fixed-dose regimen of the analog polymerase inhibitor Sovaldi and the NS5A inhibitor ledipasvir. The new drug application (NDA) restricts its bid to those with genotype 1, who make up an estimated three-quarters of the U.S. market. Nevertheless, physicians could use past clinical trials as a guide to prescribe the therapy off-label to those with other genotypes of the virus. A recent study found the combination pill, plus ribavirin, cured 100 percent of those with genotype 3. If the treatment is approved, treatment times would range between eight and 12 weeks, depending on treatment experience and the presence of cirrhosis.

For its NDA, Gilead submitted results from the three so-called ION trials, which demonstrated that a 12-week regimen of Sovaldi-ledipasvir cured between 94 and 99 percent of those with genotype 1. The cure rate for study participants with genotype 1b was 87 percent if they had been treated before and 98 to 100 percent if they were treatment naive. The cure rate for those with genotype 1a was 95 percent if they had previously failed treatment and 95 to 99 percent if it was their first treatment attempt. Eight weeks of treatment given to a treatment-naive cohort cured 93 percent of participants with genotype 1a and 98 percent of those with genotype 1b.

After granting the Sovaldi-ledipasvir combination pill priority review status, the FDA will give word about the therapy on October 10. This should kick-start a vibrant end-of-the-year melee for market share between Gilead and AbbVie, along with Bristol-Myers Squibb, which are close behind in their NDAs. In the near future, however, BMS looks like a bit more of a straggler.

On April 7, BMS filed with the FDA for approval of the company's NS5A replication complex inhibitor daclatasvir and the NS3 protease inhibitor asunaprevir to be used in combination to treat genotype 1b. In addition, BMS filed an NDA for daclatasvir's use with other hep C drugs to treat multiple genotypes of the virus.

The daclatasvir-asunaprevir combination has had relatively anemic results in clinical trials, with response rates to 24 weeks of therapy ranging between 82 percent and 90 percent among those with genotype 1b.

However, the pair's approval would set the stage for the addition of the non-nucleoside polymerase inhibitor BMS-791325, also known as '325, perhaps in another year's time. The triple combination cured about 92 percent of treatment-naive study participants with genotype 1 and 100 percent of those with genotype 4 in recent Phase II trials.

A Phase II trial reported over the winter found that 12 to 24 weeks of a combination of daclatasvir and Sovaldi, with or without ribavirin, cured between 92 and 100 percent of both treatment-naive and treatment-experienced study participants with genotypes 1, 2 and 3. This suggests that BMS may be able to pair its drug with Gilead's in order to go after some of the genotype 2 and 3 market.

On April 22, AbbVie filed an NDA for its so-called "3D" regimen, which consists of a fixed-dose combination of the protease inhibitor ABT-450 and ritonavir co-formulated with the NS5A inhibitor ombitasvir (ABT-267), as well as the non-nucleoside polymerase inhibitor dasabuvir (ABT-333), with or without ribavirin. Like Gilead, AbbVie is only setting its sights on the sizeable genotype 1 population in this application. In its NDA, the company has recommended a treatment length of 12 weeks except when treating cirrhotic genotype 1a null responders, in which case the treatment time should be doubled.

Clinical trial results for 3D have been similar to the Sovaldi-ledipasvir regimen in the six trials AbbVie submitted to the FDA in its NDA. However, AbbVie's regimen has various drawbacks when compared with Gilead's: a greater pill burden, twice-a-day dosing and the likely requirement of

ribavirin for genotype 1a treatment.

Enter the issue of cost. For months, speculation has brewed that AbbVie may seek to undercut its chief rival by pricing the 3D regimen significantly lower than the Sovaldi-ledipasvir combination. The hope is that insurance companies will nix Gilead's pill in favor of a less expensive option, and industry players have indicated they will consider such a move given the right circumstances.

"We're hoping to start a price war with a downward spiral, for a change, instead of an upward spiral," say Lynda Dee, spokesperson for the Fair Pricing Coalition, which has a long history of engaging in talks about pricing with the makers of HIV and hepatitis C therapies. "Once we get one to do it, we're hoping to get BMS to do the same thing.

"AbbVie is the queen of 'Let's lower our price so people use us for their formularies,'" Dee says. In 2003, AbbVie—then a part of Abbott—notoriously raised the price of ritonavir by 400 percent. Many HIV drugs are paired with ritonavir as a "booster" to increase the blood levels of the other medication. GlaxoSmithKline sued, accusing AbbVie of improperly raising the price of ritonavir to impede competition with AbbVie's own HIV antiretroviral Kaletra, which is a combination of lopinavir and ritonavir.. A jury found in AbbVie's favor, but litigation is ongoing.

Daniel Fierer, MD, an assistant professor of medicine in infectious diseases, also at Mount Sinai, says, "I don't see how [AbbVie has] a prayer. Unless they significantly undercut [Gilead]. But people in this country resent having to take something less good because it's cheaper. They really will have to make it a lot cheaper."

Meanwhile, in a recent editorial published in The New England Journal of Medicine, T. Jake Liang, MD, and Marc G. Ghany, MD, MHSc, who are both National Institutes of Health liver specialists, wrote that the research on the forthcoming crop of drugs is by no means the end of the discussion where hep C treatment is concerned. These regimens, Liang and Ghany point out, have been tested mostly in middle-aged white men who don't have cirrhosis, and challenges remain in treating those with cirrhosis or kidney failure.

Furthermore, as the essay points out, questions remain as to the efficacy of these new regimens in treating genotypes 4, 5 and 6, which, while more rare in the United States, are common in other parts of the world where the need for treatment is great. For example, the epidemic in Egypt—which is the country with the world's highest hep C prevalence rate at 15 percent—is almost entirely genotype 4.
