New Gilead GS 7340-Inclusive Fixed-Dose Combo Tablet Trial Announced

January 26, 2012

Gilead Sciences Inc. (Nasdaq: GILD) today announced the start of a Phase II clinical trial to evaluate a modified version of its experimental “quad” fixed-dose combination (FDC) tablet currently being reviewed by the U.S. Food and Drug Administration, according to a company announcement.

While Gilead’s FDC pill containing the booster cobicistat, the integrase inhibitor elvitegravir, Viread (tenofovir) and Emtriva (emtricitabine) is expected to be approved sometime during the first half of 2012, the company is now exploring the safety and efficacy of a combination tablet containing cobicistat-boosted elivitegravir and emtricitabine, but with GS 7340 instead of Viread.

GS 7340 is a “prodrug” of tenofovir. Prodrugs are typically inactive chemical compounds that turn into an active drug when they interact with the body’s metabolic system. GS 7340’s mechanism of action is the same at tenofovir, but it requires a dose that is 10 times lower than Viread and it provides greater effectiveness. Though Gilead announced in 2004 that it had no interest in further developing the drug, arguing that it “does not believe that GS 7340 has a profile that differentiates it to an extent that supports its continued development,” the company ended up reconsidering the drug’s potential in recent years.

In addition to developing a new FDC quad that includes GS 7340, Gilead is partnering with Janssen Therapeutics to develop a combination tablet containing cobicistat-boosted Prezista (darunavir) plus GS 7340 and Emtriva.

Tenofovir is a potent antiretroviral drug that in its base form is not well absorbed into the blood stream and is quickly eliminated from blood. To overcome this problem, Gilead Sciences made Viread, a prodrug version of tenofovir.

Viread allows for slower elimination of the tenofovir, because it takes a while for the body to transform Viread into tenofovir. That way it can reach and maintain adequate blood levels of the active drug. Unfortunately, boosting the amount of drug in the blood can also increase the amount that gets into the kidneys, which can lead to one of a potentially worrisome side effects—damage to the tubules that help the kidneys filter blood.

In an attempt to overcome this problem, and to increase the potency of the drug, Gilead experimented with stripping away the additional molecules present in Viread. In their place, the company added other molecules—thereby creating a new prodrug—that result in substantial increases of tenofovir inside the cells targeted by HIV, such as CD4 cells, but not in the blood or in

organs such as the kidneys. This was accomplished by building a new chemical chain that doesn't turn into tenofovir until it is transformed by cathepsin A2, which is produced predominately by a white blood cell called a lymphocyte. The end result was GS 7340.

In the Phase II study announced by Gilead, the GS 7340-containing FDC will be compared with Gilead's Quad FDC, now under FDA review. It is a 48-week randomized, controlled study in which a total of 150 people will receive either novel regimen. About two thirds of the study volunteers will be treated with the GS 7340-containing regimen; the remaining third will receive the Viread-containing FDC tablet.

All study volunteers will need to have HIV that is fully sensitive to both Viread and Emtriva. Earlier use of HIV treatment is now allowed, and kidney function must be normal at the time of enrollment.

Additional information about the study, including enrollment sites, can be found via clinicaltrials.gov.
