Boosting Agent Cobicistat Comparable to Norvir in Phase III Study

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Compared with Norvir (ritonavir), people living with HIV using Gilead Sciences' novel boosting agent cobicistat were just as likely to see their viral loads drop to undetectable levels and no more likely to discontinue therapy due to side effects, according to preliminary results from a Phase III study comparing both drugs in combination with Reyataz (atazanavir) and Truvada (tenofovir plus emtricitabine). The study's findings, highlighted in a December 5 statement from cobicistat's developer Gilead Sciences, will be presented in full at a scientific conference sometime in 2012, with an approval application likely to be submitted to the FDA sometime this spring.

Cobicistat, formerly known as GS-9350, is an experimental pharmacokinetic enhancer—a drug used to boost other medications in the blood to make them more effective. It is being developed as an alternative to Norvir, a protease inhibitor (PI) once used to treat HIV but now prescribed at low doses to boost the blood levels of other PIs, notably Reyataz, Lexiva (fosamprenavir), Prezista (darunavir), Aptivus (tipranavir) and Kaletra (lopinavir plus ritonavir).

Cobicistat's potential as a Norvir alternative is important. For starters, while it has a pronounced effect on the enzyme system (CYP3A) responsible for breaking down several HIV drugs, it doesn't affect other enzyme systems used by many other medications—a common problem with Norvir that contributes to numerous potentially harmful drug interactions. The drug also doesn't impair fat cell functions like Norvir does, at least not in test tube studies, meaning that cobicistat may be less likely to count fat accumulation and insulin sensitivity problems as side effects.

Gilead has been committed to testing cobicistat as a stand-alone drug in combination with other companies' drugs that generally require boosting. Gilead is also exploring cobicistat in combination with its experimental integrase inhibitor elvitegravir and Truvada as a once-daily fixed-dose combination tablet.

Study 114, a Phase III clinical trial, was conducted by Gilead to explore the effectiveness and safety of cobicistat-boosted Reyataz versus Norvir-boosted Reyataz over a 96-week period at more than 200 study sites internationally. The researchers allotted nearly 700 HIV-positive individuals starting antiretroviral therapy for the first time to receive 150 milligrams (mg) cobicistat of 100 mg Norvir, both in combination with Reyataz and Truvada (tenofovir plus emtricitabine).

Similar rates of virologic suppression—defined as a viral load below 50 copies—were maintained

through the follow-up period. After 48 weeks of treatment, 85 percent in the cobicistat group and 87 percent in the Norvir group had viral loads below 50 copies/mL. Given the similar response rates in the two groups, cobicistat was considered to be “non-inferior” to Norvir.

As for adverse health outcomes, the Gilead statement notes similar side effect-related discontinuation rates in both groups. Approximately 7.3 percent of those receiving cobicistat-boosted Reyataz plus Truvada discontinued therapy because of adverse events, compared with 7.2 percent of patients receiving Norvir-boosted Reyataz plus Truvada.

One particular adverse event was noted in the press release. Small increases in serum creatinine—a lab test used to measure kidney function—with resulting decreases in estimated creatine clearance were observed in the study. After 48 weeks of treatment, the average increase in serum creatinine was 0.14 milligrams per deciliter (mg/dL) among those receiving cobicistat, compared with a 0.09 mg/dL serum creatinine increase among those in the Norvir group.

“The increase in serum creatinine with cobicistat occurs with days of drug initiation and is reversible with values returning to [pre-treatment levels] with days after [discontinuing] cobicistat,” Gilead clarifies, adding that cobicistat didn’t have an effect on other measures of renal function, including actual glomerular filtrates rates (GFR).

“These results demonstrate that cobicistat may provide patients taking protease-based regimens with a much-needed alternative boosting agent,” Norbert Bischofberger, PhD, Gilead’s chief scientific officer, is quoted as saying in the statement. “We are now working toward a second quarter 2012 U.S. regulatory filing for cobicistat.”

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