FDA Pauses Trials of Two Experimental Long-Acting HIV Drugs

Gilead says it intends to investigate and pursue the potential of both GS-1720 and GS-4182 after some study participants experience blood cell declines.

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The Food and Drug Administration (FDA) has paused clinical trials of two investigational antiretrovirals due to safety concerns, Gilead Sciences announced June 10. The clinical hold affects two Phase II/III studies and three Phase I trials testing GS-1720 and GS-4182 alone or in combination.

GS-1720 is a novel long-acting integrase inhibitor, and GS-4182 is prodrug of lenacapavir, Gilead's HIV capsid inhibitor. Prodrugs—precursor agents that are converted to an active drug in the body—can improve oral bioavailability, allowing for lower doses and smaller pills.

The WONDERS-1 trial is evaluating a once-weekly oral combination of GS-1720 plus GS-4182 as a switch option for people currently on treatment with viral suppression, while WONDERS-2 is testing the combo for people starting HIV treatment for the first time.

The studies were paused after some participants receiving both drugs experienced decreases in their CD4 T-cell count and absolute lymphocyte count. It is not yet clear which agent is associated with the white blood cell declines. This side effect has not been seen among people using lenacapavir (Sunlenca) for HIV treatment or those receiving it for twice-yearly pre-exposure prophylaxis (PrEP) in large trials.

This is not the first time CD4 and lymphocyte decreases have been seen in studies of long-acting oral antiretrovirals. In 2021, the FDA put a clinical hold on Merck's islatravir, the first nucleoside reverse transcriptase translocation inhibitor, after HIV-positive participants in treatment trials experienced a decline in CD4 counts and HIV-negative volunteers in PrEP studies saw a drop in total lymphocyte counts.

An extensive analysis determined that the islatravir doses used in these trials were too high. The FDA subsequently lifted the hold, and treatment studies resumed using a lower dose. A combination pill containing islatravir and lenacapavir is now being evaluated in the Phase III ISLEND-1 and ISLEND-2 trials.

Likewise, Gilead plans to analyze the adverse events observed in the WONDERS trials with the hope of moving forward with GS-1720 and GS-4182.

“We intend to investigate and pursue the potential of both agents and are committed to working with regulatory authorities to resolve the issues underlying the clinical hold,” the company said in a statement.

“Gilead has multiple other long-acting oral and injectable investigational HIV treatment combinations under evaluation in clinical and preclinical studies, including combinations with weekly, monthly, quarterly and twice-yearly dosing. This hold does not impact these combinations or their respective clinical or preclinical development programs,” the statement continued. “The safety of individuals taking Gilead medicines is our foremost priority and we remain focused on pursuing advances to improve outcomes and expand options for people living with HIV.

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