Gilead Halts Study of Long-Acting Oral Antiretrovirals

WONDERS-2 trial was testing a weekly oral regimen of GS-1720 plus GS-4182 for people starting HIV treatment.

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Gilead Sciences has stopped a clinical trial testing two of its experimental long-acting antiretrovirals, GS-1720 and GS-4182, as a once-weekly oral first-line regimen, while other studies of the two drugs remain on a Food and Drug Administration (FDA) hold due to safety concerns, Fierce Biotech reports.

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

Gilead is terminating the Phase II/III WONDERS-2 trial, which was testing the combination for people starting HIV treatment for the first time; 73 participants had enrolled, according to Fierce. WONDERS-1, evaluating once-weekly GS-1720 plus GS-4182 as a switch option for people currently on treatment with viral suppression, is still paused, as are three Phase I studies.

Last June, the FDA paused trials testing the two investigational drugs alone or in combination after some participants receiving both experienced decreases in their CD4 T-cell count or absolute lymphocyte count. It is not yet clear which drug is associated with the white blood cell declines. This is not a typical side effect of integrase inhibitors, and it has not been seen among people using lenacapavir for HIV treatment (Sunlenca) or for twice-yearly pre-exposure prophylaxis (Yeztugo).

This is not the first time CD4 cell and lymphocyte decreases have derailed studies of long-acting oral antiretrovirals, and it does not necessarily mean this is the end of the line for GS-1720 or GS-4182.

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. But further analysis determined that the islatravir doses used in these trials were too high. The FDA subsequently lifted the hold, treatment studies resumed using a lower dose and a

combination pill containing doravirine and low-dose islatravir (Idvynso) was approved last month.

Fortunately, CD4 and lymphocyte counts have since returned to baseline levels or are within normal ranges for all WONDERS-2 participants. “We continue to work closely with study investigators to ensure a smooth transition for participants to standard of care HIV treatment options,” a Gilead spokesperson told Fierce Biotech.

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