Merck Will Study Lower Dose of Long-Acting Islatravir

The company will resume development of islatravir for HIV treatment but abandons monthly oral PrEP.

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Merck plans to start new clinical trials of a lower dose of its experimental antiretroviral islatravir for HIV treatment, which has been on hold due to unexpected safety concerns. But studies of islatravir for monthly pre-exposure prophylaxis (PrEP) will be discontinued, the company announced this week.

Islatravir (formerly known as MK-8591 or EFdA) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI). It has a long half-life in the body and initially showed promise for both long-acting HIV treatment and prevention.

Islatravir appeared safe and effective as a component of once-daily antiretroviral therapy in combination with Merck's nucleoside reverse transcriptase inhibitor (NNRTI) doravirine (Pifeltro). What's more, it looked promising as a component of once-weekly treatment in combination with Merck's experimental long-acting NNRTI MK-8507 and Gilead Sciences' HIV capsid inhibitor lenacapavir (Sunlenca, which was recently approved in Europe). Islatravir was also being studied for PrEP, both as a once-monthly oral regimen and as an implant, which early studies suggested could provide protection for a year.

But in December 2021, Merck announced that the Food and Drug Administration (FDA) had placed a clinical hold on trials of oral, injectable and implant formulations of islatravir. Trials of islatravir plus doravirine were put on a partial clinical hold (meaning current participants could continue to receive the medication but no new ones would be randomized), while injectable islatravir for treatment and all PrEP studies were put on a full clinical hold (meaning study participants would no longer receive the drug). In addition, Merck and Gilead suspended their study of islatravir plus lenacapavir.

This happened after trial analyses showed that HIV-positive people who received islatravir for treatment experienced declines in their CD4 T-cell counts while HIV-negative people taking islatravir for PrEP showed decreased total lymphocyte counts (lymphocytes include B cells, T cells and natural killer cells). The largest CD4 cell drops were seen in people who received islatravir plus MK-8507 (which has since been discontinued), but declines were also seen in those taking

islatravir plus doravirine or islatravir alone.

“We don’t have a full explanation right now,” Michael Robertson, MD, of Merck Research Laboratories told community representatives during a December 16 briefing. “The CD4 count is concerning, but the overall safety profile has been really excellent, so we don’t want to throw out the baby out with the bathwater.”

Merck scientists conducted extensive analyses to determine the nature of the problem and held discussions with the FDA about the fate of islatravir. This led to a plan to start new Phase III trials using a lower oral dose of islatravir.

One study will evaluate once-daily low-dose islatravir plus doravirine for previously untreated people with HIV, and two trials will test the combination as a switch option for treatment-experienced people with an undetectable viral load. Some participants currently enrolled in islatravir treatment studies will have the option to transition to the lower dose. In addition, Merck and Gilead agreed to resume the Phase II trial of once-weekly oral islatravir plus lenacapavir using the lower dose.

Even if the lower dose proves to be safe, a new once-daily regimen of islatravir plus doravirine would not be a game-changer, as several effective daily options are already available. But a once-weekly oral regimen would be a welcome new option. The current longest-acting regimen, Cabenuva (cabotegravir plus rilpivirine), is taken monthly or every other month, but it involves injections administered by a health care provider.

While treatment studies are moving forward, Merck decided to discontinue the development of once-monthly oral islatravir for PrEP “after careful evaluation and analysis,” as a lower dose may not offer long-lasting protection. The company will soon start a Phase Ib trial of a novel nucleoside reverse transcriptase translocation inhibitor candidate known as MK-8527.

“We continue to believe in the potential of the NRTTI mechanism and we are evaluating additional candidates with the goal of helping to address unmet needs in HIV prevention,” said Eliav Barr, MD, chief medical officer of Merck Research Laboratories.

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