

## Gilead pause adds to Merck's HIV doubts



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### Could Gilead soon be looking for a new partner for its long-acting project lenacapavir?

Last week, Merck & Co managed to shrug off links between its long-acting HIV project islatravir and a decrease in CD4-positive T cells. Now the asset has taken another blow, with Gilead yesterday announcing the pause of a trial of islatravir plus its long-acting contender, lenacapavir.

The group said it made the move out of an “abundance of caution”, but this might not assuage concerns about the future of Merck’s most advanced HIV asset. Indeed, at least one analyst hinted that Gilead might want to look elsewhere for an add-on to lenacapavir.

#### Other options?

Gilead, which [teamed up with Merck in March](#), previously told *Evaluate Vantage* that [all options are on the table](#), including internally developed candidates. However, Evercore ISI’s Umer Raffat, speculating about what Gilead might now pair lenacapavir with, noted that he is not aware of a suitable asset in Gilead’s pipeline.

But Gilead does have time on its side, with its oral once-daily blockbuster Biktarvy not set to lose patent protection until 2033. And right now, Gilead’s HIV woes look much less serious than Merck’s. Islatravir is a new class of HIV drug, a nucleoside reverse transcriptase translocation inhibitor, and the group ultimately hopes it could be used in longer-acting combos – a once-weekly, rather than a once-daily, pill, and even less frequent injections.

Long-acting HIV therapies are the next frontier in the disease, with companies citing compliance and stigma as reasons why patients would want to switch from the current standard of care, daily orals. [Glaxosmithkline has been the pioneer here](#), with its doublet Cabenuva already approved as a once-monthly injection; a two-monthly injection is under FDA review.

However, the sellside remains to be convinced about the sales prospects of these long-acting drugs.

#### CD4 cell count drops

The recent news from Merck will not have helped. On Friday, the company said it had stopped dosing in a [phase 2 study](#) of once-weekly islatravir plus MK-8507, a long-acting non-nucleoside reverse transcriptase inhibitor, after seeing decreases in total lymphocyte and CD4 T-cell counts in patients receiving the combo.

HIV causes a drop in the number of CD4 cells, and one of the goal of therapies is to raise CD4 count, as well as

lowering viral load; a drop in CD4 cells would therefore seem like bad news for the project's efficacy.

Merck seemed to blame MK-8507. The group said the greatest decreases were seen in patients receiving the highest doses of that project, development of which is now paused.

However, a couple of other points raised alarm bells. Merck also disclosed a dose-dependent decrease in lymphocytes in a [phase 2 study](#) testing monthly islatravir alone in pre-exposure prophylaxis (Prep), as well as a "treatment-related" mean decrease in CD4 cells in two phase 3 switching studies, [Illuminate Switch A](#) and [Illuminate Switch B](#), testing a once-daily regimen of islatravir plus doravirine.

Merck said these falls were small, but investors will no doubt look for further details when the pivotal studies, which Merck topline as positive in October, are presented.

Even if islatravir is eventually approved, Mr Raffat mooted a scenario in which patients receiving the drug would need routine CD4 cell monitoring, which would dramatically hit its sales prospects. At present, sellside consensus compiled by *Evaluate Pharma* predicts islatravir revenues of \$784m in 2026.

He also suggested that the path forward for islatravir might be as a mere daily oral, or maybe an implant "with tiny dose released daily". If this comes to pass it would wipe out much of the excitement around the Merck project.

Perhaps Gilead wanted to avoid the possibility of lenacapavir being tarred by the same brush. It seems unlikely that the group has already seen any CD4 cell drops in the combo trial, given that it [only began in October](#).

Maybe things will become clearer in the coming months but, for now, it is advantage Glaxo in the long-acting HIV space.

## Notable trials with Gilead's lenacapavir and Merck's islatravir

Setting	Dosing	Study details	Note
<i>Lenacapavir + islatravir</i>			
HIV treatment	Once-weekly oral	<a href="#">Ph2 in virologically suppressed HIV pts</a>	Enrolment "temporarily paused"
HIV treatment	Once-monthly injectable	TBC	To start 2022
<i>Lenacapavir</i>			
Heavily treatment-experienced pts	Oral lead in then SC every 6 mo	<a href="#">Ph2/3 Capella</a>	Positive data reported, filed with FDA Jun 2021
Treatment-naive HIV pts, combo with oral antiretroviral agents	Oral lead in then SC every 6 mo	<a href="#">Ph2 Calibrate</a>	<a href="#">Data reported Jul 2021</a>
Prep in men/trans/non-binary people who have sex with men	SC every 6 mo	<a href="#">Ph3 Purpose-2</a>	Completes Jan 2024
Prep in young women	SC every 6 mo	<a href="#">Ph3 Purpose-1</a>	Completes Mar 2024
<i>Islatravir</i>			
Plus MK-8507*, switch study vs Biktarvy	Weekly oral	<a href="#">Ph2 Imagine</a>	Enrolment stopped
Plus doravirine, switch study vs baseline regimen	Daily oral	<a href="#">Ph3 Illuminate Switch A</a>	Toplined positive Oct 2021
Plus doravirine, switch study vs Biktarvy	Daily oral	<a href="#">Ph3 Illuminate Switch B</a>	Toplined positive Oct 2021
Plus doravirine* in treatment-naive pts vs Biktarvy	Daily oral	<a href="#">Ph3 Illuminate Naive</a>	Completes Jan 2023
Plus doravirine* in heavily treatment-experienced pts	Daily oral	<a href="#">Ph3 Illuminate HTE</a>	Completes Jul 2024
Prep in men/transgender women who have sex with men vs Truvada/Descovy	Monthly oral	<a href="#">Ph3 3 Impower-024</a>	Completes Jan 2024
Prep in women vs Truvada	Monthly oral	<a href="#">Ph3 Impower-022</a>	Completes Jul 2024
Prep in low-risk people	Yearly implant	<a href="#">Ph2 MK-8591-043</a>	Completes Mar 2024
*Doravirine (Pifeltro) and MK-8507 are non-nucleoside reverse transcriptase inhibitors. Source: Evaluate Pharma, <a href="https://clinicaltrials.gov">clinicaltrials.gov</a> & company releases.			

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