



NEWS RELEASE

# Merck Announces Week 96 Data from Phase 2b Study Evaluating Islatravir in Combination With Doravirine in Adults With HIV-1 Infection

10/8/2020

Treatment With Islatravir and Doravirine Maintained Viral Suppression and No Viral Resistance was Identified

Company Also Presenting Phase 1/1b Results for MK-8507, a New Investigational Once-Weekly Oral HIV Agent; Company Advances MK-8507 to Phase 2

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced Week 96 data from the Phase 2b trial (NCT03272347) evaluating the efficacy and safety of islatravir, the company's investigational oral nucleoside reverse transcriptase translocation inhibitor (NRTTI), in combination with doravirine (PIFELTRO™), in treatment-naïve adults with HIV-1 infection. Week 96 findings demonstrated that the combination of islatravir and doravirine maintained virologic suppression (as measured by the number of study participants achieving HIV-1 RNA levels <50 copies/mL, similar to DELSTRIGO™(doravirine/lamivudine/tenofovir disoproxil fumarate)), and the findings were consistent with Week 48 results. Additional Week 96 data from the study show low rates of participants meeting the definition of protocol-defined virologic failure (PDVF) in both the islatravir plus doravirine and the DELSTRIGO treatment arms, and no participants in either arm met the criteria for resistance testing. Merck also announced results from Phase 1/1b studies for MK-8507, the company's investigational once-weekly oral non-nucleoside reverse transcriptase inhibitor (NNRTI), which showed that the antiviral potency and pharmacokinetics of MK-8507 support further investigation for once-weekly oral administration as part of combination antiretroviral therapy. These analyses were presented as oral and poster presentations at the virtual 2020 International Congress on Drug Therapy in HIV Infection (**HIV**

## Glasgow 2020).

“Our commitment to medical advances in HIV can be seen in the important data we are presenting at HIV Glasgow 2020, including islatravir’s potential for use in combination with doravirine as a once-daily, two-drug treatment. In addition, we are presenting data on MK-8507, which is advancing to Phase 2 investigations in combination with islatravir as a once-weekly oral regimen,” said Dr. Joan Buttrick, vice president, infectious diseases, Global Clinical Development, Merck Research Laboratories. “We continue to pursue new methods for treating HIV, as shown by our growing body of clinical research, and we look forward to sharing new data from our ongoing, global Phase 3 clinical trials for islatravir with doravirine in the future.”

PIFELTRO (doravirine, 100 mg) is indicated in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in adult patients with no prior ARV treatment history or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine.

DELSTRIGO (doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no prior ARV treatment history or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of DELSTRIGO. DELSTRIGO contains a boxed warning regarding post-treatment acute exacerbations of hepatitis B (HBV) infection. See Selected Safety Information below.

## Week 96 Efficacy and Safety Results from Phase 2b Study of Investigational 2-Drug Regimen of Islatravir with Doravirine

In this international, multicenter clinical trial, treatment-naïve adult participants with HIV-1 infection were randomly assigned (1:1:1:1) to one of four once-daily oral treatment groups: islatravir 0.25 mg (n=29), 0.75 mg (n=30), or 2.25 mg (n=31) in combination with doravirine (100 mg) and 3TC (300 mg) compared to DELSTRIGO (n=31). After a minimum of 24 weeks of treatment, participants in the islatravir treatment groups with HIV-1 RNA less than 50 copies/mL who had not met protocol-defined virologic failure (PDVF) criteria were transitioned to a two-drug regimen consisting of the same dose of islatravir plus doravirine (100 mg), without 3TC. At Week 96, at all dose levels, the combination of islatravir and doravirine maintained virologic suppression as measured by the number of study participants achieving HIV-1 RNA levels <50 copies/mL. At Week 96, 86.2% (25/29), 90.0% (27/30), and 67.7% (21/31) of participants maintained HIV-1 RNA <50 copies/mL in the 0.25 mg, 0.75mg, and 2.25 mg islatravir groups, respectively, with 81.1% (73/90) of the combined islatravir groups, as compared to 80.6% (25/31) of the DELSTRIGO group. The numerically lower response rate for the 2.25 mg islatravir group was largely driven by discontinuations through Week 48.

A lower rate of drug-related adverse events (AEs) occurred in the islatravir groups (7.8%) compared with the DELSTRIGO group (22.6%) at Week 96. No additional drug-related serious adverse events were reported in any group between Week 48 and Week 96. Based on these results, the 0.75 mg dose of islatravir will be used for further clinical development.

## Week 96 Protocol-Defined Virologic Failure (PDVF) Analysis from Phase 2b Study of Investigational 2-Drug Regimen of Islatravir with Doravirine

A Week 96 analysis of the study showed rates of PDVF were low, and all participants who discontinued due to PDVF had HIV-1 RNA levels <80 copies/mL, below the clinically significant level of 200 copies/mL. No participants met the criteria for resistance testing (HIV-1 RNA >400 copies/mL). PDVF was defined as rebound with confirmed HIV-1 RNA greater than or equal to 50 copies/mL after suppression or non-response with confirmed HIV-1 RNA greater than or equal to 50 copies/mL.

At Week 96, a total of seven participants met the definition of PDVF and discontinued from the trial. As **previously reported**, at Week 48, PDVF was confirmed in six participants, 5.6% (5/90; 4 rebound, 1 non-response) of the islatravir treatment groups combined and 3.2% (1/31; rebound) of the DELSTRIGO group. Only one additional participant in the 2.25 mg islatravir group discontinued with PDVF (rebound). None of the participants in any treatment group met criteria for resistance testing as all confirmed HIV-1 RNA for participants that met the definition of PDVF were <80 copies/mL. During the 42-day follow-up period, three out of seven participants who discontinued due to PDVF continued to have low-level viremia after switching to a new regimen.

## Week 96 Renal Safety Analysis from Phase 2b Study of Investigational 2-Drug Regimen of Islatravir with Doravirine

A Week 96 exploratory analysis showed no renal safety concerns. Serum creatinine was measured at each study visit, including Day 1, Week 48, and Week 96. Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) formula.

Median changes in serum creatinine and eGFR were minimal in all treatment groups at Week 48 and Week 96. Two participants in the 0.25 mg islatravir group had isolated instances of  $\geq 0.5$  mg/dL increase from baseline in serum creatinine that resolved by the next study visit: at Week 16 (1.7 mg/dL) in one participant; at Week 60 (1.7 mg/dL) and Week 84 (1.9 mg/dL) in the other. No participants had  $\geq 1.0$  mg/dL increase or doubling of serum creatinine. eGFR reductions greater than 30% from baseline occurred in 12% (11/90) of islatravir-treated participants and 16% (5/31) of DELSTRIGO-treated participants and were transient in most cases. eGFR <60 mL/min/1.73 m<sup>2</sup> occurred in 4% (4/90) of islatravir-treated participants and were transient in three (the fourth had eGFR <60 mL/min/1.73 m<sup>2</sup>

from baseline through Week 96). No clinically meaningful changes were observed in renal biomarkers, including urine albumin, albumin/creatinine ratio, beta-2 microglobulin/creatinine ratio, or retinol-binding protein/creatinine ratio. No dose-response relationship was observed for renal effects of islatravir in combination with doravirine, and no participant discontinued treatment due to a renal adverse event.

## Phase 1/1b Results for MK-8507

Two randomized, double-blind, placebo-controlled Phase 1 clinical trials were conducted to evaluate the safety, tolerability and pharmacokinetics of single and multiple oral doses of MK-8507 and potential for drug-drug interaction with midazolam, a CYP3A substrate, in healthy adult participants. In Study 1, participants (n=16 males) received single doses of MK-8507 or placebo from 2 mg to 400 mg. In Study 2, participants (n=24 males and females) received single doses of MK-8507 or placebo from 400 mg to 1200 mg, and multiple doses of MK-8507 or placebo (once-weekly for three weeks) from 100 mg to 400 mg. At the 400 mg once-weekly dose level, participants also received 2 mg of midazolam prior to MK-8507 dosing and co-administered with the third once-weekly dose.

The pharmacokinetics of MK-8507 support once-weekly administration for the treatment of HIV-1 infection. MK-8507 had a T<sub>max</sub> (time to maximum concentration) of two to seven hours and a mean terminal half-life (t<sub>1/2</sub>) of approximately 58-84 hours. Pharmacokinetics were approximately dose-proportional from 2 mg to 1200 mg. Adverse events reported for MK-8507 were non-serious and mild in intensity. There were no trends in vital signs, electrocardiograms or safety laboratory tests. The most common adverse events were headache, cough, and rhinorrhea.

A Phase 1b open-label, proof of concept study was also conducted to evaluate the antiviral efficacy, pharmacokinetics, safety, and tolerability of single doses of 40 mg, 80 mg, and 600 mg of MK-8507 over seven to 14 days in 18 HIV-1 infected, antiretroviral-naïve adult males (six participants per dosing arm). Single doses of MK-8507 resulted in a reduction in viral load at seven days, comparable to other NNRTIs dosed daily for the same timeframe. At seven days post-dose, a mean (95% CI) viral load reduction of 1.22 (1.52, 0.91) log<sub>10</sub> copies/mL at 40 mg, 1.50 (1.80, 1.19) log<sub>10</sub> copies/mL at 80 mg, and 1.53 (1.84, 1.23) log<sub>10</sub> copies/mL at 600 mg was observed among participants. The pharmacokinetics were similar to that observed in uninfected participants, with mean concentrations at seven days post-dose of 78.1, 214, and 1400 nM at the 40, 80 and 600 mg doses, respectively. Beginning at day 10, following a 600 mg dose, one participant experienced viral rebound with F227C, a NNRTI-associated resistant variant. All doses showed low rates of adverse events, and the most common adverse events (AEs) were nasopharyngitis (n=3) and headache (n=3). One serious AE of diffuse large B-cell lymphoma, not considered to be related to study drug, was reported.

The antiviral potency and human pharmacokinetics of MK-8507 are favorable to advancing MK-8507 to Phase 2 studies of once-weekly administration as part of combination antiretroviral therapy.

## Selected Safety Information about PIFELTRO and DELSTRIGO

### Warning: Posttreatment Acute Exacerbation of Hepatitis B (HBV)

All patients with HIV-1 should be tested for the presence of HBV before initiating ARV therapy. Severe acute exacerbations of HBV have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued products containing lamivudine or tenofovir disoproxil fumarate (TDF), which are components of DELSTRIGO. Patients coinfecting with HIV-1 and HBV who discontinue DELSTRIGO should be monitored with both clinical and laboratory follow-up for at least several months after stopping DELSTRIGO. If appropriate, initiation of anti-HBV therapy may be warranted.

PIFELTRO and DELSTRIGO are contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers (including the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the androgen receptor inhibitor enzalutamide; the antimycobacterials rifampin and rifapentine; the cytotoxic agent mitotane; and the herbal product St. John's wort (*Hypericum perforatum*)), as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO and PIFELTRO.

DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine.

Renal impairment, including cases of acute renal failure and Fanconi syndrome, have been reported with the use of TDF. DELSTRIGO should be avoided with concurrent or recent use of a nephrotoxic agent (eg, high-dose or multiple NSAIDs). Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in patients with risk factors for renal dysfunction who appeared stable on TDF.

Prior to or when initiating DELSTRIGO, and during treatment, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue DELSTRIGO in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Discontinue DELSTRIGO if estimated creatinine clearance declines below 50 mL/min.

In clinical trials in HIV-1 infected adults, TDF was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher. Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.

Immune reconstitution syndrome can occur, including the occurrence of autoimmune disorders with variable time

to onset, which may necessitate further evaluation and treatment.

Because DELSTRIGO is a complete regimen, co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.

Co-administration of PIFELTRO with efavirenz, etravirine, or nevirapine is not recommended.

If DELSTRIGO is co-administered with rifabutin, take one tablet of DELSTRIGO once daily, followed by one tablet of doravirine (PIFELTRO) approximately 12 hours after the dose of DELSTRIGO.

If PIFELTRO is co-administered with rifabutin, increase PIFELTRO dosage to one tablet twice daily (approximately 12 hours apart).

Consult the full Prescribing Information prior to and during treatment for more information on potential drug-drug interactions.

Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and TDF cannot be adjusted, DELSTRIGO is not recommended in patients with estimated creatinine clearance less than 50 mL/min.

The most common adverse reactions with DELSTRIGO (incidence  $\geq 5\%$ , all intensities) were dizziness (7%), nausea (5%), and abnormal dreams (5%). The most common adverse reactions with PIFELTRO (incidence  $\geq 5\%$ , all intensities) were nausea (7%), dizziness (7%), headache (6%), fatigue (6%), diarrhea (6%), abdominal pain (5%), and abnormal dreams (5%).

By Week 96 in DRIVE-FORWARD, 2% of adult subjects in the PIFELTRO group and 3% in the DRV+r group had adverse events leading to discontinuation of study medication.

By Week 96 in DRIVE-AHEAD, 3% of adult subjects in the DELSTRIGO group and 7% in the EFV/FTC/TDF group had adverse events leading to discontinuation of study medication.

In DRIVE-FORWARD, mean changes from baseline at Week 48 in LDL-cholesterol (LDL-C) and non-HDL-cholesterol (non-HDL-C) were pre-specified. LDL-C: -4.6 mg/dL in the PIFELTRO group vs 9.5 mg/dL in the DRV+r group. Non-HDL-C: -5.4 mg/dL in the PIFELTRO group vs 13.7 mg/dL in the DRV+r group. The clinical benefits of these findings have not been demonstrated.

In DRIVE-AHEAD, mean changes from baseline at Week 48 in LDL-cholesterol (LDL-C) and non-HDL-cholesterol (non-HDL-C) were pre-specified. LDL-C: -2.1 mg/dL in the DELSTRIGO group vs 8.3 mg/dL in the EFV/FTC/TDF group. Non-HDL-C: -4.1 mg/dL in the DELSTRIGO group vs 12.7 mg/dL in the EFV/FTC/TDF group. The clinical benefits of these

findings have not been demonstrated.

In DRIVE-SHIFT, mean changes from baseline at Week 48 in LDL-cholesterol (LDL-C) and non-HDL-cholesterol (non-HDL-C) were pre-specified. LDL-C: -16.3 mg/dL in the DELSTRIGO group vs -2.6 mg/dL in the PI + ritonavir group. Non-HDL-C: -24.8 mg/dL DELSTRIGO group vs -2.1 mg/dL in the PI + ritonavir group. The clinical benefits of these findings have not been demonstrated.

In DRIVE-AHEAD, neuropsychiatric adverse events were reported in the three pre-specified categories of sleep disorders and disturbances, dizziness, and altered sensorium. Twelve percent of adult subjects in the DELSTRIGO group and 26% in the EFV/FTC/TDF group reported neuropsychiatric adverse events of sleep disorders and disturbances; 9% in the DELSTRIGO group and 37% in the EFV/FTC/TDF group reported dizziness; and 4% in the DELSTRIGO group and 8% in the EFV/FTC/TDF group reported altered sensorium.

The safety of DELSTRIGO in virologically-suppressed adults was based on Week 48 data from subjects in the DRIVE-SHIFT trial. Overall, the safety profile in virologically-suppressed adult subjects was similar to that in subjects with no ARV treatment history.

**Serum ALT and AST Elevations:** In the DRIVE-SHIFT trial, 22% and 16% of subjects in the immediate switch group experienced ALT and AST elevations greater than 1.25 X ULN, respectively, through 48 weeks on DELSTRIGO. For these ALT and AST elevations, no apparent patterns with regard to time to onset relative to switch were observed. One percent of subjects had ALT or AST elevations greater than 5 X ULN through 48 weeks on DELSTRIGO. The ALT and AST elevations were generally asymptomatic, and not associated with bilirubin elevations. In comparison, 4% and 4% of subjects in the delayed switch group experienced ALT and AST elevations of greater than 1.25 X ULN through 24 weeks on their baseline regimen.

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to PIFELTRO or DELSTRIGO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Mothers infected with HIV-1 should be instructed not to breastfeed if they are receiving PIFELTRO or DELSTRIGO due to the potential for HIV-1 transmission.

## **About Islatravir (MK-8591)**

Islatravir (formerly MK-8591) is Merck's investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI) currently being evaluated in clinical trials for the treatment of HIV-1 infection in combination with other antiretrovirals, as well as for pre-exposure prophylaxis (PrEP) of HIV-1 infection as a single investigational agent,

across a variety of formulations.

## Our Commitment to HIV

For more than 30 years, Merck has been committed to scientific research and discovery in HIV, and we continue to be driven by the conviction that more medical advances are still to come. Our focus is on pursuing research that addresses unmet medical needs and helps people living with HIV and their communities. We remain committed to working hand-in-hand with our partners in the global HIV community to address the complex challenges that hinder continued progress.

## Our Commitment to Infectious Diseases

For more than 100 years, Merck has contributed to the discovery and development of novel medicines and vaccines to combat infectious diseases. In addition to a combined portfolio of vaccines and antibacterial, antiviral and antifungal medicines, Merck has multiple programs that span discovery through late-stage development. To learn more about Merck's infectious diseases pipeline, visit [www.merck.com](http://www.merck.com).

## About Merck

For more than 125 years, Merck, known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit [www.merck.com](http://www.merck.com) and connect with us on [Twitter](#), [Facebook](#), [Instagram](#), [YouTube](#) and [LinkedIn](#).

## Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.



Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of the global outbreak of novel coronavirus disease (COVID-19); the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2019 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (<https://www.sec.gov/>).

Please see Prescribing Information for PIFELTRO (doravirine) at:

[https://www.merck.com/product/usa/pi\\_circulars/p/pifeltro/pifeltro\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/p/pifeltro/pifeltro_pi.pdf); and Patient Information for PIFELTRO (doravirine) at:

[https://www.merck.com/product/usa/pi\\_circulars/p/pifeltro/pifeltro\\_ppi.pdf](https://www.merck.com/product/usa/pi_circulars/p/pifeltro/pifeltro_ppi.pdf)

Please see Prescribing Information for DELSTRIGO (doravirine/3TC/TDF) at:

[https://www.merck.com/product/usa/pi\\_circulars/d/delstrigo/delstrigo\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/d/delstrigo/delstrigo_pi.pdf) and Patient Information for DELSTRIGO (doravirine/3TC/TDF) at:

[https://www.merck.com/product/usa/pi\\_circulars/d/delstrigo/delstrigo\\_ppi.pdf](https://www.merck.com/product/usa/pi_circulars/d/delstrigo/delstrigo_ppi.pdf)

View source version on [businesswire.com](https://www.businesswire.com): <https://www.businesswire.com/news/home/20201008005263/en/>

Media:

Pamela Eisele

(267) 305-3558

Sarra S. Herzog

(201) 669-6570

Investors:

Peter Dannenbaum  
(908) 740-1037

Michael DeCarbo  
(908) 740-1807

Source: Merck & Co., Inc.