NEWS RELEASE

Merck Announces Topline Results from Pivotal Phase 3 Trials Evaluating Investigational, Once-Daily, Oral, Two-Drug, Single-Tablet Regimen of Doravirine/Islatravir (DOR/ISL) for the Treatment of Adults with Virologically Suppressed HIV-1 Infection

2024-12-19

Trials met efficacy success criteria for non-inferiority of DOR/ISL to comparator antiretroviral therapies in adults with virologically suppressed HIV-1

Safety profiles were generally comparable between DOR/ISL and other therapies in these trials

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced topline results from two pivotal Phase 3 trials of the investigational, once-daily, oral, two-drug, single-tablet regimen of doravirine/islatravir [DOR/ISL (100 mg/0.25 mg)] in adults with HIV-1 infection that is virologically suppressed on different antiretroviral therapy regimens [baseline antiretroviral therapy (bART)]; **MK-8591A-051** or bictegravir/emtricitabine/tenofovir alafenamidei [BIC/FTC/TAF (50 mg/200 mg/25 mg)]; **MK-8591A-052**.

The success criterion for the primary efficacy hypothesis, as measured by the percentage of participants with HIV-1 RNA levels ≥50 copies/mL at Week 48, was met in both trials. DOR/ISL was demonstrated to be non-inferior to bART in open-label trial MK-8591A-051 and non-inferior to BIC/FTC/TAF in double-blind trial MK-8591A-052. The superiority criteria were not met in trial MK-8591A-052. Primary safety objectives of both trials were also met.

The company is planning to present detailed findings from these trials at a future scientific congress and will also plan to file these data with regulatory authorities. In the U.S., doravirine is approved for the treatment of adults with HIV-1 in combination with other antiretrovirals, as a single agent (PIFELTRO) and a component of a single-tablet regimen [DELSTRIGO; doravirine, lamivudine, and tenofovir disoproxil fumarate (DOR/3TC/TDF)].

“We are encouraged by the results from these Phase 3 trials evaluating a once-daily, oral, two-drug, single-tablet regimen of doravirine and islatravir,” said Dr. Eliav Barr, senior vice president, head of global clinical development and chief medical officer, Merck Research Laboratories. “We are committed to advancing our clinical programs for islatravir in combination with other antiretrovirals as potential options to help address the needs of people living with HIV.”

Islatravir (MK-8591), Merck’s investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI), exhibits both transcriptase and translocation inhibition (which prevents nucleotide binding and incorporation to the DNA chain, resulting in immediate chain termination) and delayed chain termination (which prevents nucleotide incorporation even in the event of translocation). Islatravir is being evaluated in multiple early and late-stage clinical trials in combination with other antiretroviral therapies for the treatment of HIV-1. In addition to the MK-8591A-051 and MK-8591A-052 trials, ongoing Phase 3 trials of DOR/ISL include **MK-8591A-053** in people with HIV who had not previously received treatment (treatment-naïve), and **MK-8591A-054** evaluating open-label DOR/ISL (100 mg/0.25 mg) in individuals who participated in earlier Phase 3 trials of DOR/ISL (100 mg/0.75 mg).

About MK-8591A-051 (**NCT05631093**)

MK-8591A-051 is a Phase 3, randomized, active-controlled, open-label clinical trial evaluating a switch to investigational, oral, once-daily DOR/ISL (100 mg/0.25 mg) in adults with HIV-1 infection that has been virologically suppressed using ART. Participants (n=551) were randomized 2:1 to either switch to investigational DOR/ISL or continue with their current bART regimen through Week 48. After Week 48, all participants receive DOR/ISL through Week 144 of the trial. After Week 144, eligible participants may continue on DOR/ISL and continue trial treatment until Week 240 or when DOR/ISL becomes commercially accessible (whichever comes first). The primary efficacy (percentage of participants with HIV-1 RNA levels ≥50 copies/mL) and safety (number of participants experiencing adverse events (AEs) and discontinuing trial intervention due to AEs) endpoints were assessed at Week 48.

About MK-8591A-052 (**NCT05630755**)

MK-8591A-052 is a Phase 3, randomized, active-controlled, double-blind clinical trial evaluating a switch to investigational, oral, once-daily DOR/ISL (100mg /0.25mg) in adults with HIV-1 infection that has been virologically suppressed using BIC/FTC/TAF (50 mg/200 mg/25 mg). Participants (n=513) were randomized 2:1 to either switch to

DOR/ISL or continue on BIC/FTC/TAF through Week 144. After Week 144, eligible participants may continue on DOR/ISL and continue trial treatment until Week 240 or when DOR/ISL becomes commercially accessible (whichever comes first). The primary efficacy (percentage of participants with HIV-1 RNA levels ≥50 copies/mL) and safety (number of participants experiencing AEs and discontinuing trial intervention due to AEs) endpoints were assessed at Week 48.

Indications and usage for PIFELTRO and DELSTRIGO in the U.S.

PIFELTRO 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 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.

Selected Safety Information

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 people with concomitant HIV-1 and HBV who have discontinued products containing lamivudine or tenofovir disoproxil fumarate (TDF), which are components of DELSTRIGO. Patients coinfected 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.

Contraindications

PIFELTRO and DELSTRIGO are contraindicated when coadministered 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.

Warnings and Precautions

Severe Skin Reactions

Severe skin reactions, including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), have been reported during the postmarketing experience with doravirine-containing regimens. Discontinue PIFELTRO or DELSTRIGO, and other medications known to be associated with severe skin reactions, immediately if a painful rash with mucosal involvement or a progressive severe rash develops. Clinical status should be closely monitored, and appropriate therapy should be initiated.

New or Worsening Renal Impairment

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 people living with HIV 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.

Bone Loss and Mineralization Defects

In clinical trials in adults living with HIV, 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

Immune reconstitution syndrome can occur, including the occurrence of autoimmune disorders with variable time to onset, which may necessitate further evaluation and treatment.

Drug Interactions

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

Coadministration of PIFELTRO with efavirenz, etravirine, or nevirapine is not recommended.

If DELSTRIGO is coadministered 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 coadministered 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.

Dosage and Administration/Specific Populations

Renal Impairment

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.

Adverse Reactions

The most common adverse reactions with DELSTRIGO (incidence ≥5%, all intensities) were dizziness (7%), nausea (5%), and abnormal dreams (5%). The most common adverse reactions with PIFELTRO (incidence ≥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 participants in the PIFELTRO group and 3% in the darunavir+ritonavir (DRV+r) group had adverse events leading to discontinuation of study medication.

By week 96 in DRIVE-AHEAD, 3% of adult participants in the DELSTRIGO group and 7% in the efavirenz (EFV)/emtricitabine (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-C and 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 24 in LDL-C and 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 in the 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 participants 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 participants in the DRIVE-SHIFT trial. Overall, the safety profile in virologically-suppressed adult participants was similar to that in participants with no ARV treatment history.

Serum ALT and AST Elevations: In the DRIVE-SHIFT trial, 22% and 16% of participants 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 participants 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 participants in the delayed switch group experienced ALT and AST elevations of greater than 1.25 X ULN through 24 weeks on their baseline regimen.

Pregnancy/Breastfeeding

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.

Inform individuals with HIV-1 infection of the potential risks of breastfeeding, including: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) serious adverse reactions

in a breastfed infant similar to those seen in adults.

About Islatravir (MK-8591) and Merck's HIV Research

Islatravir (MK-8591) is Merck's investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI) under evaluation in multiple ongoing early and late-stage clinical studies in combination with other antiretrovirals for the treatment of HIV-1. Studies with islatravir are designed to offer different dosing options as potential daily and once-weekly treatments. For an overview of Merck's HIV treatment and prevention clinical development program, please click **here**.

Merck's Commitment to HIV

For more than 35 years, Merck has been committed to scientific research and discovery in HIV leading to scientific breakthroughs that have helped change HIV treatment. Our work has been pioneering in the development of new options across multiple drug classes to help those impacted by HIV. Today, we are developing a series of antiviral options designed to help people manage HIV and protect people from HIV, with the goal of reducing the growing burden of infection worldwide. We want to ensure people are not defined by HIV and our work focuses on transformational innovations, collaborations with others in the global HIV community, and access initiatives aimed at the goal of helping to end the HIV epidemic for everyone.

About Merck

At Merck, known as MSD outside of the United States and Canada, we are unified around our purpose: We use the power of leading-edge science to save and improve lives around the world. For more than 130 years, we have brought hope to humanity through the development of important medicines and vaccines. We aspire to be the premier research-intensive biopharmaceutical company in the world – and today, we are at the forefront of research to deliver innovative health solutions that advance the prevention and treatment of diseases in people and animals. We foster a diverse and inclusive global workforce and operate responsibly every day to enable a safe, sustainable and healthy future for all people and communities. For more information, visit **www.merck.com** and connect with us on **X (formerly Twitter)**, **Facebook**, **Instagram**, **YouTube** and **LinkedIn**.

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

This news release of Merck & Co., Inc., Rahway, 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 candidates that the

candidates 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 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 Annual Report on Form 10-K for the year ended December 31, 2023, and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (**www.sec.gov**).

Please see Prescribing Information for PIFELTRO (doravirine) at:

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

Please see Prescribing Information for DELSTRIGO (doravirine, lamivudine, and tenofovir disoproxil fumarate) at:
https://www.merck.com/product/usa/pi_circulars/d/delstrigo/delstrigo_pi.pdf and Patient Information for DELSTRIGO (doravirine, lamivudine, and tenofovir disoproxil fumarate)
https://www.merck.com/product/usa/pi_circulars/d/delstrigo/delstrigo_ppi.pdf

i bictegravir/emtricitabine/tenofovir alafenamide (BIKTARVY) is a registered trademark of Gilead Sciences, Inc.

Media Contacts:

Julie Cunningham
(617) 519-6264

Deb Wambold
(215) 779-2234

Investor Contacts:

Peter Dannenbaum
(732) 594-1579

Steven Graziano
(732) 594-1583

Source: Merck & Co., Inc.