NEWS RELEASE

Merck Announces New Data from Phase 3 Trials Evaluating the Investigational, Once-Daily, Oral, Two-Drug Regimen of Doravirine/Islatravir (DOR/ISL) in Adults with Virologically Suppressed HIV-1 Infection

2025-10-15

DOR/ISL data presented show minimal changes in weight and body composition and no clinically meaningful effect on fasting lipids and the homeostatic model assessment of insulin resistance (HOMA-IR) across clinical trials

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, announced today the presentation of additional data from the Phase 3 studies of the investigational, once-daily, oral, two-drug regimen of doravirine/islatravir [DOR/ISL (100mg/0.25mg)] in adults with HIV-1 infection that was virologically suppressed on bictegravir/emtricitabine/tenofovir alafenamidei [BIC/FTC/TAF (50 mg/200 mg/25 mg)] in trial **MK-8591A-052** or antiretroviral therapy [baseline antiretroviral therapy (bART)] in trial **MK-8591A-051**. These additional findings will be shared at the 20th European AIDS Conference being held in Paris and follow positive **Phase 3 data** presented at CROI 2025, which showed that the investigational two-drug regimen of DOR/ISL maintained viral suppression and demonstrated non-inferiority to the three-drug regimen BIC/FTC/TAF in MK-8591A-052 and baseline ART in MK-8591A-051, with no observed treatment-emergent resistance to DOR or ISL.

In trial MK-8591A-052, adults living with virally suppressed HIV-1 infection who switched to DOR/ISL from BIC/FTC/TAF showed minimal changes in weight and body composition at Week 48 (exploratory endpoints). These changes were comparable to trial participants who continued BIC/FTC/TAF.

In both trials, adults who switched to DOR/ISL from their current regimen (BIC/FTC/TAF or bART) saw no clinically

meaningful changes in fasting lipids (exploratory endpoint in MK-8591A-052; secondary endpoint in MK-8591A-051) or in the homeostatic model assessment of insulin resistance (HOMA-IR) (exploratory endpoints). These changes were comparable to trial participants who continued on their respective prior antiretroviral therapy, BIC/FTC/TAF or bART. Participants who entered the trials on lipid-lowering therapy were excluded from the fasting lipids analysis. The percentage of participants who modified or initiated lipid-lowering therapy during the study was comparable across the treatment groups.

“Weight and body composition are often central concerns for people living with HIV, who may face obesity and other weight-related issues,” said Dr. Chloe Orkin, dean for healthcare transformation, Queen Mary University of London. “The Week 48 results from the Phase 3 DOR/ISL trial (MK-8491A-052) are important to consider because they show minimal and similar changes in weight and body composition from baseline when participants switched to DOR/ISL.”

“Comorbid conditions play an important role in the overall care for people living with HIV. Shifts in weight, body composition and lipids can increase the risk of cardiovascular disease and complicate management of other chronic illnesses,” said Dr. Eliav Barr, senior vice president and chief medical officer, Merck Research Laboratories. “We are pleased that these data show that switching to DOR/ISL had minimal impact on weight and body composition and no clinically meaningful impact on fasting lipids in adults with virologically suppressed HIV-1 infection who switched from their current antiretroviral therapy.”

In the double-blind trial MK-8591A-052, results for changes in weight and body composition showed that both the mean change and mean percent change in weight from baseline at Week 48 were minimal and similar in both treatment groups (exploratory endpoint): the mean weight change from baseline for the DOR/ISL treatment group was -0.03 kg (95% CI: -0.54, 0.48) vs. +0.28 kg (95% CI: -0.32, 0.88) for the BIC/FTC/TAF group, and the mean percentage weight change from baseline was 0.10% (95% CI: -0.50, 0.69) for DOR/ISL (n=316), compared to 0.39% (95% CI: -0.31, 1.09) for BIC/FTC/TAF (n=163). At Week 48, 14.6% and 3.5% of participants who switched to DOR/ISL experienced a ≥5% and ≥10% weight gain from baseline, respectively, compared with 16.0% and 2.5% of participants who continued BIC/FTC/TAF. Additionally, mean percent changes in lean body mass, peripheral fat and trunk fat and mean changes in body mass index and waist-to-hip ratio were small and comparable between the two treatment groups.

Across both trials (MK-8591A-052 and MK-8591A-051), the pooled DOR/ISL group’s mean changes from baseline in fasting lipids, including total cholesterol, HDL, LDL and triglycerides were minimal, with no substantial differences from comparator groups (exploratory endpoint in MK-8591A-052; secondary endpoint in MK-8591A-051). Mean changes in fasting insulin, glucose and HOMA-IR were minimal across groups (exploratory endpoints). The proportion of participants with type 2 diabetes who modified their diabetic medication was <5% across treatment

groups. A comparable proportion of participants initiated lipid-lowering therapy (pooled DOR/ISL 4.8%, BIC/FTC/TAF 4.1%, bART 5.9%) across the two trials.

Earlier this year, the U.S. Food and Drug Administration (FDA) **accepted** the New Drug Application (NDA) for DOR/ISL and has set a target action date of April 28, 2026, for the application under the Prescription Drug User Fee Act (PDUFA).

About the Phase 3 trial MK-8591A-052

MK-8591A-052 is a Phase 3, double-blind, randomized, active-controlled clinical trial to evaluate the efficacy and safety of a switch to investigational, oral, once-daily DOR/ISL (100mg/0.25mg) in adults with HIV-1 infection that has been virologically suppressed on BIC/FTC/TAF (50mg/200mg/25mg). The primary efficacy endpoint was the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 (non-inferiority margin 4%). In this trial, 513 adults with HIV-1 who had virologic suppression for three months or more on BIC/FTC/TAF, no history of treatment failure and no known resistance to DOR were randomized (2:1) and switched to DOR/ISL (n=342) or continued treatment with BIC/FTC/TAF (n=171). The median age of participants was 47 years; 21.4% were assigned female sex at birth, 30.8% were Black or African American, and 22.8% were Hispanic or Latine. The median duration of BIC/FTC/TAF treatment prior to trial enrollment was 3.4 years (IQR 2.0-5.0).

At Week 48, the mean percent change in total lymphocyte and CD4 counts were similar for DOR/ISL and BIC/FTC/TAF. There were identical rates of discontinuation for protocol-specified decreases in total lymphocyte and/or CD4 counts (two participants (0.6%) in the DOR/ISL group and one participant (0.6%) in the BIC/FTC/TAF group).

Drug-related adverse events (AEs) and discontinuations due to drug-related AEs were similar between groups (n=35, 10.2% for DOR/ISL and n=16, 9.4% for BIC/FTC/TAF; n=4, 1.2% for DOR/ISL and n=2, 1.2% for BIC/FTC/TAF, respectively). Rates of toxicity grade 3 or 4 AEs and serious AEs were similar for DOR/ISL and BIC/FTC/TAF (n=25, 7.3% for DOR/ISL and n=13, 7.6% for BIC/FTC/TAF; n=15, 4.4% for DOR/ISL and n=11, 6.4% for BIC/FTC/TAF, respectively). The most common AEs (>6% in either study arm) were arthralgia, COVID-19, nasopharyngitis, and fatigue. One participant on DOR/ISL discontinued due to a drug-related serious AE (immune thrombocytopenia). There were two cases of low-level hepatitis B (HBV) viremia (HBV DNA <50 IU/mL) with no antigenemia or elevated transaminases in the DOR/ISL group and no cases in the BIC/FTC/TAF group; there were no cases of clinical HBV reactivation.

About the Phase 3 Trial MK-8591A-051

MK-8591A-051 is a Phase 3, open-label, randomized, active-controlled clinical trial evaluating the efficacy and safety

of a switch to investigational, oral, once-daily DOR/ISL (100mg/0.25mg) in adults with HIV-1 infection that have been virologically suppressed using bART. The primary efficacy endpoint was the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 (non-inferiority margin 4%). In this trial, 551 adults with HIV-1 RNA <50 copies/mL for three months or more on oral 2- or 3-drug ART, with no history of treatment failure and no known virologic resistance to DOR, were randomized 2:1 and switched to DOR/ISL (n=366) or continued bART (n=185), stratified by bART regimen. The median age of participants was 51 years; 39.7% were assigned female sex at birth, 45.4% were Black or African American, and 14.5% were Hispanic or Latine. At baseline, 64.2% were treated with an InSTI-based regimen, 30.3% with an NNRTI-based regimen, and 5.4% with a protease inhibitor (PI)-based regimen, with median duration on current ART of 3.8 years (IQR 2.0-6.3).

At Week 48, the mean percent change in total lymphocyte and CD4 counts were similar for DOR/ISL and bART. No participants discontinued treatment due to decrease in total lymphocyte and/or CD4 counts.

In this open-label study, drug-related AEs were more commonly reported with DOR/ISL (n=44; 12.0%) than bART (n=9; 4.9%). Rates of toxicity grade 3 or 4 AEs and serious AEs were similar for DOR/ISL and bART (n=39, 10.7% for DOR/ISL and n=18, 9.7% for bART and n=23, 6.3% for DOR/ISL and n=9, 4.9% for bART, respectively). There were no drug-related serious AEs and there were no discontinuations due to serious AEs in the DOR/ISL group; there was one drug-related serious AE and two discontinuations due to serious AEs in the bART group. The most common drug-related AEs were diarrhea (DOR/ISL 3.3%, bART 0%), fatigue (1.9%, 0.5%), dizziness (1.9%, 0.5%), abdominal distention (1.6%, 0%), weight increased (1.6%, 0%), and headache (1.6%, 1.1%).

There was one case of low-level HBV viremia with no antigenemia or elevated transaminases in the DOR/ISL group and no cases in the bART group; there were no cases of clinical HBV reactivation.

About islatravir (MK-8591) and Merck's HIV research

Islatravir (MK-8591), Merck's investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI), blocks HIV-1 replication by multiple mechanisms including inhibition of reverse transcriptase translocation, resulting in immediate chain termination and induction of structural changes in the viral DNA, resulting in delayed chain termination. Islatravir is under evaluation in multiple ongoing early and late-stage clinical trials in combination with other antiretrovirals for potential daily and once-weekly treatments for HIV-1, with islatravir serving as the anchor medicine in the treatment regimens based on its potency and resistance profile. In addition to the MK-8591A-051 and MK-8591A-052 trials, ongoing Phase 3 trials of daily DOR/ISL (100mg /0.25mg) 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). Islatravir in combination with Gilead's lenacapavir is in Phase 3 development as a novel oral once-weekly treatment for HIV-1(**NCT05052996**), and islatravir in combination with our company's investigational non-nucleoside reverse

transcriptase inhibitor (NNRTI) ulonivirine (MK-8507) is in Phase 2b development (**MK-8591B-060**) as an oral once-weekly treatment. Merck's commitment to researching NRTTIs includes MK-8527, an investigational, novel oral, once-monthly NRTTI candidate that is in Phase 3 development for HIV-1 pre-exposure prophylaxis (PrEP). 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 helped pioneer 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 their HIV and to help prevent 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 helping to end the HIV epidemic for everyone.

Indications and usage for PIFELTRO® (doravirine) and DELSTRIGO® (doravirine, lamivudine, and tenofovir disoproxil fumarate) 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 Virus (HBV) for DELSTRIGO

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. The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in adults are unknown.

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 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, 2024 and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (**www.sec.gov**).

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