*Clinical Drug Investigation*

**SUPPLEMENTARY INFORMATION**

# Clinical Pharmacokinetics of the Novel HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitor Doravirine: An Assessment of the Effect of Patient Characteristics and Drug–Drug Interactions

Sauzanne Khalilieh[1]*, Ka Lai Yee[1]*, Rosa Sanchez[1], S. Aubrey Stoch[1], Larissa Wenning[1], and Marian Iwamoto[1]

**These authors contributed equally*

[1]*Merck & Co., Inc., Kenilworth, New Jersey, USA*

**Corresponding author:** Sauzanne Khalilieh; Merck & Co., Inc., 2000 Galloping Hill Road, Kenilworth, New Jersey 07033, USA; tel: +1 908 740 7461; email: sauzanne.khalilieh@merck.com

**Table S1.** Summary of trials included in this review

| Factor/concomitant medication under investigation | Trial number [reference] | Trial design and description | Treatment | Enrolled/completed (male/female) |
|---|---|---|---|---|
| **Phase I trials in healthy participants** | | | | |
| Age/gender | MK-1439-009 [22] | • Relative bioavailability study to compare the pharmacokinetics of doravirine in male and female subjects and healthy elderly and young subjects<br>• Open-label, one-period, parallel-group | • 100 mg doravirine SD | 36/36<br>(12/24)<br><br>(elderly male, *n* = 12; elderly female, *n* = 12; young female, *n* = 12) |
| Hepatic impairment | MK-1439-019 [25] | • Influence of hepatic insufficiency on the pharmacokinetics of doravirine<br>• Two-part, open-label | • Part 1: 100 mg doravirine SD<br>• Part 2: Not conducted | 16/16<br>(12/4)<br><br>(moderate hepatic insufficient, *n* = 8; healthy control, *n* = 8) |
| Renal impairment | MK-1439-051 [24] | • Evaluation of the pharmacokinetics of doravirine in subjects with severe renal impairment<br>• Open label, parallel assignment | • 100 mg doravirine SD | 16/16<br>(11/5)<br><br>(severe renal impairment, *n* = 8; healthy control, *n* = 8) |
| Food | MK-1439-037 [23] | • Comparative fed and fasted bioavailability of doravirine<br>• Open-label, randomized, two-period, crossover | • 100 mg doravirine SD fed and fasted | 14/14<br>(7/7) |
| | MK-1439A-029 [23] | • Comparative fed and fasted bioavailability of DOR/TDF/3TC<br>• Open-label, randomized, two-period, crossover | • DOR/TDF/3TC (100 mg doravirine/300 mg TDF/300 mg lamivudine) SD fed and fasted | 14/13<br>(9/5) |
| TDF | MK-1439-003 [31] | • Evaluation of the effect of multiple doses of tenofovir on the single dose pharmacokinetics of doravirine<br>• Open label, two period, fixed sequence | • Period 1: 100 mg doravirine SD alone<br>• Period 2: 300 mg TDF QD × 18 Days and 100 mg doravirine SD on Day 14 | 8/7<br>(8/0) |

| Factor/concomitant medication under investigation | Trial number [reference] | Trial design and description | Treatment | Enrolled/completed (male/female) |
|---|---|---|---|---|
| | MK-1439-038 [31] | • A component interaction study of DOR/3TC/TDF (doravirine, lamivudine, tenofovir disproxil fumarate)<br>• Open-label, randomized, three-period, crossover | • Treatment A: doravirine 100 mg SD<br>• Treatment B: lamivudine 300 mg + TDF 300 mg SD<br>• Treatment C: doravirine 100 mg + lamivudine 300 mg + TDF 300 mg SD | 15/15 (7/8) |
| Efavirenz | MK-1439-020 [15] | • Effect of switching from efavirenz therapy to doravirine on the pharmacokinetics of doravirine<br>• Open-label, three-period, fixed-sequence, multiple-dose | • Period 1:100 mg doravirine QD Days 1–5<br>• Period 2: 600 mg efavirenz QD Days 1–14<br>• Period 3: 100 mg doravirine QD Days 1–14 | 20/17 (17/3) |
| Midazolam | MK-1439-001 [11] | • Safety and pharmacokinetics of doravirine and the effect of multiple doses of doravirine on midazolam<br>• Part 2: Double blind, randomized, placebo controlled, serial panel, rising multiple dose | • Part 2 Panel E: midazolam 2 mg SD alone; 120 mg doravirine QD × 14 days + 2 mg midazolam on Day 13 and placebo matched to doravirine | 10/9 (10/0) |
| Ritonavir | MK-1439-002 [26] | • DDI study of the effect of multiple doses of ritonavir on the single dose pharmacokinetics of doravirine<br>• Open-label, fixed-sequence, two-period | • Period 1: 50 mg doravirine SD alone<br>• Period 2: 100 mg BID ritonavir on Days 1–20 and 50 mg doravirine SD on Day 14 | 8/8 (8/-) |
| Dolutegravir | MK-1439-016 [20] | • Two-way steady-state DDI study of doravirine and dolutegravir<br>• Open-label, three-period, fixed-sequence | • Period 1: 50 mg dolutegravir QD Days 1–7<br>• Period 2: 200 mg doravirine QD Days 1–7<br>• Period 3: 200 mg doravirine QD + 50 mg dolutegravir QD Days 1–7 | 12/11 (6/6) |
| Elbasvir/grazoprevir | MK-1439-050 [27] | • DDI study of doravirine with elbasvir + grazoprevir<br>• Open-label, three-period, fixed-sequence | • Period 1: 100 mg doravirine QD Days 1–5<br>• Period 2: 50 mg elbasvir + 200 mg grazoprevir QD Days 1–10<br>• Period 3: 100 mg doravirine QD and 50 mg elbasvir + 200 mg grazoprevir QD Days 1–5 | 12/12 (5/7) |

| Factor/concomitant medication under investigation | Trial number [reference] | Trial design and description | Treatment | Enrolled/completed (male/female) |
|---|---|---|---|---|
| Ledipasvir/sofobusvir | MK-1439-053 [27] | • DDI study of doravirine with ledipasvir/sofobusvir<br>• Open-label, randomized, three-period, crossover | • Treatment A: 100 mg doravirine SD;<br>• Treatment B: 90 mg ledipasvir + 400 mg sofosbuvir SD;<br>• Treatment C: 100 mg doravirine + 90 mg ledipasvir + 400 mg sofosbuvir SD | 14/14 (12/2) |
| Ketoconazole | MK-1439-010 [26] | • DDI study of the effect of multiple oral doses of ketoconazole on the single dose pharmacokinetics of doravirine<br>• Open-label, two-period, fixed-sequence | • Period 1: 100 mg doravirine SD alone<br>• Period 2: 400 mg ketoconazole QD Days 1–10 and 100 mg doravirine SD on Day 2 | 10/10 (8/2) |
| Rifampin | MK-1439-011 [74] | • DDI study of the effect of single and multiple doses of rifampin on the single dose pharmacokinetics of doravirine<br>• Open-label, two-period, fixed-sequence | • Period 1: 100 mg doravirine SD alone<br>• Period 2: 600 mg rifampin and 100 mg doravirine SD on Day 1; 600 mg rifampin QD Days 4–18 and 100 mg doravirine SD on Day 17. | 11/10 (11/0) |
| Rifabutin | MK-1439-035 [75] | • DDI study of the effect of multiple doses of rifabutin on the single-dose pharmacokinetics of doravirine<br>• Open-label, two-period, fixed-sequence | • Period 1: 100 mg doravirine SD alone<br>• Period 2: 300 mg Rifabutin QD Days 1–16 and 100 mg doravirine SD on Day 14 | 18/12 (15/3) |
| Metformin | MK-1439-048 [29] | • DDI study of the effect of multiple doses of doravirine on metformin pharmacokinetics<br>• Open-label, two-period, fixed-sequence | • Period 1: 1000 mg metformin SD fed alone<br>• Period 2: 100 mg doravirine QD Days 1–7 fed and 1000 mg metformin SD on Day 5 fed | 14/14 (9/5) |
| Atorvastatin | MK-1439-036 [21] | • DDI study of the effect of doravirine at steady state on the pharmacokinetics of atorvastatin<br>• Open-label, two-period, fixed-sequence | • Period 1: 20 mg atorvastatin SD alone<br>• Period 2: 100 mg doravirine QD Days 1–8 and 20 mg atorvastatin SD on Day 5 | 16/14 (8/8) |
| Methadone | MK-1439-045 [30] | • DDI study of the effect of doravirine on methadone pharmacokinetics<br>• Open-label, fixed-sequence, multiple-dose | • 20–200 mg methadone QD Days 1–7 and 100 mg doravirine QD Days 2–6 | 14/14 (7/7) |
| Oral contraceptives | MK-1439-012 [26] | • DDI study of the effect of multiple oral doses of doravirine on the single dose pharmacokinetics of an oral contraceptive (ethinyl estradiol and levonorgestrel)<br>• Open-label, two-period, fixed-sequence | • Period 1: 0.15 mg/0.03 mg levonorgestrel/ethinyl estradiol SD alone<br>• Period 2: 100 mg doravirine QD Days 1–17 and 0.15 mg/0.03 mg levonorgestrel/ethinyl estradiol) SD on Day 14 | 20/19 (0/20) |

| Factor/concomitant medication under investigation | Trial number [reference] | Trial design and description | Treatment | Enrolled/completed (male/female) |
|---|---|---|---|---|
| Antacids | MK-1439-042 [28] | • DDI study of the effect of an aluminum- and magnesium-containing antacid and a proton pump inhibitor on the single-dose pharmacokinetics of doravirine<br>• Open-label, three-period, fixed-sequence | • Period 1: 100 mg doravirine SD alone<br>• Period 2: 100 mg doravirine SD + 20 mL antacid oral suspension (400 mg/5 mL aluminium hydroxide, 400mg/5 mL magnesium hydroxide, and 40 mg/5 mL simethicone) SD<br>• Period 3: 40 mg pantoprazole QD Days 1–5 and 100 mg doravirine SD on Day 5 | 14/13<br>(8/6) |
| Drug cessation | [12] | • Pharmacokinetic forgiveness<br>• Open-label | • 100 mg doravirine QD Days 1–5 | 14/14<br>(7/7) |
| **Phase I, II, and III trials in people living with HIV** | | | | |
| Phase I | MK-1439-005 [13] | • A multiple dose study to evaluate the safety, tolerability, pharmacokinetics and antiretroviral activity of doravirine<br>• Randomized, double-blind, placebo-controlled, two-panel, parallel-group trial in people living with HIV | • Panel A: 25 mg doravirine QD Days 1–7 or placebo matched to doravirine<br>• Panel B: 200 mg doravirine QD Days 1-7 or placebo matched to doravirine | 18/18<br>(18/0)<br>Doravirine: *n* = 12<br>Placebo: *n* = 6 |
| Phase IIb | MK-1439-007 (NCT01632345) [17] | • 96-week safety and efficacy of doravirine versus efavirenz<br>• Randomized, double-blind trial in ART-naive adults | • Part 1: randomized 1:1:1:1:1 to receive 25, 50, 100, or 200 mg doravirine or 600 mg efavirenz (co-administered with 300 mg TDF/200 mg FTC) QD for up to 96 weeks<br>• Part 2: new participants randomized 1:1 to 100 mg doravirine or 600 mg efavirenz QD, participants receiving doravirine in Part 1 received 100 mg doravirine QD in Part 2 | Doravirine: *n* = 232<br>Efavirenz: *n* = 108 |
| Phase III DRIVE-FORWARD | MK-1439-018 (NCT02275780) [5] | • Comparison of doravirine with ritonavir-boosted darunavir, both given with two nucleoside reverse transcriptase inhibitors<br>• Randomized, controlled, double-blind, multicenter, non-inferiority trial in ART-naive adults | • Randomized 1:1 to receive either 100 mg doravirine or 800 mg darunavir/100 mg ritonavir, plus a fixed-dose combination of 300 mg tenofovir/200 mg emtricitabine, or 600 mg abacavir/300 mg lamivudine QD for up to 96 weeks | Doravirine: *n* = 383<br>darunavir/ritonavir: *n* = 383 |

| Factor/concomitant medication under investigation | Trial number [reference] | Trial design and description | Treatment | Enrolled/completed (male/female) |
|---|---|---|---|---|
| Phase III DRIVE-AHEAD | MK-1439A-021 (NCT02403674) [4] | • Comparison of the fixed-dose combination tablet, DOR/3TC/TDF to EFV/FTC/TDF<br>• Randomized, double-blind, non-inferiority trial in ART-naive adults | • Randomized 1:1 to receive either 100 mg DOR/300 mg 3TC/300 mg TDF or 600 mg EFV/200 mg FTC/300 mg TDF QD | DOR/3TC/TDF: *n* = 364<br>EFV/FTC/TDF *n* = 364 |

3TC, lamivudine; ART, antiretroviral therapy; BID, twice daily; DDI, drug–drug interaction; DOR, doravirine; EFV, efavirenz; FTC; emtricitabine, QD, once daily;

TDF, tenofovir disoproxil fumarate; SD, single dose