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# Reduction in estimated Glomerular Filtration Rate (eGFR) Observed With Doravirine (DOR) is Caused by Inhibition of Organic Cation Transporter 2 (OCT2)

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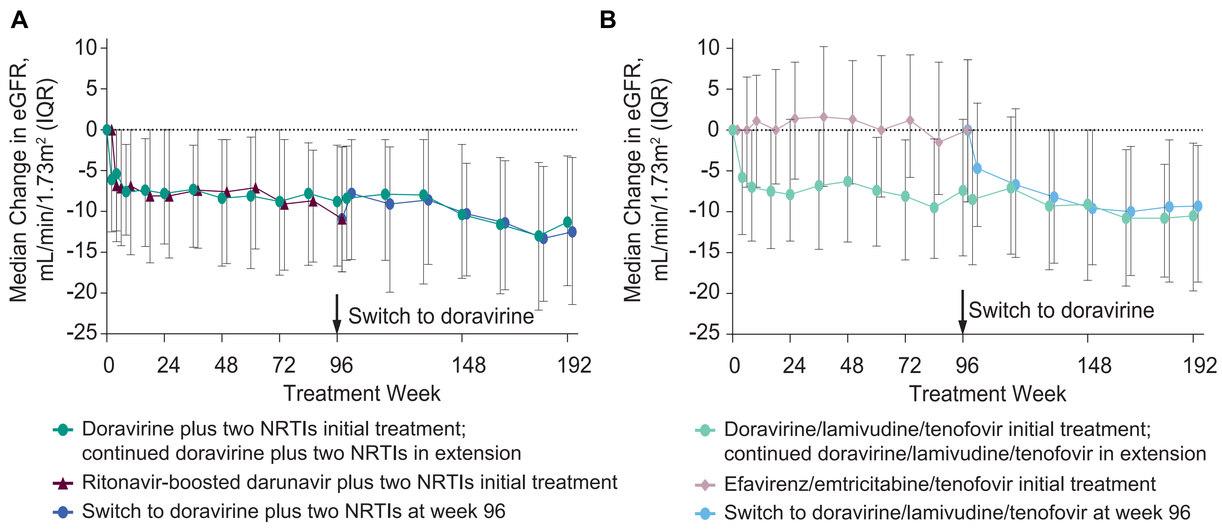
## Background

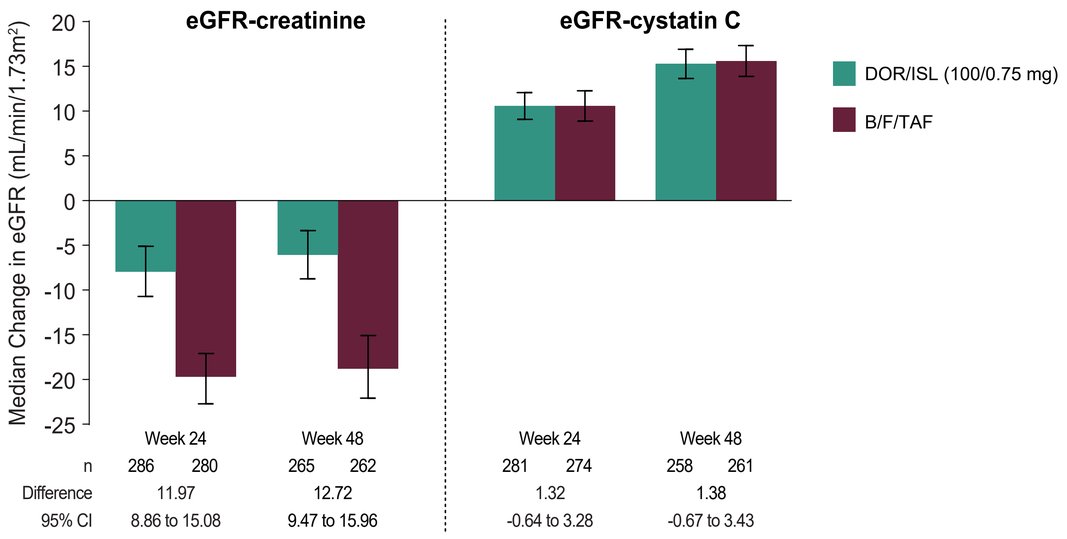
- Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) designed to address limitations associated with earlier NNRTIs, such as resistance from common NNRTI resistance-associated mutations, the neuropsychiatric events observed with efavirenz, and the food requirement and high baseline viral load exclusion associated with rilpivirine[1]
- The efficacy and safety of DOR were demonstrated in two randomized, double-blind, phase 3 studies of first-line therapy for adults living with HIV-1
  - DOR 100 mg was non-inferior to ritonavir-boosted darunavir (DRV/r), each given with 2 nucleos(t)ide reverse transcriptase inhibitors (NRTI), at week 48 and week 96 of the DRIVE-FORWARD study[2,3]
  - DOR in combination with lamivudine and tenofovir disoproxil fumarate (DOR/3TC/TDF) was non-inferior to efavirenz with emtricitabine and TDF (EFV/FTC/TDF) at week 48 and week 96 of the DRIVE-AHEAD study[4,5]
  - In both studies, the doravirine regimen maintained high rates of virologic suppression and was generally well tolerated through week 192[6]
- In the DRIVE-FORWARD and DRIVE-AHEAD studies, declines in creatinine-based eGFR of ~10 mL/min/1.73 $m^2$ were observed within a few weeks of initiating DOR, regardless of concomitant tenofovir use, and were followed by stable eGFR for up to 3.5 years (**Figure 1**)[6]

### Figure 1. Change in creatinine-based eGFR in DRIVE-FORWARD and DRIVE-AHEAD




- In a phase 3 study (8591A-020) evaluating the single-tablet regimen containing DOR 100 mg and islatravir 0.75 mg (DOR/ISL 100/0.75 mg) vs bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) as initial treatment for HIV-1, declines in creatinine-based eGFR were observed in both treatment groups, while eGFR based on cystatin C showed improvement in both groups, at weeks 24 and 48 (**Figure 2**)[7]
- Inhibition of tubular creatinine secretion has been observed with several antiretroviral agents, eg, bictegravir, cobicistat, dolutegravir, rilpivirine, and ritonavir[8-10]
- Inhibition of renal transporters involved in the active secretion of creatinine, such as organic cation transporter 2 (OCT2) and multidrug and toxin extrusion protein 1 (MATE1), has been observed with various drugs, including antiretrovirals, and such effects are reversible with removal of the drug[11]

### Figure 2. Mean change in eGFR in 8591A-020




## Objective

- To assess the possible involvement of renal transporters in the eGFR declines seen in DRIVE-FORWARD and DRIVE-AHEAD, we investigated the in vitro interaction of DOR with OCT2 and MATE1, major transporters responsible for the active renal secretion of creatinine

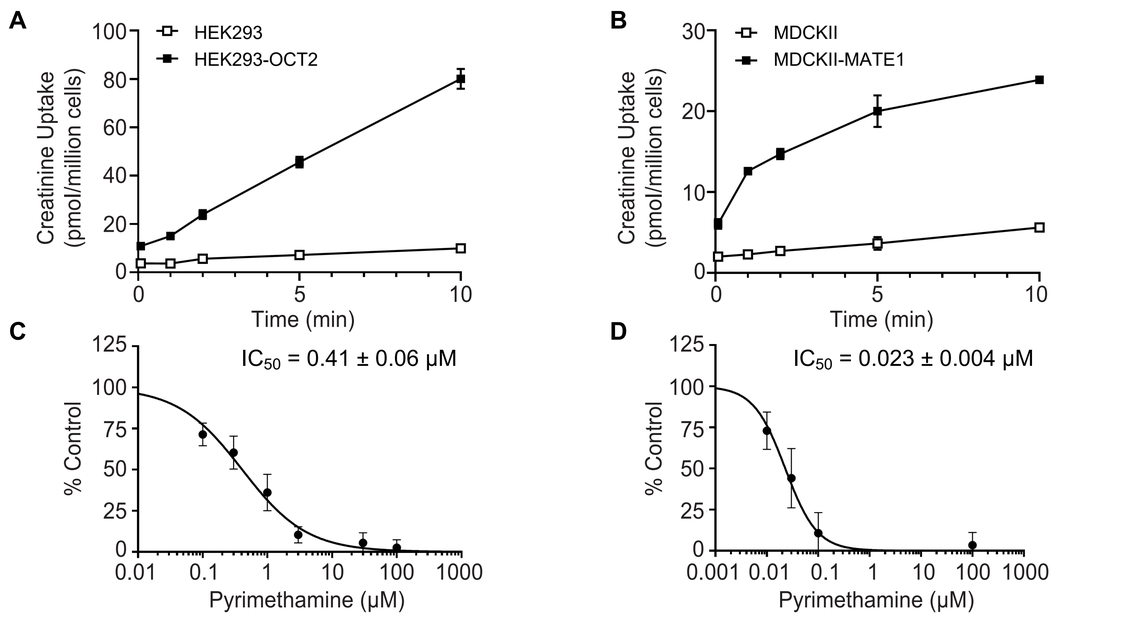
## Methods

- In vitro uptake studies of [$^{14}$C]creatinine were conducted in OCT2 stably transfected human embryonic kidney (HEK) 293 cells and MATE1 stably transfected Madin-Darby canine kidney (MDCK) II cells. For uptake time course studies, uptake was initiated by the addition of 20 µM [$^{14}$C]creatinine
- In vitro inhibition assays were established in OCT2 and MATE1 stably transfected cells using [$^{14}$C]creatinine and [$^{14}$C]metformin as probes to avoid substrate-dependent inhibition. Pyrimethamine, a known prototypic inhibitor of OCT2 and MATE1, was used to validate the functionality of the assay
- The inhibitory effects of DOR on OCT2- and MATE1-mediated uptake of [14C]creatinine and [$^{14}$C]metformin were measured; the obtained $IC_{50}$ values were used to assess substrate-dependent inhibition by comparing the inhibition potency using creatinine and metformin as probe substrates
- International Council for Harmonisation (ICH) M12 drug interaction risk assessment criteria, which were defined as the ratio of unbound maximal plasma concentration of an inhibitor at steady state after therapeutic dose ($C_{max,u}$) to half-maximal inhibitory concentration ($IC_{50}$) less than 0.1 (OCT2) and 0.02 (MATE1), respectively, were applied for drug-creatinine interaction risk assessment[12]

## Results

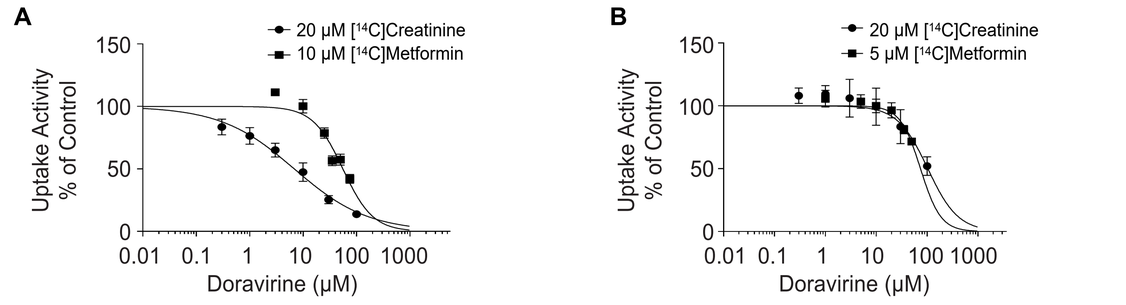
- Creatinine exhibited uptake ratios of 8- and 5-fold in OCT2- and MATE1-transfected cells, respectively, compared to parental cells (**Figures 3A** and **3B**)
- Pyrimethamine, a known inhibitor of OCT2 and MATE1 inhibited creatinine uptake by OCT2 and MATE1 with $IC_{50}$ of 0.41 and 0.023 µM, respectively, confirming robust in vitro transport activity (**Figures 3C** and **3D**)

### Figure 3. Development of in vitro inhibition assays of OCT2 and MATE1 using creatinine as a probe substrate (A and B) and pyrimethamine as positive control inhibitor (C and D)




- DOR inhibited OCT2-mediated creatinine uptake (**Figure 4A**) with an $IC_{50}$ of 6.9 µM (~12-fold above DOR unbound $C_{max}$), suggesting that eGFR reduction observed after initiation of DOR may be associated with inhibition of OCT2
- When metformin rather than creatinine was used as the OCT2 in vitro probe, a 10-fold higher $IC_{50}$ for OCT2 inhibition was observed for DOR (67 µM)
- As previously demonstrated, DOR does not affect the pharmacokinetics of metformin,[13] suggesting that DOR inhibition of OCT2 is substrate-dependent
- Finally, DOR inhibited only ~48% of MATE1-mediated creatinine uptake at 100 µM, which is comparable to the magnitude of inhibition observed for metformin uptake (**Figure 4B**)

### Figure 4. The inhibitory effect of doravirine on OCT2- (A) and MATE1- (B) mediated uptake of creatinine and metformin




## Conclusions

- At clinically relevant exposures, DOR inhibits OCT2- but not MATE1-mediated creatinine transport
- These in vitro observations mechanistically illustrate that the reduction in creatinine-based eGFR calculations of ~10 mL/min/1.73 $m^2$ observed with DOR is caused by inhibition of renal creatinine transport by DOR and does not reflect a reduction in renal function
- These findings are consistent with clinical data showing improvement in eGFR compared to baseline, when calculated using cystatin-C, in adults receiving the DOR/ISL (100/0.75 mg) combination as initial therapy for HIV-1[7]
- To gain further understanding of the eGFR changes observed with DOR regimens, cystatin-C is being measured in the Opti-DOR study of DOR/3TC/TDF (NCT05924438) and in phase 3 studies of DOR/ISL (100/0.25 mg) (NCT05631093, NCT05630755, NCT05705349) that are currently ongoing

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### Disclosures

Rebeca M. Plank is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) and may own stock and/or options in the company.

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