P048

Renal Safety Through 96 Weeks in a Phase 2 Trial (P011) of Islatravir and Doravirine in Treatment-Naïve Adults With HIV-1

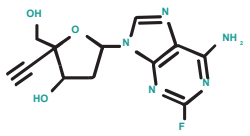
Frank A. Post[1]; Ciaran J. McMullan[2]; Giovanni Di Perri[3]; Jean-Michel Molina[4]; Stephanie O. Klopfer[2]; Anjana Grandhi[2]; Karen Eves[2]; Deborah Hepler[2]; Carey Hwang[2]; Todd A. Correll[2]

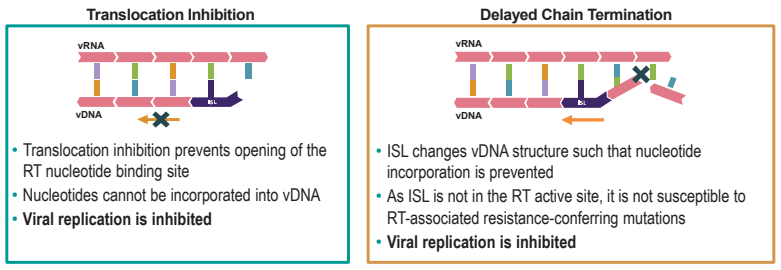
[1]King's College Hospital NHS Foundation Trust, London, UK; [2]Merck & Co., Inc., Kenilworth, NJ, USA; [3]University of Turin, Turin, Italy; [4]University of Paris Diderot and St-Louis Hospital, Paris, France

Background

- Islatravir (ISL, MK-8591) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection
- Doravirine (DOR) is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV-1
- The combined attributes of ISL and DOR create the potential for a potent, simple 2-drug regimen that may address some of the long-term safety and toxicity concerns of traditional regimens
- Protocol 11 is a Phase 2b dose-ranging trial of DOR + ISL (NCT03272347)
  - Virologic suppression among participants receiving ISL + DOR was high at Week 48 and maintained through Week 96[1,2]
  - ISL + DOR was generally well tolerated at all doses, with few drug-related AEs; 3 of 90 participants in the combined ISL groups discontinued due to AEs through Week 96[2]
  - The 0.75 mg dose of ISL was selected for further clinical development[3]

Islatravir, a First-in-Class Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI) With Multiple Mechanisms of Action





Multiple mechanisms contribute to the high potency of ISL against HIV-1 (including drug-resistant variants) and its high barrier to resistance

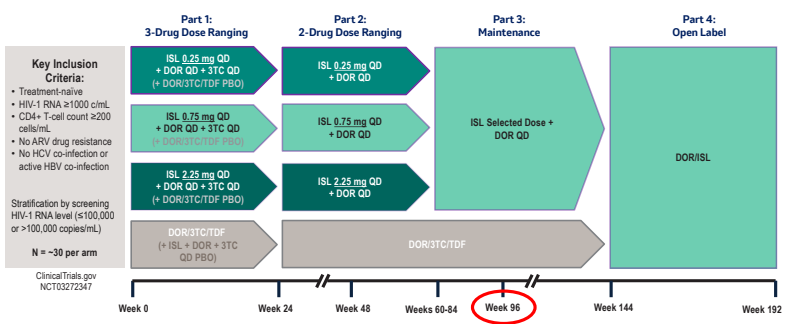
ISL, islatravir; RT, reverse transcriptase; vDNA, viral DNA; vRNA, viral RNA.

Renal Disease and HIV

- Increasing prevalence of chronic kidney disease (CKD) among people living with HIV (PLWHIV); associated with significant morbidity and mortality[4]
- Risk factors for CKD: hypertension, diabetes, CVD, family history, black African ethnicity, viral hepatitis, low CD4 count, smoking, older age, concomitant nephrotoxic drugs[5]
- Increasing age of PLWHIV and long-term exposure to ART contribute to the burden of renal disease
- Antiretroviral drugs associated with renal toxicity include tenofovir disoproxil fumarate (TDF), atazanavir, and ritonavir-boosted protease inhibitors (PI/r)
  - Risk factors for TDF nephrotoxicity: higher age, lower baseline renal function, duration of exposure, and concurrent use of PI/r or cobicistat[4]
  - TDF/FTC + efavirenz associated with significantly lower risk of CKD than TDF with elvitegravir/c or PI/r[6]
  - No difference in discontinuation for renal adverse events between unboosted tenofovir alafenamide (TAF) and unboosted TDF[7]
- Here we present the renal safety profile of ISL (0.25, 0.75, and 2.25 mg QD) given with DOR (100 mg QD) through Week 96 of the Phase 2b trial

Methods

Figure 1. Protocol 011: Phase 2 Dose-Ranging Trial of ISL + DOR



After 24 weeks of dosing in Part 1, participants who are virologically suppressed (HIV-1 RNA <50 copies/mL) at the Week 20 visit and have not met any viral failure criteria are eligible to switch to Part 2 of the trial at Week 24. Participants with HIV-1 RNA levels ≥50 copies/mL at Week 20 will remain in Part 1 until HIV-1 RNA is <50 copies/mL and they have not met any of the viral failure criteria, at which point they transition to Part 2 at their next visit.

Exploratory Objective: To evaluate the renal safety profile of ISL + DOR compared with DOR/3TC/TDF over 96 weeks

Endpoints evaluated:

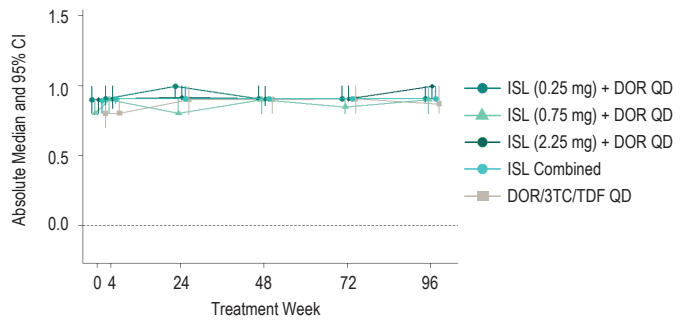
- Serum creatinine, measured at each study visit
- Estimated glomerular filtration rate (eGFR) calculated by MDRD equation
- Renal biomarkers (urine analytes)
  - Albumin/creatinine ratio
  - Retinol-binding protein/creatinine ratio
  - Beta-2 microglobulin/creatinine ratio

Results

Table 1. Participant Baseline Characteristics by Treatment Group

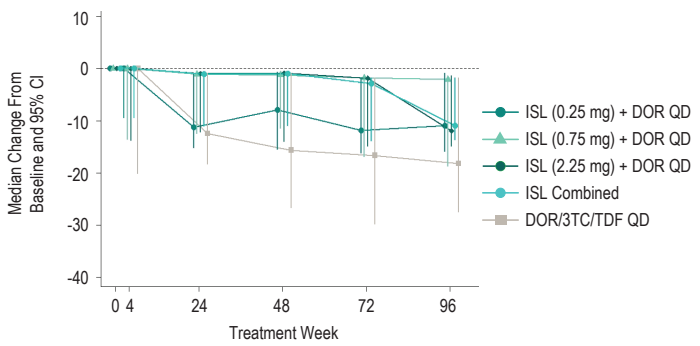
	ISL 0.25 mg + DOR + 3TC QD	ISL 0.75 mg + DOR + 3TC QD	ISL 2.25 mg + DOR + 3TC QD	DOR + ISL Dose Groups Combined	DOR/3TC/ TDF QD
	N=29	N=30	N=31	N=90	N=31
Sex n (%)					
Male	29 (100.0)	27 (90.0)	28 (90.3)	84 (93.3)	28 (90.3)
Age (years)					
Median (min, max)	27.0 (19, 75)	28.0 (18, 51)	29.0 (19, 67)	28.5 (17, 75)	27.0 (18, 56)
Race/ethnicity n (%)					
Black or African American	5 (17.2)	6 (20.0)	8 (25.8)	19 (21.1)	5 (16.1)
White	23 (79.3)	24 (80.0)	21 (67.7)	68 (75.6)	24 (77.4)
Hispanic or Latino	14 (48.3)	19 (63.3)	12 (38.7)	45 (50.0)	15 (48.4)
CD4+ T-cell count (cells/mm^3)					
Median (min, max)	415.0 (199, 889)	535.5 (178, 828)	416.0 (185, 1122)	445.5 (178, 1122)	473 (224, 1321)
Plasma HIV-1 RNA (log_{10} copies/mL)					
Median (min, max)	4.6 (3.5, 6.2)	4.5 (3.0, 5.8)	4.7 (3.1, 5.8)	4.6 (3.0, 6.2)	4.2 (3.3, 6.1)
≤100,000 copies/ mL, n (%)	22 (75.9)	24 (80.0)	22 (71.0)	68 (75.6)	26 (83.9)
Serum creatinine (mg/dL)					
Median (min, max)	0.9 (0.6, 1.2)	0.8 (0.5, 1.2)	0.9 (0.5, 1.1)	0.9 (0.5, 1.2)	0.8 (0.6, 1.0)
eGFR (mL/min/1.73 m^2)					
Median (min, max)	105.8 (59.2, 173.6)	115.2 (66.7, 158.9)	108.2 (69.5, 161.7)	107.6 (59.2, 173.6)	117.4 (84.1, 208.2)

Figure 2. Serum Creatinine, Median (mg/dL)



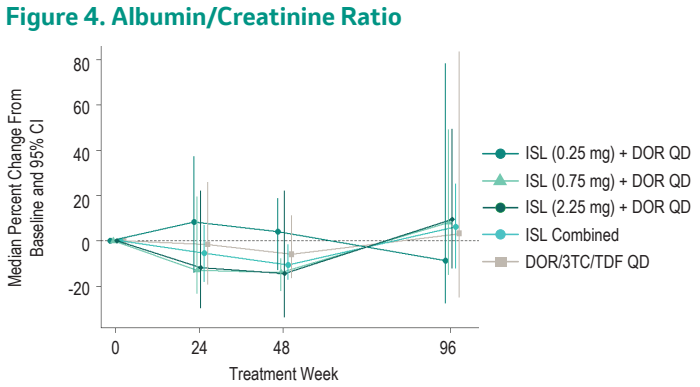
- Two participants (in ISL 0.25 mg group) had ≥0.5 mg/dL increase from baseline in serum creatinine: (1) 1.7 mg/dL at Week 16; (2) 1.7 mg/dL at Week 60 and 1.9 mg/dL at Week 84. All had resolved by the next study visit
- No participants had ≥1.0 mg/dL increase or doubling of serum creatinine from baseline

Figure 3. eGFR by MDRD (mL/min/1.73 m^2)



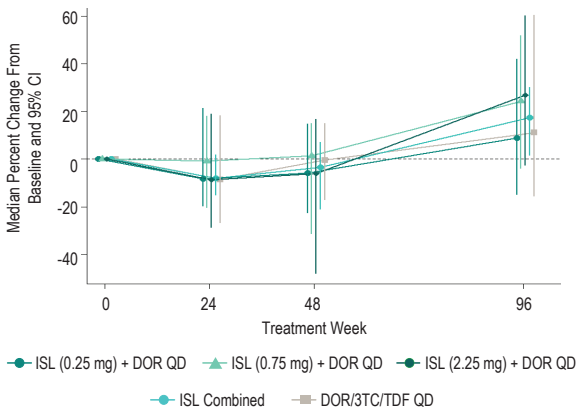
- eGFR reductions >30% from baseline occurred in 11 (12%) ISL participants and 5 (16%) DOR/3TC/TDF participants and were transient in most cases
- eGFR <60 mL/min/1.73 m^2 occurred in 4 (4%) ISL participants and was transient in 3 (fourth had eGFR <60 from baseline to Week 96)

Figure 4. Albumin/Creatinine Ratio



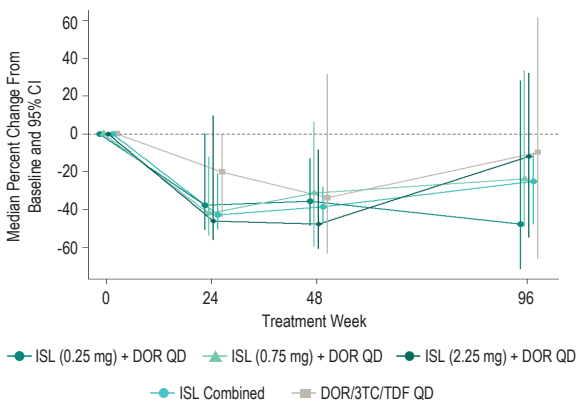
- Minimal effect on albumin/creatinine ratio, with no difference across treatment groups

Figure 5. Retinol-Binding Protein/Creatinine Ratio



- Minimal effect on retinol-binding protein/creatinine ratio, with no difference across treatment groups

Figure 6. Beta-2 Microglobulin/Creatinine Ratio



- No difference in beta-2 microglobulin/creatinine ratio across treatment groups was observed

Conclusions

- No renal safety concerns were found for DOR + ISL in this exploratory analysis from the Phase 2 trial
  - Similar changes in serum creatinine and eGFR across all treatment groups
  - Similar changes across treatment groups in renal biomarkers: albumin/creatinine, retinol-binding protein/creatinine, and beta-2 microglobulin/creatinine ratios
  - No dose-response relationship for renal effects of DOR + ISL
  - No discontinuations due to renal adverse events
- Phase 3 clinical trials will provide additional data on the renal safety profile of DOR/ISL

Additional DOR + ISL data at HIV Glasgow 2020:

Molina J-M, et al. Islatravir in combination with doravirine maintains HIV-1 viral suppression through 96 weeks.

Orkin C, et al. Analysis of protocol-defined virologic failure through Week 96 from a Phase 2 trial (P011) of islatravir and doravirine in treatment-naïve adults with HIV-1 infection.

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Principal Investigators

Chile: A Afani, M Campos, C Chahin Anania

France: F Ajana, O Bouchaud, C Katlama, J-M Molina, P Morlat, F Raffi, Y Yazdanpanah

United Kingdom: M Johnson, C Orkin, A Ustianowaki, A Clarke

United States: D Asmuth, D Berger, C Bettacchi, E DeJesus, C Dietz, D Goldstein, C McDonald, J Sims, G Crofoot, D Cunningham

Disclosure

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