P010

Total lymphocyte and CD4+ T-cell count changes in participants receiving islatravir (0.25 mg, 0.75 mg, and 2.25 mg once daily) and doravirine ± lamivudine: post hoc analysis from a phase 2b dose-ranging study (P011)

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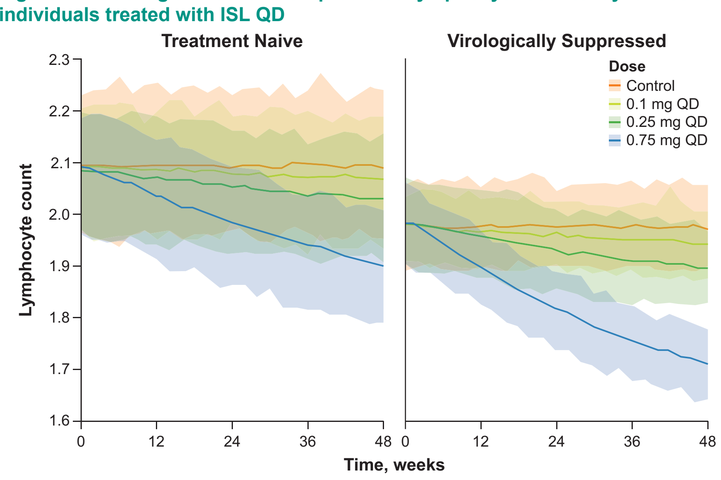
Background

- Islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor (NRTTI), inhibits reverse transcriptase by multiple actions, including translocation inhibition and delayed chain termination, and is being studied for HIV-1 treatment and prevention[1-4]
- In a phase 2b dose-ranging study, naive participants who received ISL + doravirine (DOR) combined with lamivudine (3TC) achieved and maintained high rates of virologic suppression[5]
  - The proportions of participants who met the criteria for protocol-defined virologic failure (PDVF, confirmed HIV-1 RNA ≥50 copies/mL) were low and similar across treatment groups
  - No participants met criteria for viral resistance testing
- DOR/ISL (100 mg/0.75 mg) QD was initially selected to be evaluated in a phase 3 clinical development program[6]
- Exposure-related decreases in total lymphocytes and lymphocyte subset counts were observed across ISL programs[7]
  - In the DOR/ISL (100 mg/0.75 mg) QD phase 3 program, reductions in total lymphocyte and lymphocyte subset counts were observed
  - Higher frequencies and magnitude of changes were observed in higher-dose ISL trials (60 mg and 120 mg once monthly; 20 mg once weekly) compared with DOR/ISL (100 mg/0.75 mg) QD
- A post hoc analysis of lymphocyte data from a dose-ranging phase 2b study (P011) was conducted to identify ISL doses that may not impact lymphocyte and CD4+ T-cell counts while maintaining efficacy (**Figures 1 and 2; Tables 1 and 2**)[8]

Figure 1. Modeling and simulation-predicted lymphocyte counts: dynamics for individuals treated with ISL QD



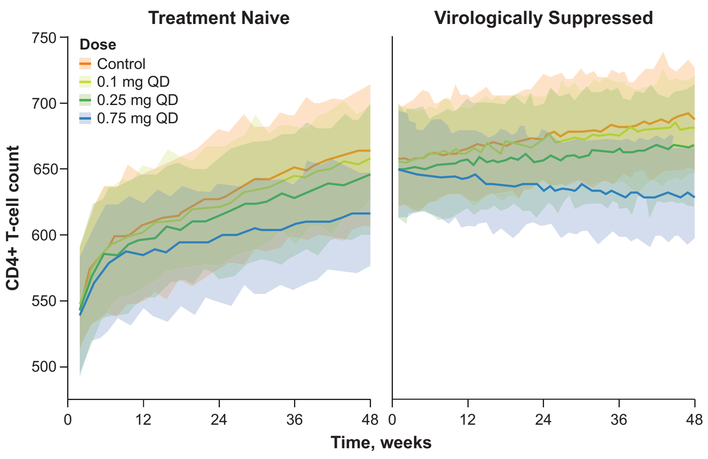
ISL, islatravir; QD, once daily.
Solid lines, median of the predicted lymphocyte counts across simulated trials. Shaded regions, 95% CI.

Table 1. Predicted lymphocyte counts and change from baseline as ratio of ISL to control at week 48

ISL QD dose, mg	Predicted lymphocyte counts, mean (95% PI)	Predicted change from baseline, mean ratio of ISL:control (95% PI)
Standard ART	1.97 (1.90-2.06)	–
0.1	1.94 (1.88-2.01)	0.993 (0.942-1.05)
0.25	**1.89 (1.83-1.97)**	**0.975 (0.927-1.03)**
0.75	1.71 (1.64-1.77)	0.910 (0.870-0.963)

ART, antiretroviral therapy; ISL, islatravir; PI, predicted interval; QD, once daily.

Figure 2. Modeling and simulation-predicted CD4+ T-cell counts: dynamics for individuals treated with ISL QD



ISL, islatravir; QD, once daily.
Solid lines, median of the predicted CD4+ T-cell count across simulated trials. Shaded regions, 95% CI.

Table 2. Predicted CD4+ T-cell counts and change from baseline as ratio of ISL to control at week 48

ISL QD dose, mg	Predicted CD4+ T-cell counts, mean (95% PI)	Predicted change from baseline, mean ratio of ISL:control (95% PI)
Standard ART	719 (664-766)	–
0.1	713 (671-752)	0.992 (0.931-1.07)
0.25	**700 (649-753)**	**0.984 (0.914-1.05)**
0.75	668 (630-711)	0.934 (0.876-0.994)

ART, antiretroviral therapy; ISL, islatravir; PI, predicted interval; QD, once daily.

Objective

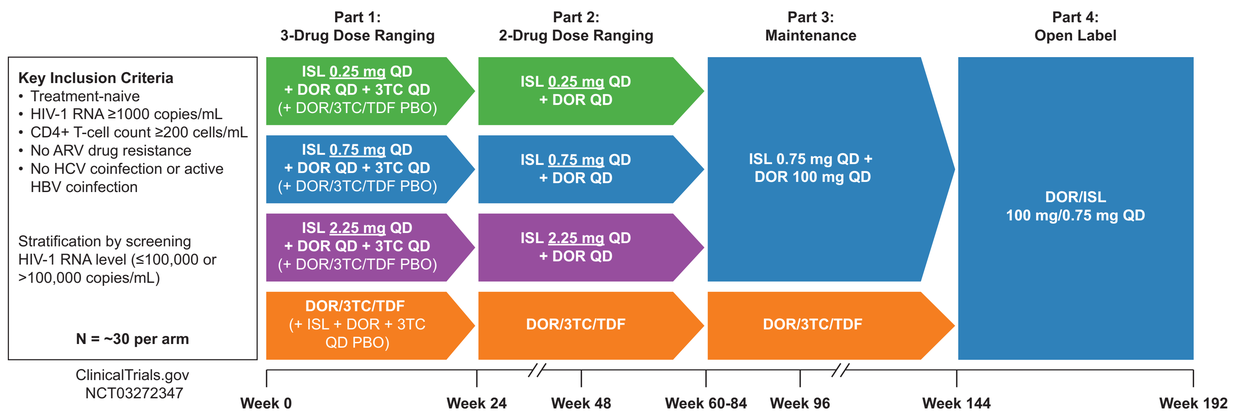
- To determine the effect of ISL 0.25 mg, 0.75 mg, and 2.25 mg QD on total lymphocyte and lymphocyte subset counts in the ISL phase 2b dose-ranging study

Methods

Study population

- Protocol 011 is a phase 2b dose-ranging trial of ISL+DOR (**Figure 3**)

Figure 3. Study design for protocol 011



3TC, lamivudine; ARV, antiretroviral; DOR, doravirine; HBV, hepatitis B virus; HCV, hepatitis C virus; ISL, islatravir; PBO, placebo; QD, once daily; TDF, tenofovir disoproxil fumarate.
After 24 weeks of dosing in part 1 of the trial, participants who were virologically suppressed (HIV-1 RNA <50 copies/mL) at the week 20 visit and who had not met any viral failure criteria were eligible to switch to part 2 at week 24. Participants with HIV-1 RNA levels ≥50 copies/mL at week 20 remained in part 1 until their HIV-1 RNA was <50 copies/mL and they had not met any of the viral failure criteria, at which point they transitioned to part 2 at their next visit. Part 2 evaluated the 2-drug dose-ranging maintenance phase. Part 3 evaluated the selected dose (0.75 mg) of ISL, in combination with DOR 100 mg QD.

Protocol 011 post hoc analyses

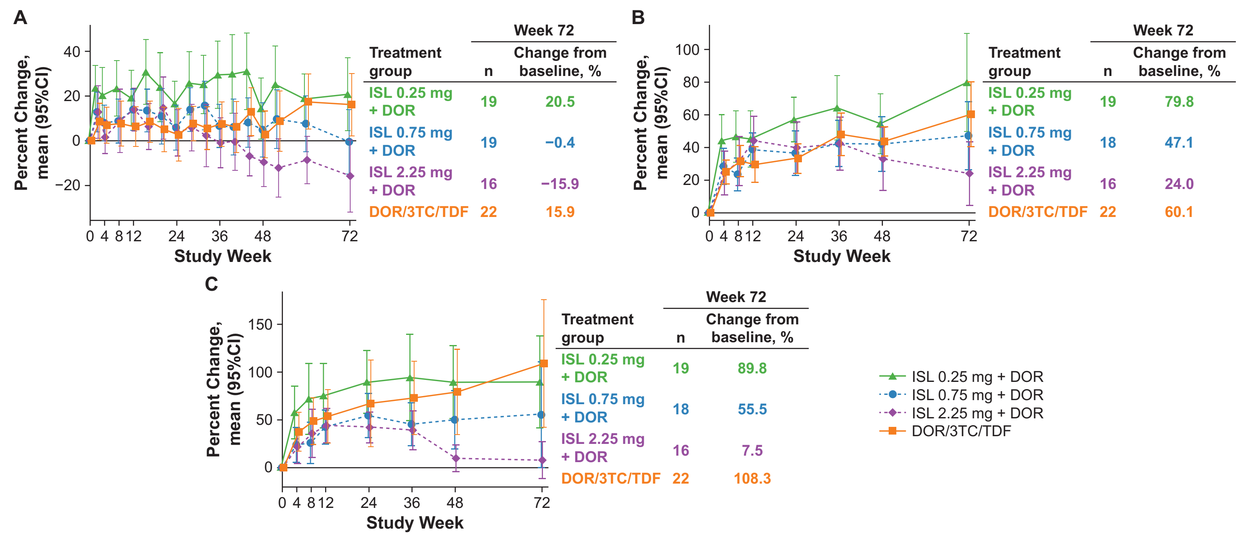
- To identify a daily ISL dose in persons with HIV who have minimal to no changes in total lymphocyte and lymphocyte subset counts, a post hoc analysis was conducted in a phase 2b dose-ranging study evaluating ISL 0.25, 0.75, and 2.25 mg + DOR 100 mg (±3TC) compared with DOR/3TC/TDF
- Mean percent change (95% CI) from baseline in total lymphocyte, CD4+ T-cell, and B-cell counts were analyzed
  - Parts 1 and 2 through week 72 (prior to ISL 0.75 mg dose conversion)
    - Participants who switched to ISL 0.75 mg before week 72 were excluded from the week 72 analysis but were included in all time points prior to switch
    - Parts 1 and 2 analyses used study (day 1) baseline
  - Part 3 (after ISL 0.75 mg dose conversion) through week 144
    - Part 3 analyses used part 3 baseline (last measurement prior to dose conversion)
    - Time was measured relative to dose conversion/time in part 3
- Incidence of infections and other hematology parameters (neutrophil counts, platelet counts, and hemoglobin levels) were examined through week 144

Results

Protocol P011 parts 1 and 2: changes in lymphocyte and lymphocyte subsets

- Mean percent changes from baseline (95% CI) in total lymphocyte, CD4+ T-cell, and B-cell counts were similar for ISL 0.25 mg compared with DOR/3TC/TDF and were more favorable than ISL 0.75 mg and ISL 2.25 mg groups (**Figure 4**)

Figure 4. Mean percent changes from baseline in (A) total lymphocyte counts, (B) CD4+ T-cell counts, and (C) B-cell counts for parts 1 and 2 through week 72

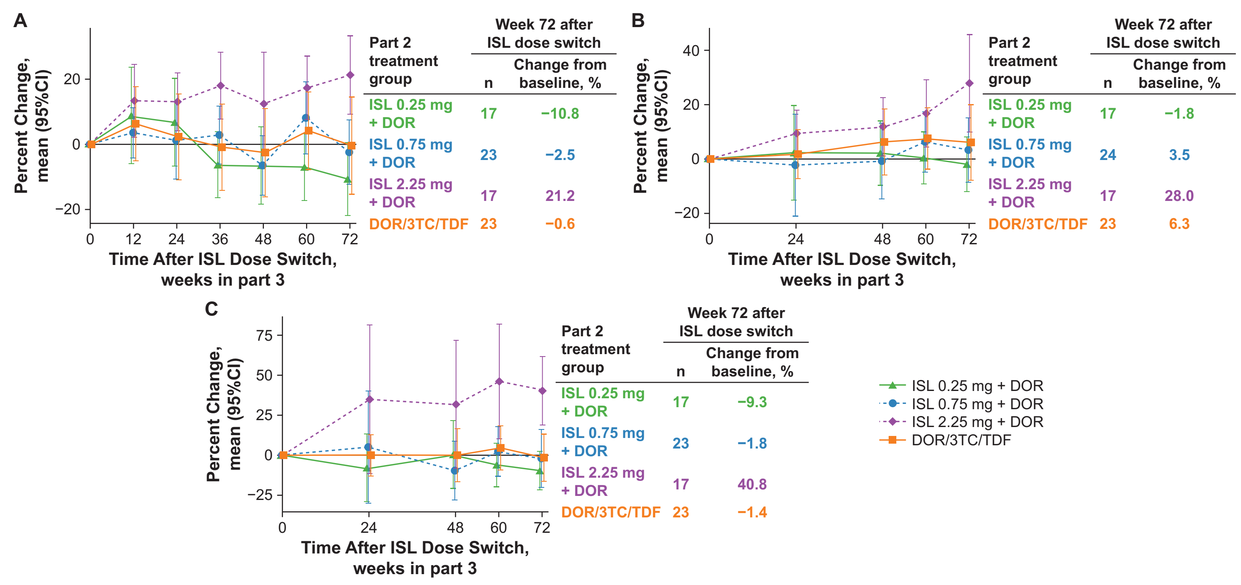


3TC, lamivudine; DOR, doravirine; ISL, islatravir; QD, once daily; TDF, tenofovir disoproxil fumarate.
At week 72, mean absolute CD4+ T-cell counts were 752 cells/mm^3 (n = 19) for ISL 0.25 mg, 787 cells/mm^3 (n = 18) for ISL 0.75 mg, 646 cells/mm^3 (n = 16) for ISL 2.25 mg, and 759 cells/mm^3 (n = 22) for DOR/3TC/TDF.

Protocol P011 part 3: changes in lymphocyte and lymphocyte subsets after switching to DOR/ISL (100 mg/0.75 mg)

- A decrease in ISL dose from 2.25 mg to 0.75 mg resulted in dose-dependent increases in total lymphocyte, CD4+ T-cell, and B-cell counts (**Figure 5**)

Figure 5. Mean percent changes from time of switch to ISL 0.75 mg in (A) total lymphocyte counts, (B) CD4+ T-cell counts, and (C) B-cell counts in part 3



3TC, lamivudine; DOR, doravirine; ISL, islatravir; QD, once daily; TDF, tenofovir disoproxil fumarate.
Participants switched to ISL 0.75 mg between study weeks 60-84, with the majority switching at study week 72. On this figure, week 0 = time of switch.

Safety

- Incidence of adverse events in the infections and infestations system organ class was not increased in ISL-treated participants compared with those participants treated with DOR/3TC/TDF (**Table 3**)
- Two participants reported Centers for Disease Control and Prevention AIDS/HIV–defining category C events: pulmonary tuberculosis (ISL 2.25 mg, day 813) and Burkitt's lymphoma (ISL 0.25 mg, day 674)
  - Both events were considered not related to study medication
  - Neither participant had reduced total lymphocyte or CD4+ T-cell counts around the time these events occurred

Table 3. Adverse events in the infections and infestations system organ class (incidence ≥10% in ≥1 treatment groups) weeks 0-144

	ISL 0.25 mg + DOR n (%)	ISL 0.75 mg + DOR n (%)	ISL 2.25 mg + DOR n (%)	DOR/3TC/TDF n (%)
Participants in population	29	30	31	31
Infections and infestations	**19 (65.5)**	**22 (73.3)**	**18 (58.1)**	**22 (71.0)**
Bronchitis	2 (6.9)	7 (23.3)	1 (3.2)	5 (16.1)
COVID-19	0 (0)	3 (10.0)	1 (3.2)	1 (3.2)
Gastroenteritis	1 (3.4)	1 (3.3)	1 (3.2)	4 (12.9)
Influenza	3 (10.3)	1 (3.3)	1 (3.2)	3 (9.7)
Nasopharyngitis	2 (6.9)	9 (30.0)	2 (6.5)	7 (22.6)
Pharyngitis	1 (3.4)	3 (10.0)	0 (0)	4 (12.9)
Sinusitis	4 (13.8)	0 (0)	0 (0)	1 (3.2)
Syphilis	5 (17.2)	8 (26.7)	2 (6.5)	6 (19.4)
Tonsilitis	2 (6.9)	3 (10.0)	1 (3.2)	0 (0)
Upper respiratory tract infection	2 (6.9)	3 (10.0)	3 (9.7)	3 (9.7)

3TC, lamivudine; DOR, doravirine; ISL, islatravir; TDF, tenofovir disoproxil fumarate.

- Mean changes from baseline in neutrophil and platelet counts and hemoglobin levels were similar across ISL dose groups and comparable with the DOR/3TC/TDF group (**Table 4**)

Table 4. Hematology assessments for parts 1 and 2 (weeks 0-72)

	ISL 0.25 mg + DOR n = 19		ISL 0.75 mg + DOR n = 19		ISL 2.25 mg + DOR n = 16		DOR/3TC/TDF n = 22	
	Baseline	Mean change week 72 (95% CI)	Baseline	Mean change week 72 (95% CI)	Baseline	Mean change week 72 (95% CI)	Baseline	Mean change week 72 (95% CI)
Neutrophils, 10^9/L	3.00	0.17 (−0.21 to 0.56)	3.25	0.24 (−0.62 to 1.10)	2.49	0.78 (−0.01 to 1.57)	2.77	0.62 (0.10-1.14)
Hemoglobin, g/dL	14.29	0.50 (0.08-0.92)	14.77	−0.06 (−0.45 to 0.33)	14.60	−0.01 (−0.59 to 0.56)	14.12	0.39 (−0.08 to 0.85)
Platelets, 10^9/L	256.95	18.58 (−7.79 to 44.95)	237.37	24.58 (−0.45 to 49.61)	238.50	14.25 (−14.52 to 43.02)	256.50	8.86 (−8.65 to 26.37)

3TC, lamivudine; DOR, doravirine; ISL, islatravir; TDF, tenofovir disoproxil fumarate.

Conclusions

- Exposure-related decreases in total lymphocyte, CD4+ T-cell, and B-cell counts were observed in participants receiving ISL doses ≥0.75 mg QD
- Effects on total lymphocyte and lymphocyte subset counts were comparable for the ISL 0.25 mg group and the DOR/3TC/TDF group
  - Comparable, robust increases in CD4+ T-cell counts were observed in the ISL 0.25 mg and DOR/3TC/TDF groups for parts 1 and 2 through week 72
- A 3-fold decrease in ISL dose (from 2.25 mg to 0.75 mg) resulted in dose-dependent increases in total lymphocyte, CD4+ T-cell, and B-cell counts
- Incidence of adverse events in the infections and infestations system organ class was not increased in ISL-treated participants compared with those participants treated with DOR/3TC/TDF
- No effects on other hematology parameters were observed
- These data support advancement of the new dosing regimen DOR/ISL (100 mg/0.25 mg) QD into a phase 3 clinical development program in treatment-naive and virologically stable switch populations, which has been opened to enrollment (**Table 5**)

Table 5. DOR/ISL (100 mg/0.25 mg) QD phase 3 program

Study	Study Intervention	Design	Population	N
051	DOR/ISL (100 mg/0.25 mg) QD compared with baseline ART	Open-label; 2:1 randomization	Virologically suppressed HIV-1	500
052	DOR/ISL (100 mg/0.25 mg) QD compared with BIC/FTC/TAF	Blinded; 2:1 randomization	Virologically suppressed HIV-1	500
053	DOR/ISL (100 mg/0.25 mg) QD compared with BIC/FTC/TAF	Blinded; 1:1 randomization	Treatment-naive HIV-1	500
054	DOR/ISL (100 mg/0.25 mg) QD	Open-label, single arm, de-escalation	HIV-1	1000-1300

ART, antiretroviral therapy; BIC, bictegravir; DOR, doravirine; FTC, emtricitabine; ISL, islatravir; QD, once daily; TAF, tenofovir alafenamide.

Acknowledgments

The authors thank all the individuals who participated in this study. The contributions of the investigators and their staff are also gratefully recognized. Medical writing and/or editorial assistance was provided by Jared Cochran, PhD, and Andrea Humphries, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Presented at the British HIV Association Spring Conference 2023; April 24-26, 2023; Gateshead, United Kingdom