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)

Background
- **Materials** (ISL), a nucleoside reverse transcriptase/transcription inhibitor (NRTI/NRTT), initiates reverse transcriptions by multiple actions, including transcription inhibition and decreased chain termination, and is being studied for HIV-1 treatment and prevention.

- In a phase 1b dose-ranging study, patients who received ISL + doravirine (DOR) combined with lamivudine (3TC) achieved and maintained high rates of virologic suppression.

- The proportions of patients who met the criteria for protocol-defined virologic failure (PDRF; confirmed HIV-1 RNA >200 copies/mL) were low and similar across treatment groups.

- ISL dose groups were selected based on the safety, efficacy, and tolerability profile of ISL and the potential for dose-ranging.

Protocol 011 is a phase 2b dose-ranging trial of ISL + DOR (Blinded; 2:1 randomization).

- Two participants reported Centers for Disease Control and Prevention AIDS/HIV--defining category C events: pulmonary tuberculosis (ISL 2.25 mg, DOR/ISL (100 mg/0.75 mg) QD) and Clostridium difficile enteritis (ISL 2.25 mg, DOR/ISL (100 mg/0.75 mg) QD) in the ISL 2.25 mg dose group.

- An analysis of lymphocyte subsets in relation to ISL dose shows that 28-day ISL dose switch (ISL 0.25 mg QD to ISL 2.25 mg QD) was not associated with adverse events.

- Exposure-related decreases in total lymphocytes and lymphocyte subset counts were observed across ISL programs.

- Study Intervention

- Mean changes from baseline in neutrophil and platelet counts and hemoglobin levels were similar across ISL dose groups and comparable with the Standard ART group.

- Incidence of infections and other hematologic parameters (neutrophil counts, platelet counts, and hemoglobin levels) were examined through week 144.

- 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 Standard ART.

- Participants randomized to ISL 0.25 mg, 0.75 mg, and 2.25 mg QD were switched to ISL 2.25 mg QD between study weeks 60-84, with the majority switching at study week 72.

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

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

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

Conclusions
- Exposure-related decreases in total lymphocytes and CD4+ T-cell counts were observed in participants receiving ISL doses ≥0.75 mg QD.

- Effects on total lymphocyte and lymphocyte subset counts in the ISL 0.25 mg QD group and the DOR/3TC/TDF group are consistent with findings in other studies of ISL + DOR and ISL + 3TC.

- 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.

- Both events were considered not related to study medication.

- Neither patient had reduced total lymphocyte or CD4+ T-cell counts around the time these events occurred.

- Time After ISL Dose Switch, weeks in part 3

Table 3. Adverse events in the infections and infestations system organ class associated with ISL+DOR/3TC/TDF (in all treatment groups) weeks 5-144

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

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

- Mean percent changes from baseline (%) 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 similar for ISL 0.75 mg and 2.25 mg QD (Figure 4).

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

- 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).

- Mean percent changes from time of switch ISL 0.75 mg (A) total lymphocyte counts, (B) CD4+ T-cell counts, and (C) B-cell counts in part 1

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- Present data support advancement of the new dosing regimen DOR/ISL (100 mg/25 mg) QD into a phase 3 clinical development program in treatment-naive and virologically stable populations, which has been opened to enrollment (Table 5).

Table 5. DOR/ISL (100 mg/25 mg) QD phase 3 program

References