MODELING TO OPTIMIZE ISLATRAVIR QW DOSE IN HIV VIROLOGICALLY SUPRESSED PWH

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BACKGROUND

Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) being studied for HIV-1 treatment and prevention. ISL dose/exposure-related decreases in total lymphocytes and CD4+ T cell counts were observed across ISL clinical trials, with higher frequencies and magnitude of changes observed in ISL higher-dose regimens [20 mg once weekly (QW); 60 and 120 mg once monthly (QM)]. Data from Phase 2 and 3 ISL treatment and Preexposure Prophylaxis (PrEP) trials were used to develop models that describe the changes in lymphocytes and CD4+ T cells in relationship to intracellular PBMC islatravir triphosphate (ISL-TP) concentrations. Optimized doses were identified to achieve efficacy thresholds and similar CD4+ T cell and lymphocyte changes compared to standard antiretroviral therapy (ART).

METHODS

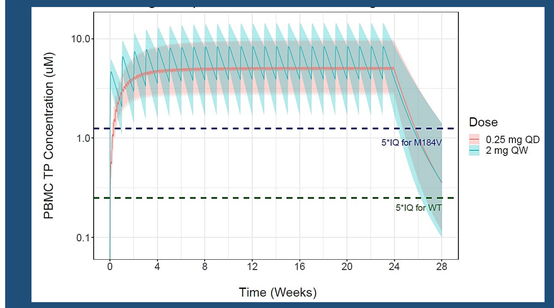
An ISL popPK model was developed incorporating ISL PK data from once daily (QD) and QW doses. Subsequently an ISL popPKPD model was developed incorporating longitudinal CD4+ T cell and total lymphocyte data from long-term ISL studies. Additionally, CD4+ T cell changes were summarized across approved ART regimens for the virologically suppressed population to compare to PK/PD model predictions. Revised ISL QW doses were selected based on simulated doses providing ISL exposures ensuring coverage for wild-type (WT) and M184I/V variants as well as CD4+ T cell and total lymphocyte changes comparable to standard ART in switch population.

RESULTS

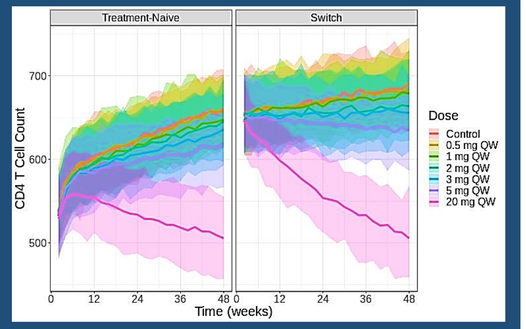
- CD4+ T cell and lymphocyte models adequately describe data from ISL QD Treatment and Phase 2 QM PreP
  - Phase 2 QD dose ranging study in treatment naïve (P011) shown
  - Phase 3 QD treatment in virologically suppressed (P018) shown
- No intrinsic factors were identified that impacted ISL-exposure related changes in CD4+ T cells or lymphocytes

ISL 2 mg QW is predicted to rapidly achieve efficacious exposures for wild-type and M184I/V HIV variants and have similar CD4+ T cell and lymphocyte changes as standard ART for virologically suppressed PWH.

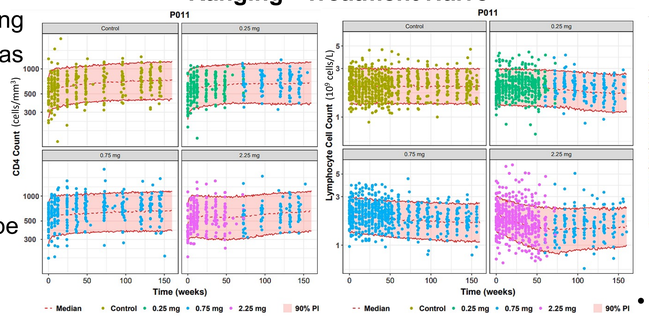
Predicted ISL-TP Concentrations Rapidly Achieve Efficacious Levels for WT and M184I/V following 0.25 mg QD and 2 mg QW



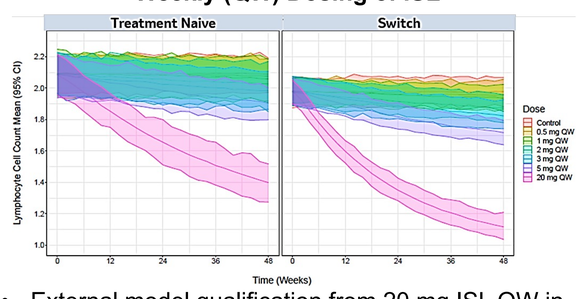
Predicted CD4+ T Cell Changes following Once Weekly (QW) Dosing of ISL



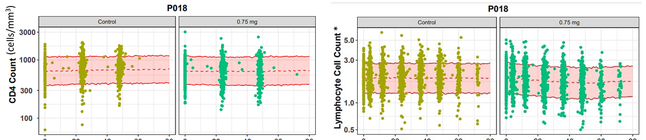
Model Accurately Describes Phase 2 QD Dose Ranging - Treatment Naïve



Predicted Lymphocyte Changes following Once Weekly (QW) Dosing of ISL



Model Accurately Describes Phase 3 QD – Virologically Suppressed

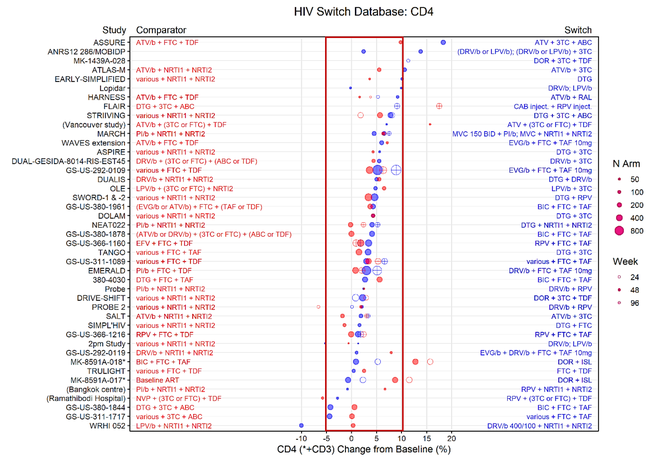


- External model qualification from 20 mg ISL QW in Virologically Suppressed (P013) supports QW predictions

ISL Dose (mg)	CD4+ T Cell Mean CBL (95% CI) Observed P013 (ISL 20 mg + MK-8507 100 mg)		Predicted CD4+ T Cell Mean CBL (95% CI) Model (ISL 20 mg QW)
	24 doses (N=27)	>12 doses (N=38)	
20 mg QW	-7.57 (-16.68, -1.54).	-12.8 (-20.3, -5.3)	-13.7 (-17.0, -9.9)

CBL - Change from Baseline

Benchmarking CD4+ T Changes Across Virologically Suppressed Clinical Trials



- CD4+ T Cell Percent Changes from Baseline in Virologically Suppressed Trials Falls between -5 to +10% (red box)

Predicted CD4+ T Cell and Lymphocytes Increases for ISL 2 mg QW are Similar to Standard ART

ISL QW Dose (mg)	Predicted Mean (95% CI) CD4+ T Cell Count 48 Weeks	Predicted Change from Baseline Ratio of ISL vs Control (95% CI) 48 Weeks
Standard ART	750 (706, 799)	-
2	725 (683, 775)	0.959 (0.905, 1.04)

* Mean (95%CI) for the predicted CD4+ T Cell Count at baseline in the Standard ART group was 717 (673, 763)

ISL QW Dose (mg)	Predicted ISL Mean (95% CI) Lymphocyte Cell Count (10^3/µL) 48 Weeks	Predicted Change from Baseline Ratio of ISL vs Control (95% CI) 48 Weeks
Standard ART	1.98 (1.88, 2.07)	-
2	1.87 (1.78, 1.96)	0.948 (0.900, 1.01)

* Mean (95%CI) for the predicted Lymphocyte Cell Count at baseline in the Standard ART group was 1.98 (1.87, 2.06)

CONCLUSIONS

Efficacy - ISL 0.25 mg QD and 2 mg QW predicted to rapidly achieve efficacious exposures for wild-type virus and M184I/V variants

CD4+ T Cell and Lymphocytes - ISL 0.25 mg QD and 2 mg QW predicted to have similar lymphocyte and CD4+ T cell increases compared to standard ART

ADDITIONAL KEY INFORMATION

ISL 2mg + LEN 300mg QW is be evaluated in a phase 2 study in virologically suppressed PWH (NCT05052996)