Confidential

Modeling Accurately Predicts Efficacious Islatravir QW Dose with no Lymphocyte and CD4 Changes

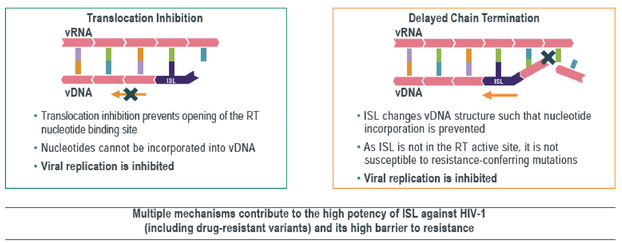
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BACKGROUND

- Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) being studied for HIV-1 treatment (**Figure 1**).
- Exposure-related decreases in total lymphocyte and CD4+ T-cell counts were observed across ISL clinical trials, with greater changes observed in ISL higher-dose regimens.
- Models that describe changes in lymphocytes and CD4+ T-cells in relation to intracellular ISL-triphosphate (TP) concentrations were used to optimize the QW dose for HIV treatment.
- Modeling was used to identify an ISL QW dose that provides efficacious concentrations with no negative impact on lymphocyte or CD4+ T-cell counts.
- ISL 2 mg QW was predicted to achieve efficacy thresholds and similar lymphocyte and CD4+ T-cell dynamics compared to standard antiretroviral therapy (ART).
- Subsequently, a Phase 2 study was initiated (GS-US-563-6041, N=104) with virologically suppressed (VS) people with HIV-1 randomized 1:1 to switch from once-daily (QD) oral bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) to oral QW ISL 2 mg + lenacapavir (LEN) 300 mg (NCT05052996)[3].

Figure 1. Islatravir, a NRTTI with Multiple Mechanisms of Action



ISL, islatravir; NRTTI, nucleoside reverse transcriptase translocation inhibitor; RT, reverse transcriptase; vDNA, viral DNA; vRNA, viral RNA

OBJECTIVE

Evaluate consistency between Phase 2 efficacy and lymphocyte and CD4+ T-cell results with predictions from previously developed PopPK and PK/PD models

Phase 2 efficacy and lymphocyte and CD4+ T-cell results are consistent with predictions that ISL 2 mg QW in combination with LEN is ***highly efficacious*** with ***no negative impact on lymphocyte or CD4+ T-cell counts***.

ISL 2 mg/LEN 300 mg is currently in Phase 3 with the ***potential to be the first oral QW treatment option***.

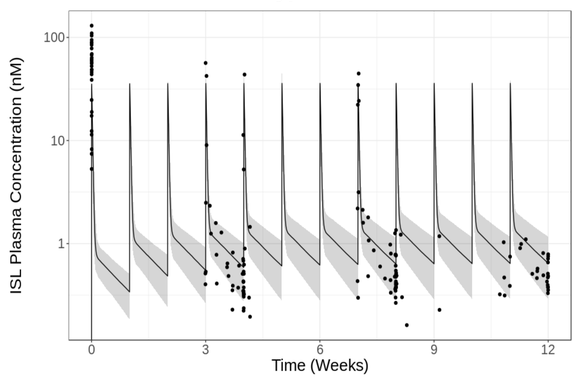
METHODS

- Simulations were performed using a previously developed ISL PopPK model[1,2]; observed ISL plasma concentrations from Phase 2 participants served as inputs to predict ISL-TP exposures, which were not directly measured
- Previously developed ISL PK/PD models[1,2] were used to simulate lymphocyte and CD4+ T-cell counts using PopPK-predicted ISL-TP exposures for Phase 2 participants as input

RESULTS

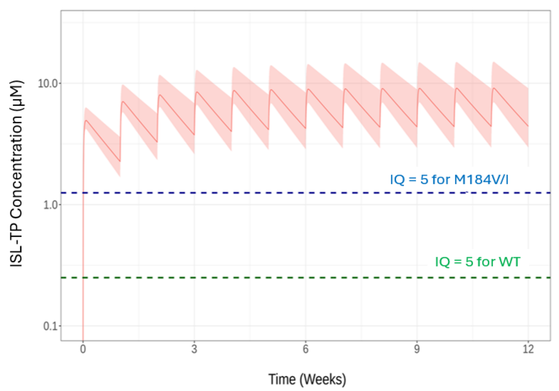
- Observed Phase 2 plasma ISL exposures were consistent with the predicted range (**Figure 2**)
- Predicted ISL-TP exposures for the Phase 2 participants exceeded PK thresholds for M184V/I variants and for wild-type (WT) HIV-1 (**Figure 3**)
  - At Week 24 in the Phase 2 study, ISL + LEN oral QW maintained virologic suppression rates (94.2%, 49/52) comparable to the standard of care, B/F/TAF QD (94.2%, 49/52)[3]

Figure 2. Observed ISL Plasma Exposures in Phase 2 Participants and Simulated ISL Plasma Exposures for 2 mg QW (Simulations Performed Prior to Phase 2 Study)



**ISL, islatravir; QW, once weekly;
Black points – observed ISL concentrations;
Solid Lines – Median prediction;
Shaded bands – 95% individual prediction interval**

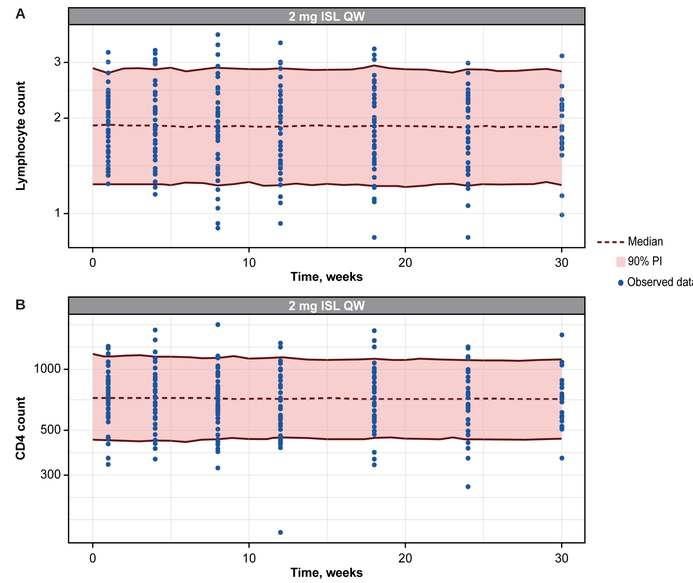
Figure 3. Predicted ISL-TP Concentrations in Phase 2 Participants Following ISL 2 mg QW Dosing



**IQ, inhibitory quotient; ISL-TP, islatravir triphosphate;
QW, once weekly; WT, wild type;
Solid Lines – Median prediction;
Colored bands – 95% individual prediction interval**

- As previously predicted[1], lymphocyte and CD4+ T-cell counts showed no decline in ISL+LEN-treated participants (**Figure 4**)

Figure 4. Predicted and Observed (A) lymphocyte counts and (B) CD4+ T-cell counts following ISL 2 mg QW



**ISL, islatravir; PI, prediction interval; QW, once weekly;
n = 1000*, reps = 100; *1000 sampled from the GS-US-563-6041 population (n = 52);
lymphocyte cell count = 10^3 cells/mm^3; CD4+ T-cell count = cells/mm^3;**

CONCLUSIONS

- At Week 24 in the Phase 2 study, ISL + LEN oral QW maintained high virologic suppression rates (94.2%, 49/52)[3]
- Phase 2 efficacy results are consistent with predictions that ISL 2 mg QW in combination with LEN is highly efficacious
- Lymphocyte and CD4+ T-cell counts showed no decline in ISL+LEN-treated Phase 2 participants as predicted
- These results support further clinical development and the continued use of modeling to predict outcomes and inform decisions; ISL 2 mg/LEN 300 mg QW is being evaluated in two Phase 3 studies (NCT06630286; NCT06630299)

REFERENCES

1. Vargo RC et al. Presented at Conference on Retroviruses and Opportunistic Infections (CROI); February 19-22, 2023; Seattle, Washington. Abstract 497.
2. Longo D et al. Presented at HIV Drug Therapy Glasgow; November 10-13, 2024; Glasgow, United Kingdom.
3. Colson AE et al. Presented at IDWeek; October 16-19, 2024; Los Angeles, California. Abstract 577.