Modeling-Supported Islatravir Dose Selection for Phase 3

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ABSTRACT

Background: Islatravir (ISL) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection. Single doses of ISL as low as 0.5 mg showed robust efficacy in a proof-of-concept (POC) clinical trial and established an inhibitory quotient (IQ; ratio of drug exposure to potency) of 5 for ISL for wild-type HIV-1. In a Phase 2 clinical trial (NCT03272347), participants who initiated ISL+doravirine (DOR) in combination with lamivudine (3TC) and switched to ISL+DOR no earlier than Week 24 had high efficacy at Week 48 as measured by HIV-1 RNA <50 c/mL. Data through Week 48 showed that exposure–response was flat, indicating an achievement of maximal efficacy at the ISL doses examined (0.25, 0.75, and 2.25 mg). Modeling and simulation, along with in vitro potency data, were used to select the dose for further clinical development of ISL most appropriate for HIV-1 treatment-naive, virologically suppressed, and heavily-treatment experienced (HTE) populations.

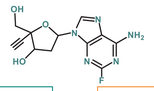
Methods: A population pharmacokinetic model for ISL and its active moiety, ISL-triphosphate (ISL-TP), has been developed based on Phase 1 and Phase 2 data in healthy participants and people living with HIV-1 (PLWH) and used to examine the Phase 2 exposure–response relationship. The population pharmacokinetic model was also used to predict the percentage of participants expected to have ISL-TP concentrations sufficient to have antiviral activity against common nucleoside reverse transcriptase inhibitor (NRTI)-resistant viruses (eg, M184V, etc).

Results: Based on an analysis of in vitro potency data, Phase 1b POC efficacy, and Phase 2 data, a dose of ISL 0.75 mg QD is expected to provide maximal efficacy in treatment-naive PLWH and also be highly efficacious in virologically suppressed and HTE participants. Based on the in vitro potency and supported by the POC data for ISL, the expected concentrations of ISL-TP after a single 0.75-mg dose are sufficient to suppress both wild-type virus and HIV-RT–resistant variants. ISL-TP accumulates after multiple dosing, resulting in higher IQ at steady state. Simulations show that most patients would rapidly surpass the IQ threshold for all common HIV-RT–resistant variants.

Conclusions: ISL 0.75 mg QD, in combination with DOR 100 mg QD, is appropriate for further evaluation in a development program consisting of treatment-naive, virologically suppressed, and HTE PLWH.

BACKGROUND

Figure 1. Islatravir, a First-in-Class NRTTI with Multiple Mechanisms of Action

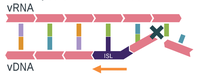


Translocation Inhibition



- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- Viral replication is inhibited

Delayed Chain Termination

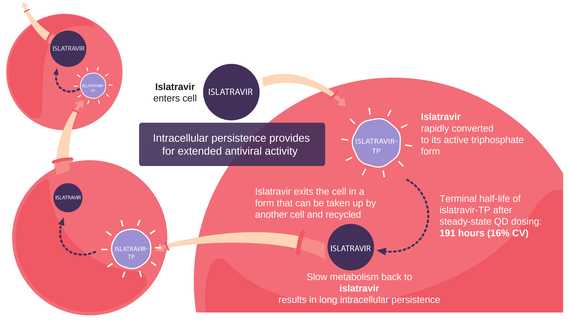


- ISL changes vDNA structure such that nucleotide incorporation is prevented
- As ISL is not in the RT active site, it is not susceptible to resistance-conferring mutations
- Viral replication is inhibited

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

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

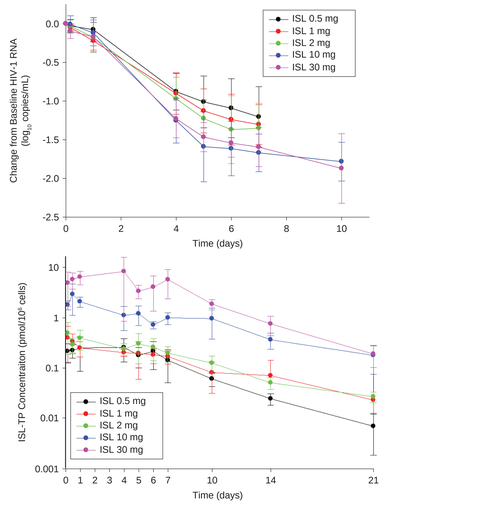
Figure 2. Islatravir Properties Contribute to Differentiated Pharmacokinetic (PK) and Long Half-life



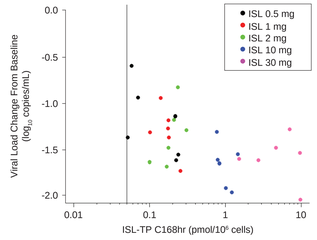
ISL Phase 1b Data Indicate Doses That Provide IQ ≥5 Against Wild-Type Have Robust Antiviral Efficacy

- The proof-of-concept study in naive-to-treatment people living with HIV (PLWH) showed that single ISL doses as low as 0.5 mg and ISL-triphosphate (ISL-TP) concentrations in peripheral blood mononuclear cells (PBMCs) as low as 0.05 pmol/10^6 cells provide robust efficacy
- Inhibitory quotient (IQ) is the ratio of trough concentration (C_{trough}) and in vitro potency (IC_{50}) and describes the relationship between antiviral potency, PK, and virologic outcomes
- These data were instrumental in establishing an IQ threshold for ISL of 5

Figure 3. Single ISL Doses as Low as 0.5 mg Show Antiviral Activity and an IQ ≥5



ISL Dose (mg)	Placebo-Corrected Viral Load Decline at Day 7
30	-1.57
10	-1.64
2	-1.32
1	-1.28
0.5	-1.18

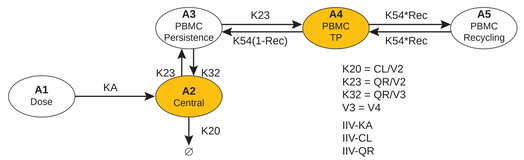


METHODS

Population Pharmacokinetic Model Simultaneously Describes ISL in Plasma and ISL-TP in PBMCs

- A population PK model that describes ISL concentrations in plasma and ISL-TP concentrations in PBMCs, and the interaction of the two, has been developed from pooled data from Phase 1 studies (P001, P002, P003, and P009) and one Phase 2 study (P011)
- The model captured the full dataset well and was found to be stable and reproducible
- A covariate analysis was performed, and no covariates were found to significantly improve the model fits
- A population PK model was used to simulate ISL-TP concentration profiles for exposure–response analysis and an analysis of ISL IQ for different NRTI-resistant variants

Figure 4. Population PK Model Describing ISL and ISL-TP Concentrations

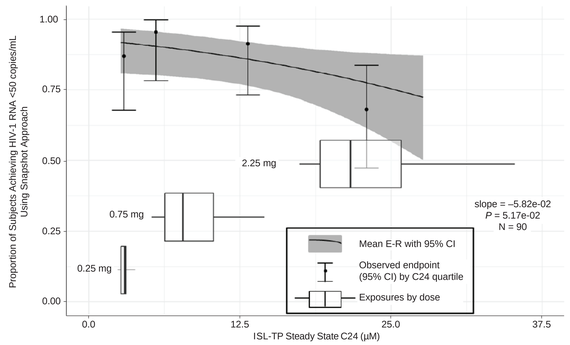


RESULTS

ISL-TP Exposure–Response Modeling Shows All Phase 2 Doses Are on the Plateau of Efficacy

- Participants in a Phase 2 clinical trial who initiated ISL+doravirine (ISL+DOR) in combination with lamivudine (3TC) and switched to ISL+DOR no earlier than Week 24 had high efficacy at Week 48 as measured by HIV-1 RNA <50 copies/mL
- The population PK model was used to examine the exposure–response for ISL at the doses examined in Phase 2
- Data through Week 48 showed that exposure–response was flat, indicating an achievement of maximal efficacy at the ISL doses examined (0.25, 0.75, and 2.25 mg)

Figure 5. ISL-TP Exposure-Response Modeling



Solid black line represents mean predicted exposure–response (E-R) relationship. Shaded area represents the 95% confidence interval of the prediction over the 5th to 95th percentile of exposures. Markers summarize the observed endpoint and 95% confidence interval by ISL-TP C24 quantile. Horizontal boxplots denote the distribution of individual exposures at different doses as indicated from P011, showing the median, 25th, and 75th percentiles, and the whiskers correspond to the 5th and 95th percentiles.

ISL 0.75 mg QD Has Higher Wild-Type IQ Than NRTIs Approved for HIV Treatment

- Once exposure–response was determined to be flat in P011, IQ was leveraged to further understand the ISL's antiviral activity against both wild-type and NRTI-resistant variants
- ISL potency and PK allow for generation of high IQ values against wild-type virus
- ISL 0.75 mg QD demonstrates wild-type IQ = 113 at Day 8 and wild-type IQ = 164 at steady state
- Marketed doses of 3TC, emtricitabine (FTC), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF) demonstrate wild-type IQs of 2.29 to 36.9 at steady state

Drug	Dose	Active Form	IC_{50} (fmol/10^6 cells) Mean ± SD	C_{trough} (fmol/10^6 cells) Mean (CV%)	N	WT IQ (90% CI)
ISL	0.75 mg QD	ISL-TP	9.74 ± 4.06[a]	Day 1 = 200 (22)[d]	90	21 (10-31)
				Day 8 = 1100 (25)[e]	90	113 (73-152)
				SS = 1600 (35)[f]	30	164 (106-223)
3TC	150 mg BID/ 300 mg QD	3TC-TP	635 ± 331[b]	SS = 2620 (112)[g-j]	68	4.13 (1.47-6.79)
FTC	200 mg QD	FTC-TP	113[c]	SS = 4160 (63.7)[j-l]	64	36.9 (32.1-41.7)
TAF	25 mg QD	TFV-DP	41.5 ± 19.7[b]	SS = 311 (19.8)[m,n]	160	7.48 (3.37-11.6)
TDF	300 mg QD	TFV-DP	41.5 ± 19.7[b]	SS = 95.0 (59.7)[j,k,o]	63	2.29 (1.00-3.58)

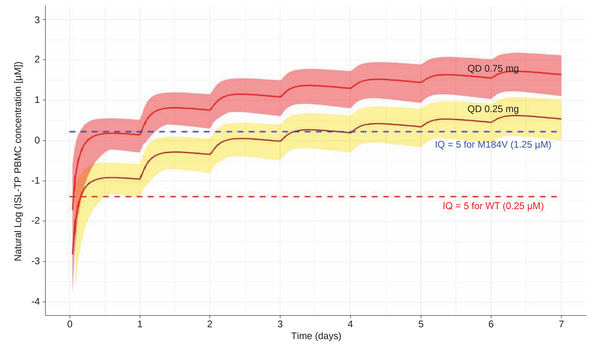
WT, wild-type; IQ, inhibitory quotient; ISL, islatravir; 3TC, lamivudine; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TP, triphosphate; DP, diphosphate; SS, steady state.

[a]N=4. [b]N=2. [c]N=1. [d]Estimated ISL-TP Day 1 concentrations from Phase 2, P011, participants living with HIV. [e]Estimated ISL-TP Day 7 concentrations from Phase 2, P011, participants living with HIV. [f]Estimated ISL-TP steady-state concentrations from Phase 2, P011, participants living with HIV. [g]Moore KH, et al. *AIDS*. 1999;13:2239-2250. [h]Rodriguez JR, et al. *Antimicrob Agents Chemother.* 2000;44(11):3097-3100. [i]Yuen GJ, et al. *Antimicrob Agents Chemother.* 2004;48(1):176-182. [j]Jackson A, et al. *J Acquir Immune Defic Syndr.* 2013;62(3):275-281. [k]Seifert SM, et al. *AIDS Res Hum Retroviruses.* 2017;32(10/11):981-991. [l]Wang LH, et al. *AIDS Res Hum Retroviruses.* 2004;20(11):1173-1182. [m]*Clinical Pharmacology Review.* NDA208215 FTC/TAF. [n]Ruane PJ, et al. *J Acquir Immune Defic Syndr.* 2013;63(4):449-455. [o]Pruvost A, et al. *Antimicrob Agents Chemother.* 2009;53(5):1937-1943.

ISL 0.75 mg QD is Expected to Provide Quick and Full Antiviral Activity Against M184V

- Within two doses, ISL 0.75 mg QD generates ISL-TP concentrations high enough to provide antiviral activity against M184V with an IQ of 5
- IQ values for M184V increase with additional daily dosing of IS due to accumulation of ISL-TP
- ISL 0.25 mg QD quickly provides adequate antiviral activity against wild-type virus but requires approximately 1 week to generate sufficient ISL-TP levels to cover M184V

Figure 6. ISL 0.75 mg QD Simulations Predict Antiviral Activity Against WT and M184V Virus



ISL 0.75 mg QD Provides High IQs Against Wild-Type and Common NRTI-Resistant Variants

- ISL 0.75 mg QD was selected to provide antiviral activity against wild-type and common NRTI-resistant variants, including M184V, quickly
- Antiviral activity against 69ins + M184I/V (NRTI-resistant variant conferring highest potency shift to ISL [21-fold; exceedingly rare]) is provided by Day 8
- IQs increase as ISL-TP accumulates, resulting in IQ ≥5 by Day 8 for all NRTI-resistant variants
- Higher doses of ISL are not predicted to substantially expand the NRTI-resistant variants predicted to meet the threshold IQ

Virus	Fold Shift From Wild-Type IC_{50}	ISL 0.75 mg QD IQ, Day 1	ISL 0.75 mg QD IQ, Day 8	ISL 0.75 mg QD IQ, Steady State
Wild-type	1	21	113	175
M184V	5	4	23	35
69ins + M184I/V	21	1	5	8

Greater Than 90% of Participants Predicted to Have IQ >5 for the Least Susceptible NRTI-Resistant Variants

- The ISL population PK model was also used to predict ISL-TP PBMC profiles for 5000 HIV-1 patients
- These simulations were used to examine the proportion of patients, dosed with ISL QD, at one day, one week, and at steady state that would be expected to have ISL-TP PBMC concentrations allowing for an IQ ≥5 for common NRTI-resistant variants
- With ISL 0.75 mg QD dosing, 100% of participants are predicted to have full inhibitory activity (IQ >5) against M184V by Day 8
- With ISL 0.75 mg QD dosing, >90% of participants are predicted to have full inhibition activity (IQ >5) against rare variant (21-fold less susceptible than wild-type to ISL) by steady state

Virus	% of Participants Receiving ISL 0.75 mg QD IQ >5, Day 1	% of Participants Receiving ISL 0.75 mg QD IQ >5, Day 8	% of Participants Receiving ISL 0.75 mg QD IQ >5, Steady State
Wild-type	100	100	100
M184V	~50	100	100
69ins + M184I/V	0	57	91

CONCLUSION

ISL 0.75 mg QD, in combination with DOR 100 mg QD, is appropriate for further evaluation in Phase 3 consisting of treatment-naíve, virologically suppressed, and highly-treatment experienced PLWH.

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