P047

Analysis of Protocol-Defined Virologic Failure Through Week 96 From a Phase 2 Trial (P011) of Islatravir and Doravirine in Treatment-Naïve Adults With HIV-1 Infection

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Background

- Islatravir (ISL, MK-8591) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection
- Doravirine (DOR) is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV-1
- The combined attributes of ISL and DOR create the potential for a potent, simple, 2-drug regimen that may address some of the long-term safety and toxicity concerns of traditional regimens
- Protocol 11 is a phase 2b dose-ranging trial of DOR + ISL (NCT03272347)
  - Virologic suppression among participants who switched to ISL + DOR was high at week 48 and maintained through week 96[1,2]
  - ISL + DOR was generally well tolerated at all doses, with few drug-related AEs; three of 90 participants in the combined ISL groups discontinued due to AEs through week 96[2]
  - The 0.75 mg dose of ISL was selected for further clinical development[3]

Current Analysis Objectives

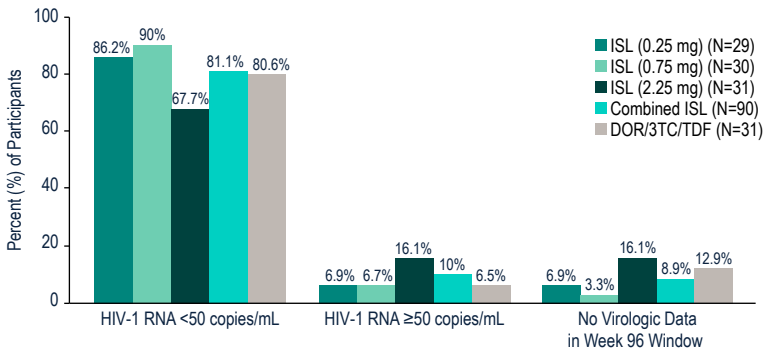
Objective: To characterize participants who discontinued with protocol-defined virologic failure from the PN011 Phase 2b trial of islatravir (ISL) and doravirine (DOR) through week 96

Protocol-Defined Virologic Failure (PDVF) is defined as:

- Viral Rebound
  - HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study

    or
  - Confirmed HIV-1 RNA >1 log increase from the HIV-1 RNA nadir after a >1 log decrease in HIV-1 RNA from baseline at any time during the study
- Nonresponse
  - ≥200 copies/mL at any time from week 24 through week 48
  - Confirmed HIV-1 RNA ≥50 copies/mL at week 48
- Initial PDVF HIV-1 must be confirmed by an additional measurement within 2 weeks

Figure 1. Virologic Outcomes at Week 96[2] (FDA Snapshot Approach)



The numerically lower response rates for ISL (2.25 mg) + DOR group was largely driven by discontinuations through week 48.

Table 1. Protocol-Defined Virologic Failure (PDVF) at Week 96

	ISL (0.25 mg) + DOR[a] QD	ISL (0.75 mg) + DOR[a] QD	ISL (2.25 mg) + DOR[a] QD	DOR/3TC/TDF QD
	N=29	N=30	N=31	N=31
Protocol-defined virologic failure				
Nonresponder, n (%)	0 (0)	0 (0)	1 (3.2)	0 (0)
Rebounder with HIV-1 RNA >50 copies/mL, n (%)	2 (6.9)	2 (6.7)	1 (3.2)	1 (3.2)
Rebounder with HIV-1 RNA >200 copies/mL, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Details on participants with HIV-1 RNA ≥50 copies/mL not classified as PDVF				
Early discontinuation, n (%)	0 (0)	0 (0)	3 (9.7)	1 (3.2)
Reasons for early discontinuation			2 lost to follow-up, 1 participant withdrawal	1 protocol violation for exclusionary criteria

- A total of 7 participants discontinued due to PDVF through week 96
  - 6 participants discontinued with PDVF during weeks 0-48
- Between weeks 48 and 96 one participant (rebounder in 2.25 mg group) discontinued with PDVF
- All participants with PDVF had confirmatory HIV-1 RNA levels <80 copies/mL and no participants met the criteria for resistance testing

[a]In the 2.25 mg group, the lost to follow-up discontinuations occurred at week 12 and week 28; the participant withdrawal discontinuation occurred at week 8. In the DOR/3TC/TDF group, the protocol violation exclusionary criteria discontinuation occurred at week 2.

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Disclosure

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References

1. Molina J-M, et al. Islatravir (ISL, MK-8591) at doses of 0.25 to 2.25 mg QD in combination with doravirine maintains viral suppression through 48 weeks in adults with HIV-1 infection. Presented at IAS Conference on HIV Science 2019; July 21-24, 2019; Mexico City, Mexico.
2. Molina J-M, et al. Islatravir in combination with doravirine maintains HIV-1 viral suppression through 96 weeks. To be presented at Drug Therapy Glasgow 2020; October 25-28, 2020; Glasgow, Scotland.
3. Rudd DJ, et al. Modeling-supported islatravir dose-selection for phase 3. Presented at Conference on Retroviruses and Opportunistic Infections (CROI) 2020; March 8-11, 2020; Boston, Massachusetts, USA.

Presented at HIV Drug Therapy-Glasgow 2020; October 5-8, 2020.

Table 2. Summary of HIV-1 RNA Levels by Study Visit for Participants With PDVF at Week 96

Group	Baseline	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 60	Wk 72
1: ISL (0.25)+ DOR+3TC	66,774	927	746	94	70	<50	<50	<50	<50	<50	<50	<50	<50	**51**[a] (79)			
2: ISL (0.25)+ DOR+3TC	153,790	3,551	1,344	552	412	106	<50	132 <50	**93**[a] (55)								
3: ISL (0.75)+ DOR+3TC	626,957	1,497	680	665	248	151	151	<50	**87**[a] (58)								
4: ISL (0.75)+ DOR+3TC	4,916	147	125	62	<50	<50	<50	<50	<50	<50	<50	<50	**77**[a] (53)				
5: ISL (2.25)+ DOR+3TC	413,236	4,244	2,308	1,098	772	424	343	172	81	85	84	103	72	**93**[a] (50)			
6: DOR/3TC/ TDF	437,894	2,951	2,012	771	34	75	<50	<50	**59**[a] (55)								
7: ISL (2.25)+ DOR+3TC	259,507	2,441	1,671	930	306	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50	**79**[a] (70)

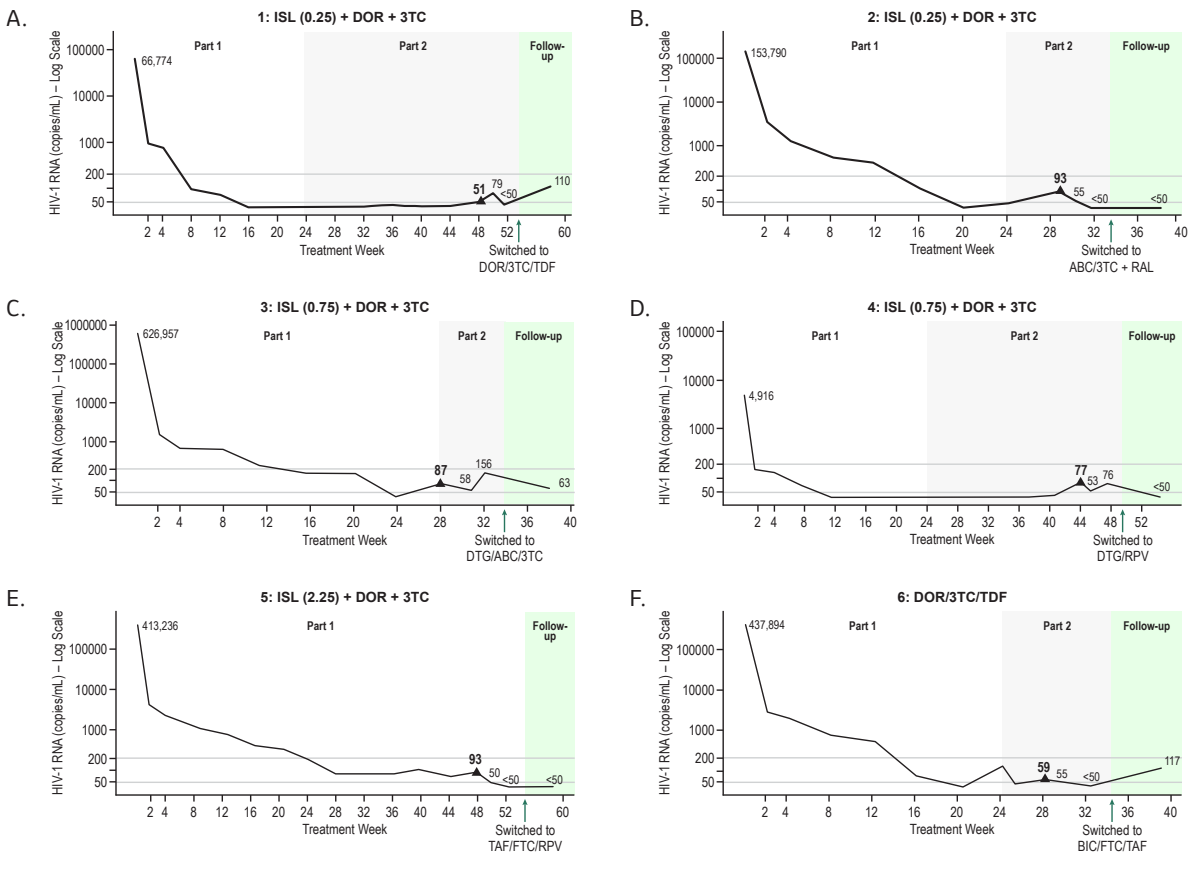
Protocol-defined virologic failure (PDVF) for this study is defined as one of the following: 1. Rebounder: Confirmed HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study or confirmed HIV-1 RNA >1 log increase from the HIV-1 RNA nadir after a >1 log decrease in HIV-1 RNA from baseline at any time during the study; or 2. Nonresponder: Confirmed HIV-1 RNA ≥200 copies/mL at any time from week 24 through week 48 or confirmed HIV-1 RNA ≥50 copies/mL at week 48.
[a]Initial PDVF value (Confirmation value).

Participant 7, the rebounder in the 2.25 mg ISL group, is the only discontinuation due to PDVF that occurred between weeks 48 and 96.

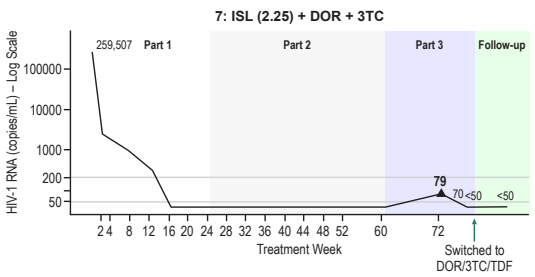
HIV-1 RNA level (copies/mL) prior to suppression
<50 copies/mL first achieved and after suppression
≥50 and <200 copies/mL after suppression
≥200 copies/mL after suppression

Figure 2. Summary of HIV-1 RNA Levels by Study Visit

Participants who discontinued with PDVF during weeks 0-48



Participants who discontinued with PDVF during weeks 48-96



- Five of seven participants with PDVF in all groups had a baseline HIV-1 RNA level of >100,000 copies/mL
- Five of seven participants with PDVF in all groups had an additional HIV-1 RNA level of <50 prior to changing to a new regimen
- Three of seven participants with PDVF in all groups continued to have low-level viremia after switching to a new regimen

Conclusions

- Participants who initiated on ISL+DOR in combination with 3TC and switched to ISL+DOR had high efficacy at week 96 as measured by HIV-1 RNA <50 copies/mL, comparable to that of DOR/3TC/TDF
- Rates of PDVF were low, and all participants who discontinued due to PDVF had confirmed HIV-1 RNA levels <80 copies/mL
- Between weeks 48 and 96 one participant discontinued with PDVF
- No participant in any treatment group met criteria for resistance testing (>400 copies/mL)
- During the limited 42-day follow-up period, 3 out of 7 participants who discontinued due to PDVF continued to have low-level viremia after switching to a new regimen

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