P-389

Switching to Doravirine/Islatravir (100 mg/0.25 mg) Once Daily Maintains Viral Suppression Through Week 48 in the Presence of Archived NNRTI Resistance-Associated Mutations and/or M184I/V in Proviral DNA

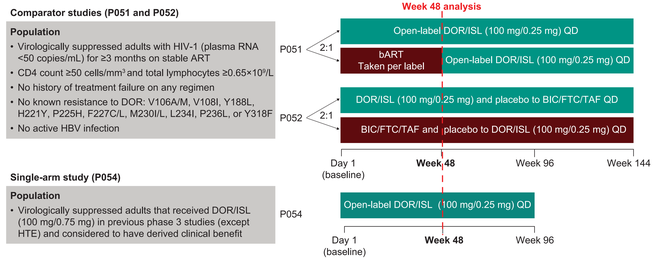
Tracy L. Diamond; Anjana Grandhi; Monica Fuszard; Yayun Xu; Uchechukwu Nwoke; Ying Zhang; Stephanie Klopfer; Karen Eves; Jaime Benner; Mengchun Li; Wayne Greaves; Rima Lahoulou; Jason Kim; Michelle C. Fox; Ernest Asante-Appiah

Merck & Co., Inc., Rahway, NJ, USA

Background

- Doravirine/islatravir (DOR/ISL; 100 mg/0.25 mg) is an investigational once-daily (QD) single-tablet regimen comprised of DOR, an approved non-nucleoside reverse transcriptase inhibitor (NNRTI), and ISL, a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- DOR and ISL have potent in vitro activity against clinically relevant variants bearing resistance-associated mutations (RAMs) in reverse transcriptase (RT) and exhibit non-overlapping and complementary resistance profiles[1,2]
- Switching to DOR/ISL (100 mg/0.25 mg) is being investigated for the treatment of virologically suppressed adults living with HIV-1 in three phase 3 studies: MK-8591A-051 (P051), MK-8591A-052 (P052), and MK-8591A-054 (P054) **(Figure 1)**

Figure 1. Study designs for phase 3 studies of DOR/ISL (100 mg/0.25 mg) in virologically suppressed adults

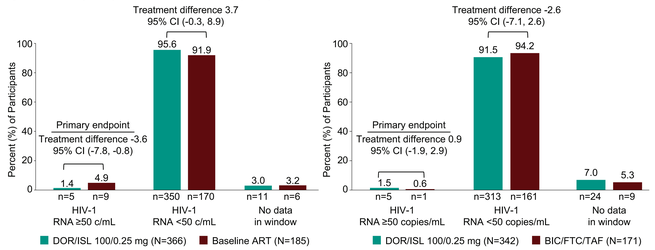


Note: Resistance analysis was not required for enrollment; M184I/V was not exclusionary.

HBV, hepatitis B virus; HTE, heavily treatment experienced.

- Switching to DOR/ISL (100 mg/0.25 mg) maintained high rates of viral suppression (HIV-1 RNA <50 copies/mL) through Week 48 in P051, P052, and P054, including among participants with pre-existing NNRTI RAMs and/or M184I/V in proviral DNA[3-6]
  - DOR/ISL was non-inferior to baseline antiretroviral therapy (bART) in P051 and BIC/FTC/TAF in P052 based on the primary endpoint (percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48)[3,4]
  - No treatment-emergent resistance to either DOR or ISL was observed through Week 48 in the 3 studies[3-5]

Figure 2. Efficacy analyses at Week 48 (FDA Snapshot) for P051 and P052



Objective

- Examine the prevalence and impact of pre-existing RAMs at baseline in proviral DNA on viremia outcomes among participants who received DOR/ISL through Week 48 in P051, P052, and P054

Methods

- Baseline resistance analysis was performed retrospectively on proviral DNA by GenoSure Archive assay (Monogram Biosciences) using whole blood samples collected on Day 1
- Resistance analysis was performed using RAMs in RT associated with each class based on published literature and curated databases[7,8] **(Table 1)**

Table 1. List of RT RAMs evaluated for each drug class

Protein	ARV class	Major RAMs	Minor RAMs
RT	NNRTI	A98G, L100I, K101E/P, K103N/S, V106A/M/T, V108I, E138A/G/K/Q/R, Y181C/I/V, Y188C/H/L/A/E/S, F227C/I/L/R/V, M230I/L, L234I, Y318F	V90I, K101H, K103R, V106I, V179D/F/L/T, H221Y, P225H, F227H, P236L
	- DOR	V106A/M, V108I, Y188L, F227C/L/V, M230I/L, L234I, Y318F	H221Y, P225H, P236L
	NRTI	M41L, A62V, K65E/N/R, D67N, T69D/N, T69N, K70E/R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, K219E/N/Q/R	E44D, V118I, T215A/C/D/E/G/H/I/L/N/S/V

Major RAMs confer larger reductions in susceptibility. Minor RAMs occur after emergence of a major RAM, confer smaller reductions in susceptibility, or may be accessory mutations that increase fitness.[8]

- Viremia outcomes based on HIV-1 RNA values (cobas HIV-1) through Week 48 were defined by the following mutually exclusive categories:
  - Participants who discontinued study with confirmed HIV-1 RNA ≥200 copies/mL (DISC)
  - Participants with low-level viremia (LLV, confirmed HIV-1 RNA ≥50 copies/mL without meeting discontinuation criteria)
  - Participants with transient viremia (TV, HIV-1 RNA ≥50 copies/mL at any on-treatment visit preceded and followed by HIV-1 RNA <50 copies/mL)

Results

Baseline resistance analysis in proviral DNA

- Baseline proviral DNA data were available for approximately 90% of participants in each study

Table 2. Prevalence of pre-existing RT RAMs observed in >5% of participants with baseline proviral DNA data in any study arm

Protein	RAM	P051		P052		P054	Pooled
		DOR/ISL (100 mg/0.25 mg)	Baseline ART	DOR/ISL (100 mg/0.25 mg)	BIC/FTC/TAF	DOR/ISL (100 mg/0.25 mg)	DOR/ISL (100 mg/0.25 mg)
		N = 322 n (%)	N = 166 n (%)	N = 309 n (%)	N = 152 n (%)	N = 596 n (%)	N=1227 n (%)
RT	**Any NNRTI RAM**	**79 (24.5)**	**33 (19.9)**	**82 (26.5)**	**41 (27.0)**	**162 (27.2)**	**323 (26.3)**
	K103N/R/S	34 (10.6)	11 (6.6)	38 (12.3)	16 (10.5)	53 (8.9)	125 (10.2)
	E138A/G/K/Q/R	21 (6.5)	7 (4.2)	18 (5.8)	9 (5.9)	39 (6.5)	78 (6.4)
	Any NRTI RAM	**59 (18.3)**	**25 (15.1)**	**62 (20.1)**	**32 (21.1)**	**132 (22.1)**	**253 (20.6)**
	V118I	20 (6.2)	11 (6.6)	18 (5.8)	10 (6.6)	49 (8.2)	87 (7.1)
	M184I/V	20 (6.2)	5 (3.0)	24 (7.8)	10 (6.6)	26 (4.4)	70 (5.7)

Note: RAMs were sometimes present as mixtures with wild-type or other mutations within the same codon.

- The prevalence of RT RAMs was comparable between studies and treatment groups
- Among 1,227 participants switched to DOR/ISL (100 mg/0.25 mg) across P051, P052, and P054;
  - 323 (26.3%) had pre-existing NNRTI RAMs
  - 70 (5.7%) had pre-existing M184I/V
- K103N/R/S, E138K/Q, and M184I/V were the most prevalent major RAMs observed in RT at baseline

Table 3. Prevalence of pre-existing DOR RAMs

RAM	P051		P052		P054	Pooled
	DOR/ISL (100 mg/0.25 mg)	Baseline ART	DOR/ISL (100 mg/0.25 mg)	BIC/FTC/TAF	DOR/ISL (100 mg/0.25 mg)	DOR/ISL (100 mg/0.25 mg)
	N=322 n (%)	N=166 n (%)	N=309 n (%)	N=152 n (%)	N=596 n (%)	N=1,227 n (%)
Any DOR RAM	**7 (2.2)**	**7 (4.2)**	**15 (4.9)**	**3 (2.0)**	**21 (3.5)**	**43 (3.5)**
V108I	2 (0.6)	3 (1.8)	3 (1.0)	2 (1.3)	7 (1.2)	12 (1.0)
V106A/M	4 (1.2)	0	1 (0.3)	0	4 (0.7)	9 (0.7)
P225H	1 (0.3)	0	3 (1.0)	1 (0.7)	3 (0.5)	7 (0.6)
H221Y	0	1 (0.6)	4 (1.3)	1 (0.7)	3 (0.5)	7 (0.6)
M230I/L	0	0	2 (0.6)	0	2 (0.3)	4 (0.3)
F227C/L/V	1 (0.3)	1 (0.6)	0	0	2 (0.3)	3 (0.2)
Y188L	2 (0.6)	0	0	1 (0.7)	0	2 (0.2)
Y318F	0	1 (0.6)	2 (0.6)	0	0	2 (0.2)
L234I	0	0	1 (0.3)	0	0	1 (0.0)
P236L	0	1 (0.6)	0	0	0	0

- Although a history of DOR resistance was exclusionary, DOR RAMs were detected in 3.5% of participants that switched to DOR/ISL (100 mg/0.25 mg) across P051, P052, and P054
- V108I was the most prevalent DOR RAM; observed at <2% in all DOR/ISL groups

Viremia outcomes in participants with baseline proviral DNA data

Table 4. Viremia outcomes through Week 48 in participants with proviral DNA data at baseline

Participant(s) with:		P051 DOR/ISL (100 mg/0.25 mg)	P051 Baseline ART	P052 DOR/ISL (100 mg/0.25 mg)	P052 BIC/FTC/TAF	P054 DOR/ISL (100 mg/0.25 mg)	Pooled DOR/ISL (100 mg/0.25 mg)
Archived proviral DNA data	**All**	**N=322**	**N=166**	**N=309**	**N=152**	**N=596**	**N=1227**
	DISC (%)	3* (0.9)	0	2 (0.6)	0	1 (0.2)	6* (0.5)
	LLV (%)	5 (1.6)	6 (3.6)	5 (1.6)	2 (1.3)	13 (2.2)	23 (1.9)
	TV (%)	15 (4.7)	17 (10.2)	18 (5.8)	8 (5.3)	38 (6.4)	71 (5.8)

*Includes 2 participants who were ineligible for enrollment due to having either a previous history of virologic failure or previous documentation of DOR resistance (Y188L).

DISC=discontinued with confirmed HIV-1 RNA ≥200 copies/mL; LLV=low-level viremia; N=participants with archived proviral DNA data; TV=transient viremia.

- Viremia outcomes in participants with proviral DNA data were comparable between treatment groups across all 3 studies
- The number of participants who discontinued due to viremia was low; transient viremia was the most common category - observed in ≤10% across studies and treatment groups.

Table 5. Viremia outcomes through Week 48 in participants with or without NNRTI RAMs or M184I/V at baseline

Participant(s) with:		P051 DOR/ISL (100 mg/0.25 mg)	P051 Baseline ART	P052 DOR/ISL (100 mg/0.25 mg)	P052 BIC/FTC/TAF	P054 DOR/ISL (100 mg/0.25 mg)	Pooled DOR/ISL (100 mg/0.25 mg)
No NNRTI RAMs or M184I/V	**All**	**223**	**128**	**203**	**101**	**408**	**834**
	DISC (%)	0	0	2 (1.0)	0	1 (0.2)	3 (0.4)
	LLV (%)	4 (1.8)	6 (5.7)	0	2 (2.0)	3 (0.7)	7 (0.8)
	TV (%)	12 (5.4)	15 (9.0)	13 (6.4)	5 (5.0)	21 (5.1)	46 (5.5)
NNRTI RAMs	**All**	**79**	**33**	**82**	**41**	**162**	**323**
	DISC (%)	2* (2.5)	0	0	0	0	2* (0.6)
	LLV (%)	1 (1.3)	0	3 (3.7)	0	9 (5.6)	13 (4.0)
	TV (%)	3 (3.8)	2 (6.1)	4 (4.9)	2 (4.9)	14 (8.6)	21 (6.5)
M184I/V	**All**	**20**	**5**	**24**	**10**	**26**	**70**
	DISC (%)	1* (5.0)	0	0	0	0	1* (1.4)
	LLV (%)	0	0	2 (8.3)	0	1 (3.8)	3 (4.3)
	TV (%)	0	0	1 (4.2)	1 (10.0)	3 (11.5)	4 (5.7)
Both NNRTI RAMs and M184I/V†	**All**	**7**	**1**	**15**	**4**	**13**	**35**
	DISC (%)	1* (14.3)	0	0	0	0	1* (2.9)
	LLV (%)	0	0	2 (13.3)	0	1 (3.8)	3 (8.6)
	TV (%)	0	0	1 (6.7)	0	2 (15.4)	3 (8.6)

*Includes participant(s) who were ineligible for enrollment due to having either a previous history of virologic failure or previous documentation of DOR resistance (Y188L).

†Participants with Both NNRTI RAMs and M184I/V were also included in the separate rows for NNRTI RAMs and M184I/V.

DISC=discontinued with confirmed HIV-1 RNA ≥200 copies/mL; LLV=low-level viremia; TV=transient viremia.

- The percentage of participants in each viremia category was comparable in the presence or absence of NNRTI RAMs and/or M184I/V
- Among DOR/ISL participants from the 3 studies, the number of participants with both NNRTI RAMs and M184I/V at baseline was small (35) and 7 had viremia
  - 1 participant who discontinued with confirmed HIV-1 RNA ≥200 copies/mL prior to Week 48 was ineligible for enrollment due to previous documentation of Y188L
  - 3 participants had low-level viremia; 1 (P052) had resolved at Week 48, 1 (P052) withdrew from study with low-level viremia prior to Week 48, and 1 (P054) still had low-level viremia at Week 48
  - 3 participants had transient viremia ≥50 copies/mL that had resolved at Week 48

Table 6. Viremia outcomes through Week 48 in DOR/ISL participants with DOR RAMs at baseline

Participant(s) with:		P051 DOR/ISL (100 mg/0.25 mg)	P052 DOR/ISL (100 mg/0.25 mg)	P054 DOR/ISL (100 mg/0.25 mg)	Pooled DOR/ISL (100 mg/0.25 mg)
DOR RAMs	**All**	**7**	**15**	**21**	**43**
	DISC (%)	2* (28.6)	0	0	2* (4.6)
	LLV (%)	0	0	0	0
	TV (%)	0	0	4 (19.0)	4 (9.3)
DOR RAMs and M184I/V	**All**	**2**	**3**	**3**	**8**
	DISC (%)	1* (50.0)	0	0	1* (12.5)
	LLV (%)	0	0	0	0
	TV (%)	0	0	1 (33.3)	1 (12.5)

*Includes participant(s) who were ineligible for enrollment due to having either a previous history of virologic failure or previous documentation of DOR resistance (Y188L).

DISC=discontinued with confirmed HIV-1 RNA ≥200 copies/mL; LLV=low-level viremia; TV=transient viremia.

- Among 43 DOR/ISL participants with DOR RAMs at baseline across the 3 studies, 6 had viremia
  - 2 participants discontinued with confirmed HIV-1 RNA ≥200 copies/mL (P051); both were ineligible for enrollment due to previous history of virologic failure (n=1) or previous documentation of DOR resistance (Y188L; n=1)
  - 4 participants (P054) had transient viremia ≥50 copies/mL that had resolved at Week 48
- Out of 8 DOR/ISL participants with both DOR RAMs and M184I/V across the 3 studies, 2 had viremia
  - 1 participant who discontinued with confirmed HIV-1 RNA ≥200 copies/mL was ineligible for enrollment due to previous documentation of Y188L
  - 1 participant had transient viremia ≥50 copies/mL that had resolved at Week 48

Conclusions

- Viremia outcomes (discontinuations, low-level viremia, and transient viremia) were comparable across treatment groups and studies.
- The presence or absence of NNRTI RAMs and/or M184I/V in proviral DNA did not impact viremia outcomes through Week 48 in participants switching to DOR/ISL (100 mg/0.25 mg) in phase 3 clinical studies.

References

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