WEPEB019

Switching to Doravirine/Islatravir (100 mg/0.25 mg) Once-Daily Maintained Viral Suppression in the Presence of Archived M184I/V Resistance-Associated Mutations in Proviral DNA

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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-nucleotide 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]
- Switching to DOR/ISL (100 mg/0.25 mg) is being investigated for the treatment of virologically suppressed adults living with HIV-1 in 3 Phase 3 studies: MK-8591A-051 (P051), MK-8591A-052 (P052), and MK-8591A-054 (P054) (**Figure 1**)
- Switching to DOR/ISL (100 mg/0.25 mg) maintained high rates of virologic suppression (HIV-1 RNA <50 copies/mL) through Week 48 in P051, P052, and P054; DOR/ISL was non-inferior to baseline antiretroviral therapy (bART) in P051 and BIC/FTC/TAF in P052 based on the primary end-point (percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48)[2,3]
- This analysis examined the impact of preexisting RAMs in proviral DNA on the virologic response to DOR/ISL (100 mg/0.25 mg) through Week 48 in P051, P052, and P054 with a primary focus on NNRTI RAMs and M184I/V

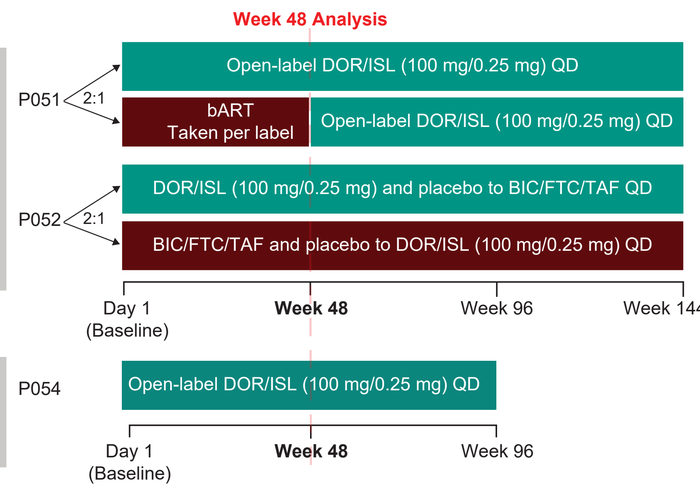
Methods

- Resistance analysis was performed using RAMs associated with each viral protein and class based on published literature and curated databases[4,5] (**Table 1**)
  - Each study was analyzed based on the protein targets of the antiretroviral (ARV) regimens evaluated:
    - P051: RT (NNRTI, NRTI), integrase (InSTI), protease (PI)
    - P052: RT (NNRTI, NRTI), integrase (InSTI)
    - P054: RT (NNRTI, NRTI)
  - Baseline resistance analysis was performed retrospectively on proviral DNA by GenoSure Archive assay (Monogram Biosciences) using whole blood samples collected on Day 1
  - Post-baseline genotypic (GenoSure PRIme) and phenotypic (PhenoSense or PhenoSense Integrase) resistance analyses (Monogram Biosciences) were performed on viral RNA from participants who discontinued with confirmed HIV-1 RNA ≥200 copies/mL; any missense mutation that emerged at a position associated with viral resistance was documented
    - Plasma pharmacokinetic (PK) results for DOR and ISL were used to assess adherence
  - Treatment-emergent RAMs were determined by comparison of baseline (proviral DNA) and post-baseline (viral RNA) genotyping results
- Virologic outcomes were defined as follows:
  - Participants with HIV-1 RNA <50 copies/mL at Week 48
  - Participants with HIV-1 RNA ≥50 copies/mL at Week 48 (includes participants who discontinued before Week 48 with last on-treatment HIV-1 RNA ≥50 copies/mL)
  - Participants who discontinued with confirmed HIV-1 RNA ≥200 copies/mL

Figure 1. Study Designs for Phase 3 Studies of DOR/ISL (100 mg/0.25 mg) in Virologically Suppressed Adults

Comparator studies (P051 and P052)

Population
- Virologically suppressed adults with HIV-1 (plasma RNA <50 copies/mL) for ≥3 months on stable ART
- CD4 T cell count ≥50 cells/mm^3 or total lymphocytes ≥0.65×10^9/L
- No history of treatment failure on any regimen
- No known resistance to DOR: V106A/M, V108I, Y188L, H221Y, P225H, F227C/L, M230I/L, L234I, P236L, or Y318F
- No active HBV infection



Single-arm study (P054)

Population
- Virologically suppressed adults that received DOR/ISL (100 mg/0.75 mg) in previous Phase 3 studies (except HTE) and considered to have derived clinical benefit

HBV, hepatitis B virus; HTE, heavily treatment experienced

Table 1. List of RAMs Evaluated for Each Protein and 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
Integrase	InSTI	H51Y, T66A/I/K, E92G/Q, G118R, F121Y, G140A/C/R/S, Y143C/H/R, S147G, Q148H/K/R, S153A/F/Y, N155H/S, R263K	M50I, L74M, T97A, E138A/K/T, E157K/Q, G163K/R
Protease	PI	L24I, V32I, L33F, M36I/L/V, M46I/L, I47A/V, G48V, I50L/V, F53Y, I54A/L/M/S/T/V, G73A/C/S/T, T74P, L76V, V82A/F/L/M/S/T, N83D, I84A/C/V, I85V, N88D/S, L90M	L10F/I/R/V, V11I, K20M/R/T, D30N, K43T, F53Y, Q58E, I62V, H69K/R, A71T/V, V77I, L89I/M/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[5]

Results

Baseline Resistance Analysis

Table 2. Prevalence of Preexisting 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)	Group 2: 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)
Integrase	**Any InSTI RAM**	**124 (38.5)**	**68 (41.0)**	**88 (28.5)**	**37 (24.3)**		
	M50I	91 (28.3)	53 (31.9)	49 (15.9)	23 (15.1)		
	E157K/Q	13 (4.0)	9 (5.4)	19 (6.1)	9 (5.9)		
Protease	**Any PI RAM**	**280 (87.0)**	**149 (89.8)**				
	M36I/L/V	166 (51.6)	87 (52.4)				
	V77I	86 (26.7)	44 (26.5)				
		*PI RAMS I62V, H69KR, L89I/M/V, A71T/V, L10F/I/R/V, and K20M/R/T were also present in both arms at >5%					

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

- The prevalence of class-specific RAMs were 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 preexisting NNRTI RAMs and 70 (5.7%) had preexisting M184I/V
- K103N/R/S, E138K/Q, and M184I/V were the most prevalent major RAMs observed in RT at baseline
- Most of the RAMs observed in >5% of participants were minor RAMs that do not confer resistance to DOR or ISL

Table 3. Prevalence of Preexisting 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 (0.0)	1 (0.3)	0 (0.0)	4 (0.7)	9 (0.7)
P225H	1 (0.3)	0 (0.0)	3 (1.0)	1 (0.7)	3 (0.5)	7 (0.6)
H221Y	0 (0.0)	1 (0.6)	4 (1.3)	1 (0.7)	3 (0.5)	7 (0.6)
M230I/L	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.3)	4 (0.3)
F227C/L/V	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.3)	3 (0.2)
Y188L	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	2 (0.2)
Y318F	0 (0.0)	1 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.2)
L234I	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)
P236L	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- Preexisting DOR RAMs were rare, 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 study groups

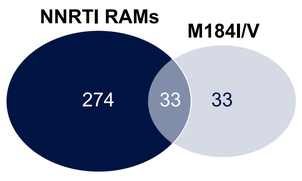
Table 4: Week 48 Virologic Outcomes in Participants With Preexisting NNRTI RAMs or M184I/V in Proviral DNA

	P051*	P052		P054	Pooled
PARTICIPANTS WITH:	DOR/ISL (100/0.25 mg)	Baseline ART	DOR/ISL (100/0.25 mg)	BIC/FTC/TAF	DOR/ISL (100/0.25 mg)	DOR/ISL (100/0.25 mg)
Proviral DNA Data:	**N = 322**	**N = 166**	**N = 309**	**N = 152**	**N=596**	**N=1227**
Virologic Data at Week 48 n/N (%)	313/322 (97.2)	161/166 (97.0)	285/309 (92.2)	145/152 (95.4)	570/596 (95.6)	1168/1227 (95.2)
– HIV-1 RNA <50 c/mL at Week 48, m (%)	309 (98.7)	153 (95.0)	280 (98.2)	144 (99.3)	560 (98.2)	1149 (98.4)
– HIV-1 RNA ≥50 c/mL at Week 48, m (%)	4* (1.3)	8 (5.0)	5 (1.8)	1 (0.7)	10 (1.8)	19 (1.5)
→Discontinued w/ confirmed HIV-1 RNA ≥200 c/mL	3*	0	2	0	1	6*
Proviral DNA Data and Virologic Data at Week 48	**N=313**	**N=161**	**N=285**	**N=145**	**N=570**	**N=1168**
Any NNRTI RAMs at Baseline, n/N (%)	77/313 (24.6)	33/161 (20.5)	75/285 (26.3)	39/145 (26.9)	155/570 (27.2)	307/1168 (26.3)
– HIV-1 RNA <50 c/mL at Week 48, m (%)	74 (96.1)	31 (93.9)	73 (97.3)	39 (100.0)	150 (96.8)	297 (96.7)
– HIV-1 RNA ≥50 c/mL at Week 48, m (%)	3* (3.9)	2 (6.1)	2 (2.7)	0 (0.0)	5 (3.2)	10 (3.3)
→Discontinued w/ confirmed HIV-1 RNA ≥200 c/mL	2*	0	0	0	0	2*
M184I/V at Baseline, n/N (%)	20/313 (6.4)	4/161 (2.5)	20/285 (7.0)	8/145 (5.5)	26/570 (4.6)	66/1168 (5.7)
– HIV-1 RNA <50 c/mL at Week 48, m (%)	19 (95.0)	4 (100.0)	18 (90.0)	8 (100.0)	25 (96.2)	62 (93.9)
– HIV-1 RNA ≥50 c/mL at Week 48, m (%)	1* (5.0)	0 (0.0)	2 (10.0)	0 (0.0)	1 (3.8)	4 (6.1)
→Discontinued w/ confirmed HIV-1 RNA ≥200 c/mL	1*	0	0	0	0	1*

c/mL, copies/mL
*Two participants that discontinued with confirmed HIV-1 RNA ≥200 copies/mL in P051 were later determined to be ineligible for enrollment due to either previous history of virologic failure (n=1) or previous documentation of DOR resistance (n=1). Both had preexisting NNRTI RAMs (including Y188L) and 1 had preexisting M184I/V.

- Most participants with baseline proviral DNA data (>92%) have virologic data at Week 48
- Overall, >93% of DOR/ISL participants with preexisting NNRTI RAMs or M184I/V in proviral DNA maintained virologic suppression (HIV-1 RNA <50 copies/mL)

Figure 2: Participants Treated With DOR/ISL With Preexisting NNRTI RAMs and M184I/V in Proviral DNA



- Among participants treated with DOR/ISL with virologic data at Week 48 and preexisting NNRTI RAMs (n=307) or M184I/V (n=66), 33 participants had both NNRTI RAMs and M184I/V
- 88% (29/33) of DOR/ISL participants with both NNRTI RAMs and M184I/V had HIV-1 RNA <50 copies/mL at Week 48 and only 1 discontinued with confirmed HIV-1 RNA ≥200 copies/mL

Post-baseline Resistance Analysis

- Seven participants treated with DOR/ISL (P051, 3; P052, 2; P054, 2) met the criteria for post-baseline resistance testing through Week 48 and had samples submitted (**Table 5**)

Table 5: Genotypic Analysis for DOR/ISL Participants That Discontinued With Confirmed HIV-1 RNA ≥200 copies/mL

Participant	Study	HIV-1 Subtype	Baseline RAMs in Proviral DNA[a]	HIV-1 RNA copies/mL at Sequencing (Study Week)	RAMs in Viral RNA	Treatment Emergent RAMs
Participants without post-baseline results due to assay failure						
1	P052	B	NNRTI: NONE NRTI: NONE	287/486 (Week 36)	Assay Failed	ND
2	P054	AE	NNRTI: V179V/I NRTI: NONE	332 (Week 12)	Assay Failed	ND
3[b]	P054	Assay Failed	Assay Failed	227 (Week 48)	Assay Failed	ND
Participants who were later determined to be ineligible for enrollment						
4	P051	B	NNRTI: **V106M**, **Y188L**/W, **F227L**, K101A NRTI: M41L, D67N, T69D, V118I, L210W, T215Y, K219R, E44A, V75M, M184T	38800 (Week 4)	NNRTI: **V106M**, **F227L**, K101A, Y188W NRTI: M41L, D67N, T69D, V118I, L210W, T215Y, K219R, E44A, V75M, M184T	NNRTI: NONE NRTI: NONE
5	P051	B	NNRTI: A98A/G, K103K/N, V106V/I, **Y188Y/L** NRTI: M41M/L, E44E/D, D67D/N, K70K/R, V118V/I, M184M/I/V, L210L/W, T215T/N/S/Y, K219K/R	4780 (Week 12)	NNRTI: A98G, V106I, **Y188L** NRTI: M41L, E44D, V118I, M184V, L210W, T215Y, K219R	NNRTI: NONE NRTI: NONE
Participants with PK results indicating likely nonadherence						
6	P051	C	NNRTI: NONE NRTI: NONE	2220 (Week 48)	NNRTI: NONE NRTI: T215T/I	NNRTI: NONE NRTI: T215T/I
7	P052	B	NNRTI: NONE NRTI: T69T/N	83900 (Week 48)	NNRTI: NONE NRTI: T69T/N	NNRTI: NONE NRTI: NONE

ND, not determined
[a]DOR RAMs are shown in **bold**.
[b]Participant #3 is not included in Table 4 due to assay failure in resistance test performed at baseline

- Three participants who met the criteria for post-baseline resistance testing did not have results, due to assay failure (**Table 5**)
- Post-baseline genotypic and phenotypic results were available for 4 participants (P051=3, P052=1)
- Two participants (#4 and #5) from P051 had multidrug resistance at baseline and viremia (including DOR RAMs and changes at M184) with phenotypic fold-shifts appearing as expected based on the genotypic profiles (DOR >Max; ISL 7- to 20-fold)
  - Both participants were later determined to be ineligible for enrollment due to either previous history of virologic failure (n=1) or previous documentation of DOR resistance (n=1); these were the only 2 participants with preexisting DOR RAMs including Y188L (**Table 3**) that discontinued
- Two participants (#6 [P051] and #7 [P052]) had low or undetectable DOR and/or ISL plasma exposures indicating likely nonadherence
  - #6 had an NRTI revertant, T215T/I, detected at viremia that did not alter the potency of any of the ARVs evaluated (fold-shift 0.55-1.24)
  - #7 had T69T/N present at baseline and viremia that did not alter potency of any of the ARVs evaluated (fold-shift 0.39-1.14)
- **No treatment-emergent resistance to either DOR or ISL**

Conclusion

Switching to DOR/ISL (100 mg/0.25 mg) maintains viral suppression through Week 48 in Phase 3 clinical studies, including among participants with preexisting NNRTI RAMs and/or M184I/V in proviral DNA.

References

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