Islatravir in Combination With Doravirine Maintains HIV-1 Viral Suppression Through 96 Weeks

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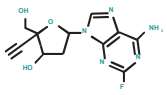
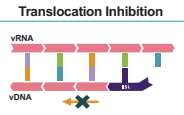
Background

- 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 similar to DOR/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF)[1]
  - ISL + DOR was generally well tolerated at all doses, with few drug-related AEs; 2 of 90 participants in the combined ISL groups discontinued due to AEs[1]
  - The 0.75 mg daily dose of ISL was selected for further clinical development[2]

Islatravir, a First-in-Class Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI) With Multiple Mechanisms of Action

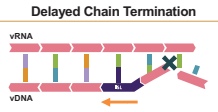


Translocation Inhibition



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

Delayed Chain Termination

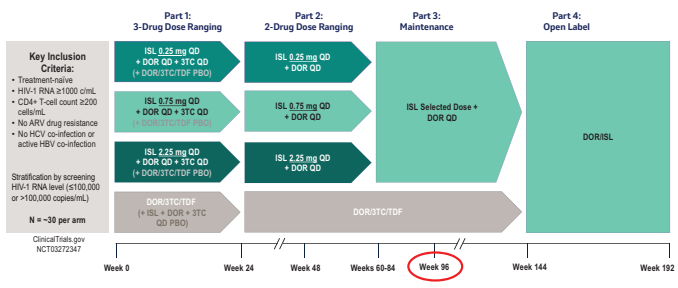


- ISL changes vDNA structure such that nucleotide incorporation is prevented
- As ISL is not in the RT active site, it is not susceptible to RT-associated resistance-conferring mutations
- **Viral replication is inhibited**

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

ISL, islatravir; RT, reverse transcriptase; vDNA, viral DNA; vRNA, viral RNA.

Figure 1. Protocol 011: Phase 2 Dose Ranging Trial of ISL+DOR

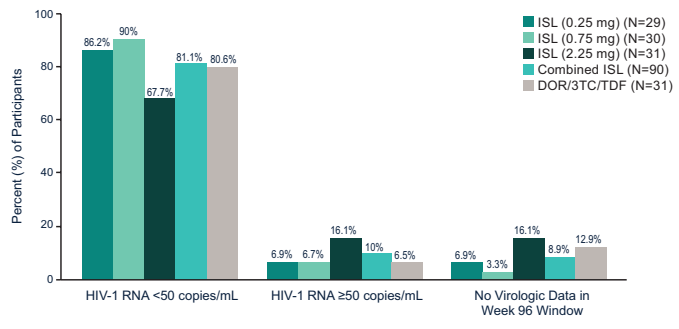


After 24 weeks of dosing in Part 1, participants who are virologically suppressed (HIV-1 RNA <50 copies/mL) at the Week 20 visit and have not met any viral failure criteria are eligible to switch to Part 2 of the trial at Week 24. Participants with HIV-1 RNA levels ≥50 copies/mL at Week 20 will remain in Part 1 until the HIV-1 RNA is <50 copies/mL and they have not met any of the viral failure criteria, at which point they transition to Part 2 at their next visit.

Table 1. Participant Baseline Characteristics by Treatment Group

	ISL (0.25 mg) + DOR + 3TC QD	ISL (0.75 mg) + DOR + 3TC QD	ISL (2.25 mg) + DOR + 3TC QD	ISL Combined	DOR/3TC/ TDF
	N=29	N=30	N=31	N=90	N=31
Sex					
Male, n (%)	29 (100.0)	27 (90.0)	28 (90.3)	84 (93.3)	28 (90.3)
Age (years)					
Median (min, max)	27.0 (19, 75)	28.0 (18, 51)	29.0 (19, 67)	28.5 (17, 75)	27.0 (18, 56)
Race					
Black or African American, n (%)	5 (17.2)	6 (20.0)	8 (25.8)	19 (21.1)	5 (16.1)
White, n (%)	23 (79.3)	24 (80.0)	21 (67.7)	68 (75.6)	24 (77.4)
Ethnicity					
Hispanic or Latino, n (%)	14 (48.3)	19 (63.3)	12 (38.7)	45 (50.0)	15 (48.4)
Baseline CD4+ T-cell count (cells/mm^3)					
Median (min, max)	415.0 (199, 889)	535.5 (178, 828)	416.0 (185, 1122)	445.5 (178, 1122)	473 (224, 1321)
Baseline plasma HIV-1 RNA (log_{10} copies/mL)					
Median (min, max)	4.6 (3.5, 6.2)	4.5 (3.0, 5.8)	4.7 (3.1, 5.8)	4.6 (3.0, 6.2)	4.2 (3.3, 6.1)
≤100,000 copies/mL, n (%)	22 (75.9)	24 (80.0)	22 (71.0)	68 (75.6)	26 (83.9)
>100,000 copies/mL, n (%)	7 (24.1)	6 (20.0)	9 (29.0)	22 (24.4)	5 (16.1)

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



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

Table 2. Virologic Outcomes Through Week 96

	ISL (0.25 mg) + DOR QD	ISL (0.75 mg) + DOR QD	ISL (2.25 mg) + DOR QD	ISL Combined	DOR/3TC/ TDF QD
	N=29	N=30	N=31	N=90	N=31
Outcome (FDA snapshot approach)					
HIV-1 RNA <50 copies/ mL, n (%)	25 (86.2)	27 (90.0)	21 (67.7)	73 (81.1)	25 (80.6)
HIV-1 RNA ≥50 copies/ mL, n (%)	2 (6.9)	2 (6.7)	5 (16.1)	9 (10.0)	2 (6.5)
No virologic data at Week 96 window, n (%)	2 (6.9)	1 (3.3)	5 (16.1)	8 (8.9)	4 (12.9)
Reasons for no virologic data in window					
Discontinued due to death or AE[a], n (%)	0	0	2 (6.5)	2 (2.2)	1 (3.2)
Discontinued for other reasons[b], n (%)	1 (3.4)	1 (3.3)	3 (9.7)	5 (5.6)	3 (9.7)
On treatment but missing data, n (%)	1 (3.4)	0	0	1 (1.1)	0
Outcome (observed failure approach)	N=27	N=29	N=26	N=82	N=27
HIV-1 RNA <50 copies/ mL, n (%)	25 (92.6)	27 (93.1)	21 (80.8)	73 (89.0)	25 (92.6)
Response (HIV-1 RNA <50 copies/mL) by Baseline HIV-1 RNA (observed failure approach)					
HIV-1 RNA ≤100,000 copies/mL, n/N (%)	20/21 (95.2)	23/24 (95.8)	17/19 (89.5)	60/64 (93.8)	22/23 (95.7)
HIV-1 RNA >100,000 copies/mL, n/N (%)	5/6 (83.3)	4/5 (80.0)	4/7 (57.1)	13/18 (72.2)	3/4 (75.0)

[a]Includes participants who discontinued because of adverse event (AE) or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[b]Other reasons include lost to follow-up, physician decision, protocol deviation, withdrawal by subject.

The treatment groups are the original group designations given at randomization. Participants in Groups 1-3 receiving ISL dropped 3TC when they switched to Part 2 of the trial.

Observed failure approach missing study Week 96 data are dropped from the analysis if the last on-treatment result was a success.

- Only one additional participant was listed as having HIV-1 RNA ≥50 copies/mL between Weeks 48 and 96

Table 3. Protocol-Defined Virologic Failure (PDVF) at Week 96

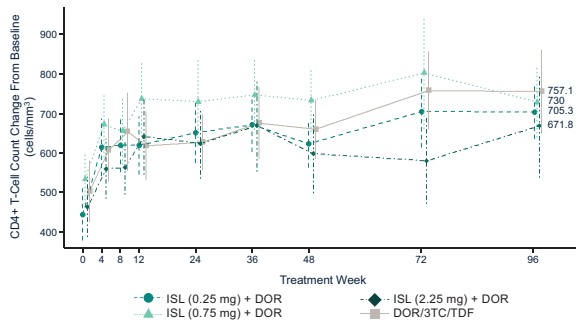
	ISL (0.25 mg) + DOR[a] QD	ISL (0.75 mg) + DOR[a] QD	ISL (2.25 mg) + DOR[a] QD	ISL Combined	DOR/3TC/ TDF QD
	N=29	N=30	N=31	N=90	N=31
Protocol-Defined Virologic Failure					
Nonresponder[b], n (%)	0 (0)	0 (0)	1 (3.2)	1 (1.1)	0 (0)
Rebounder with HIV-1 RNA >50 copies/mL, n (%)	2 (6.9)	2 (6.7)	1 (3.2)	5 (5.5)	1 (3.2)
Rebounder with HIV-1 RNA >200 copies/mL, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a]Participants initially received ISL+DOR+3TC and switched to ISL+DOR during Part 2 of the study.

[b]Protocol-defined virologic failure (PDVF) for this study is defined as one of the following: 1. Rebounder: Confirmed (two consecutive measures at least 1 week apart) 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 (two consecutive measures at least 1 week apart) 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 (two consecutive measures at least 1 week apart) HIV-1 RNA ≥200 copies/mL at any time from Week 24 through Week 48, or confirmed (two consecutive measures at least 1 week apart) HIV-1 RNA ≥50 copies/mL at Week 48.

- All participants with PDVF had confirmatory HIV-1 RNA levels <80 copies/mL
- No participants met the criteria for resistance testing
- Only one additional participant discontinued with PDVF (rebounder in 2.25 mg group) between weeks 48 and 96
- Five of seven participants with PDVF had a baseline HIV-1 RNA level of >100,000 copies/mL
- Five of seven participants with PDVF had an additional HIV-1 RNA level of <50 prior to changing to a new regimen

Figure 3. Absolute CD4+ T-Cell (95% CI) Count Over Time



[a]Participants initially received ISL+DOR+3TC and switched to ISL+DOR during Part 2 of the study.

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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.
2. Rudd DJ, et al. Modeling-supported islatravir dose-selection for Phase 3. Presented at Conference on Retroviruses and Opportunistic Infections (CROI) 2020.

https://bit.ly/3btgbAb

Table 4. Adverse Event (AE) Summary (Weeks 0-96)

	ISL (0.25 mg) + DOR[a] QD	ISL (0.75 mg) + DOR[a] QD	ISL (2.25 mg) + DOR[a] QD	Combined ISL	DOR/3TC/ TDF QD
Number of participants, N	29	30	31	90	31
≥1 AE, n (%)	25 (86.2)	27 (90.0)	22 (71.0)	74 (82.2)	27 (87.1)
Drug-related AE, n (%)	0	3 (10.0)	4 (12.9)	7 (7.8)	7 (22.6)
Serious AE, n (%)	1 (3.4)	3 (10.0)	1 (3.2)	5 (5.6)	3 (9.7)
Discontinued due to AE, n (%)	1 (3.4)	0	2 (6.5)	3 (3.3)	1 (3.2)
Discontinued due to drug-related AE, n (%)	0	0	2 (6.5)	2 (2.2)	1 (3.2)

[a]Participants initially received ISL+DOR+3TC and switched to ISL+DOR during Part 2 of the study.

- There were no deaths
- A higher rate of drug-related AEs was reported for DOR/3TC/TDF participants compared with ISL
- No additional ISL participants reported drug-related AEs, while 3 participants in the DOR/3TC/TDF reported drug-related AEs during Weeks 48-96
- No additional drug-related serious AEs were reported in any group during Weeks 48-96
- Two participants in the 2.25 mg ISL group discontinued due to a drug-related AE (one with diarrhea/nausea/vomiting and one with HBV reactivation) and one participant in the DOR/3TC/TDF group discontinued due to a drug-related AE (worsening of congenital long QT syndrome)

Table 5. Most Common AEs With Incidence >10% in One or More Treatment Groups (Weeks 0-96)

	ISL (0.25 mg) + DOR[a] QD	ISL (0.75 mg) + DOR[a] QD	ISL (2.25 mg) + DOR[a] QD	Combined ISL	DOR/3TC/ TDF QD
Headache, n (%)	4 (13.8)	2 (6.7)	4 (12.9)	10 (11.1)	2 (6.5)
Vitamin D deficiency, n (%)	0	5 (16.7)	4 (12.9)	9 (10.0)	1 (3.2)
Nausea, n (%)	1 (3.4)	4 (13.3)	3 (9.7)	8 (8.9)	3 (9.7)
Arthralgia, n (%)	1 (3.4)	2 (6.7)	4 (12.9)	7 (7.8)	1 (3.2)
Diarrhea, n (%)	1 (3.4)	4 (13.3)	2 (6.5)	7 (7.8)	6 (19.4)
Oropharyngeal pain, n (%)	3 (10.3)	3 (10.0)	1 (3.2)	7 (7.8)	1 (3.2)
Vomiting, n (%)	3 (10.3)	2 (6.7)	2 (6.5)	7 (7.8)	2 (6.5)
Anxiety, n (%)	2 (6.9)	4 (13.3)	0	6 (6.7)	0
Rash, n (%)	3 (10.3)	2 (6.7)	1 (3.2)	6 (6.7)	1 (3.2)
Pain in extremity, n (%)	3 (10.3)	1 (3.3)	0	4 (4.4)	1 (3.2)

[a]Participants initially received ISL+DOR+3TC and switched to ISL+DOR during Part 2 of the study.

- Infectious disease-related AEs of nasopharyngitis, syphilis, bronchitis, influenza, exposure to communicable disease, and sinusitis were also reported with a frequency of >10% in one or more treatment group, of which no cases were ever considered to be drug-related

Table 6. Grade 3 or 4 Laboratory Abnormalities With Incidence ≥2 Participants in One or More Treatment Groups (Weeks 0-96)

	ISL (0.25 mg) + DOR[a] QD	ISL (0.75 mg) + DOR[a] QD	ISL (2.25 mg) + DOR[a] QD	Combined ISL	DOR/3TC/ TDF
Fasting Triglycerides (mg/dL)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Grade 3: >500–1000	2/29 (6.9)	0/30 (0.0)	1/29 (3.4)	3/88 (3.4)	0/26 (0.0)
Alanine Aminotransferase (IU/L)					
Grade 3: 5.0 to <10.0 x ULN	0/29 (0.0)	1/30 (3.3)	2/31 (6.5)	3/90 (3.3)	1/31 (3.2)
Creatine Kinase (IU/L)					
Grade 3: 10.0 to <20.0 x ULN	4/29 (13.8)	0/30 (0.0)	0/31 (0.0)	4/90 (4.4)	1/31 (3.2)
Grade 4: ≥20.0 x ULN	1/29 (3.4)	2/30 (6.7)	3/31 (9.7)	6/90 (6.7)	1/31 (3.2)
Creatinine (mg/dL)					
Grade 3: >1.8 - <3.5 x ULN or Increase to 1.5 to <2.0 x above baseline	3/29 (10.3)	1/30 (3.3)	0/31 (0.0)	4/90 (4.4)	2/31 (6.5)

[a]Participants initially received ISL+DOR+3TC and switched to ISL+DOR during Part 2 of the study

- In an analysis of laboratory value changes from baseline, no dose-related trends were observed
- All Grade 3 and 4 creatine kinase abnormalities/elevations resolved while on study drug
  - All cases except for one were confirmed as exercise-related
  - The other elevation was due to a newly diagnosed HCV infection
- All Grade 3 creatinine abnormalities/elevations resolved while on study drug

Conclusions

- ISL+DOR demonstrated efficacy in maintaining viral suppression through week 96 following treatment initiation with ISL+DOR+3TC
  - 6/90 participants in the ISL groups combined and 1/31 participant in the DOR/3TC/TDF group discontinued with PDVF through week 96
    - Between weeks 48 and 96 one participant discontinued with PDVF1 (superscript the 1 after PDVF)
  - No participant in any treatment group met criteria for resistance testing (All confirmed HIV-1 RNA for PDVF was <80 copies/mL)
- ISL+DOR was generally well tolerated through week 96
  - 3/90 participants in the ISL arms discontinued due to AEs
  - Among the 90 participants taking ISL, no specific drug-related AE (at both system organ class or preferred term level) occurred in more than 5% of combined ISL participants
  - No additional drug-related serious AEs were reported in any group during weeks 48-96

Results demonstrate that ISL+DOR has the potential to be a potent 2-drug regimen and is currently being studied in a comprehensive Phase 3 program

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