Islatravir Metabolic Outcomes in a Phase 2b Trial of Treatment-Naïve Adults with HIV-1

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Background

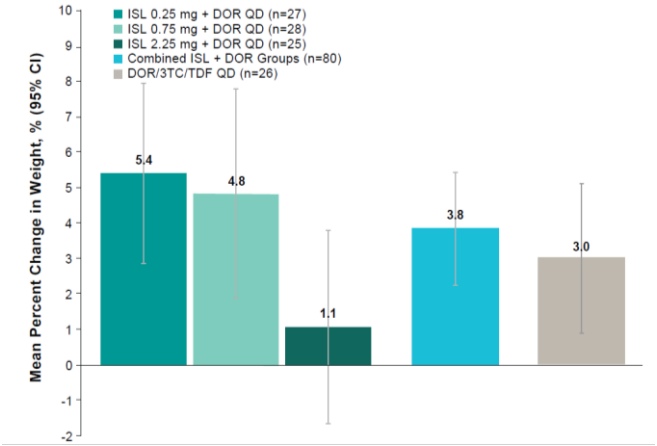
- Certain components of approved ART have been associated with long-term adverse events (AEs), including weight gain, loss of bone mineral density (BMD), and metabolic abnormalities[2,3]
- The combined attributes of islatravir (ISL, MK-8591), a First-in-Class NRTTI With Multiple Mechanisms Of Action, and doravirine (DOR), A Next-Generation NNRTI create the potential for a potent, simple, 2-drug regimen with efficacy comparable with approved regimens, that may address some of the long-term safety and toxicity concerns of traditional regimens
- A Phase 2b Dose-ranging Trial of DOR + ISL is Currently Ongoing. ISL + DOR was generally well tolerated at all doses, with few drug-related Aes
- To further characterize the effects of ISL regimens, exploratory metabolic outcomes from Phase 2b trial were examined

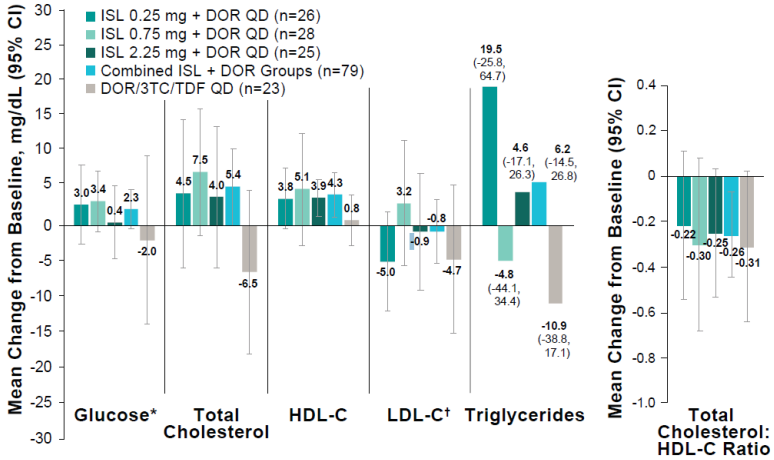
2. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. December 2019. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last accessed January 2020; **3.** European AIDS Clinical Society. European Guidelines for the treatment of HIV-positive adults in Europe Version 10.0. November 2019. Available at: https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf. Last accessed January 2020;

Exploratory Metabolic Endpoints, And Baselines Characteristics

- weight, body mass index (BMI), dual-energy X-ray absorptiometry (DEXA) scans, and fasting plasma glucose and lipids in all randomized participants at baseline through Week 48 were evaluated
- BMD and body-fat distribution were assessed using DEXA
  - Hip and spine BMD, and peripheral and trunk fat were analyzed
  - DEXA scans were evaluated by central imaging reader, blinded to study treatment (Bioclinica, Princeton, NJ, USA)
- Fasting plasma levels were assessed for glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides
- Baseline weight and metabolic characteristics were comparable across groups

Change in Mean Weight And Fasting Metabolic Parameters at Week 48



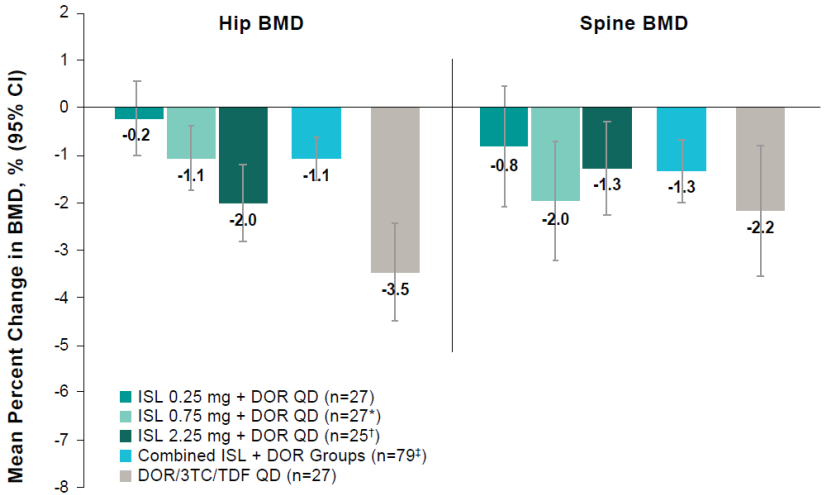


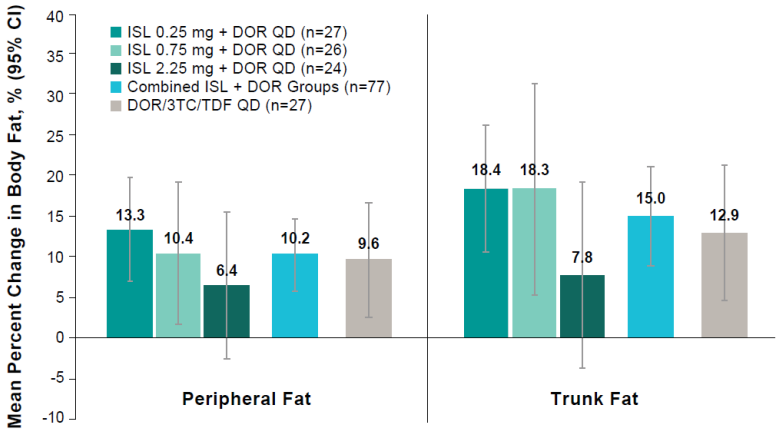
Mean absolute change in weight at Week 48 was 4.25, 3.65, 0.74, and 2.09 kg in the ISL 0.25 mg, ISL 0.75 mg, ISL 2.25 mg, and DOR/3TC/TDF groups, respectively

Of the 121 total participants, 5 participants initiated lipid-lowering therapy during the study period (ISL 0.25 mg, n=1; ISL 0.75 mg, n=1; DOR/3TC/TDF, n=3)

3TC, lamivudine; CI, confidence interval; DOR, doravirine; ISL, islatravir; QD, once daily; TDF, tenofovir disoproxil fumarate.

Mean % Change in BMD and Peripheral and Trunk Fat at Week 48





*n=26 for spine BMD. †n=24 for spine BMD. ‡n=77 for spine BMD.; 3TC, lamivudine; BMD, bone mineral density; CI, confidence interval; DOR, doravirine; ISL, islatravir; QD, once daily; TDF, tenofovir disoproxil fumarate.

Conclusions

- Change in weight and BMI was similar in the ISL + DOR groups and DOR/3TC/TDF group, and was consistent with the average weight gain among the general adult population (0.5–1.0 kg per year)[1]
- ISL + DOR regimens had a lower impact on hip BMD than DOR/3TC/TDF, while changes in spine BMD were similar
- Changes in peripheral and trunk fat were similar in the ISL + DOR groups and DOR/3TC/TDF group
- Changes in glucose and lipid levels were modest and the differences across groups were non-significant; furthermore, total cholesterol:HDL-C ratios were similar across groups
- The minimal effects on body composition and metabolic parameters demonstrated in this Phase 2b study support the ongoing development of ISL + DOR in a Phase 3 clinical development program

1. Hutfless S et al. Strategies to Prevent Weight Gain Among Adults Comparative Effectiveness Review No 97. Agency for Healthy Research and Quality. March 2013.