Once-Weekly Oral Islatravir/Lenacapavir Versus Daily Bictegravir/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed Adults With HIV-1: Week 48 Subgroup Analyses of the Phase 3 ISLEND-1 Trial

P050

ISLEND-1

Jürgen K Rockstroh[1], Anthony Mills[2], Benoit Trottier[3], Shawn Hassler[4], Manoj Dalmia[5], Bertrand Lebouché[6], Cynthia Gay[7], Alvaro Mena de Cea[8], Clara Lehmann[9], Hartmut Stocker[10,11], Javier Morales-Ramirez[12], Michael Sension[13], Marta Boffito[14], Michinori Shirano[15], Shan-Yu Liu[16], Ke Chen[17], Fadi Shihadeh[16], Jason Kim[17], Renée-Claude Mercier[16], Hadas Dvory-Sobol[16], Cyril Llamoso[17], Devi SenGupta[16], Chloe Orkin[18] for the ISLEND-1 Study Team

[1]University Hospital Bonn, Bonn, Germany; [2]Mills Clinical Research at Men's Health Foundation, Los Angeles, CA, USA; [3]Clinique de Médecine Urbaine du Quartier Latin, Montréal, Quebec, Canada; [4]Optimus Medical, San Francisco, CA, USA; [5]Brooklyn Clinical Research, Brooklyn, NY, USA; [6]McGill University Health Centre, Montréal, Quebec, Canada; [7]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [8]Hospital Universitario A Coruña, A Coruña, Spain; [9]Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany; [10]Epimed GmbH, Berlin, Germany; [11]St. Joseph Krankenhaus Berlin-Tempelhof, Berlin, Germany; [12]Clinical Research Puerto Rico Inc., San Juan, Puerto Rico, USA; [13]CAN Community Health Care, Inc., Fort Lauderdale, FL, USA; [14]Chelsea and Westminster Hospital – PPDS, London, UK; [15]Osaka City General Hospital, Osaka, Japan; [16]Gilead Sciences, Inc., Foster City, CA, USA; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]SHARE Collaborative, Blizard Institute, Faculty of Medicine and Dentistry, Queen Mary University of London, London, UK

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Conclusions

- In the diverse population enrolled in the Phase 3 ISLEND-1 trial, sex at birth, older age, race, ethnicity, geographic region, presence of M184V/I mutation at baseline, and baseline CD4+ T-cell count did not impact the efficacy or safety of once-weekly oral islatravir/lenacapavir (ISL/LEN)
- High rates of virologic suppression and a consistent safety profile were observed through Week 48 across all subgroups
- These results support the potential of ISL/LEN to be the first complete, once-weekly, oral single-tablet regimen (STR) for a diverse population of people with HIV-1

Plain Language Summary

- In the ongoing ISLEND-1 trial, researchers studied a new treatment for HIV called islatravir/lenacapavir (ISL/LEN). Participants took one ISL/LEN tablet once a week. The treatment was as good at controlling HIV as bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), a commonly used HIV medicine taken once a day
- In this analysis, researchers looked at whether sex, age, race, or ethnicity affected how well ISL/LEN worked or how safe it was. They found that ISL/LEN worked just as well regardless of these factors
- The results suggest that once-weekly ISL/LEN may be a suitable treatment for many different people living with HIV

Introduction

- Despite high efficacy, daily oral antiretroviral therapy can be challenging for some people with HIV-1, driving interest in less frequent dosing strategies[1,2]
- The combination of ISL, a nucleoside reverse transcriptase translocation inhibitor,[3,4] and LEN, a capsid inhibitor,[5] is being developed as a complete once-weekly oral STR for virologically suppressed people with HIV-1
- In the broad population of people with HIV-1 in the Phase 3 ISLEND-1 trial, switching to once-weekly oral ISL/LEN demonstrated noninferior efficacy to continuing once-daily oral bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) at Week 48, and ISL/LEN was well tolerated[6]
  - None of the 304 participants on ISL/LEN and 1 of the 303 (0.3%) participants on B/F/TAF had HIV-1 RNA ≥ 50 copies/mL[a] (difference: -0.3% [95.002% CI: -1.4%, 0.8%]). Correspondingly, 284 (93%) and 280 (92%) participants had HIV-1 RNA < 50 copies/mL (difference: 1.0% [95% CI: -3.2%, 5.2%])

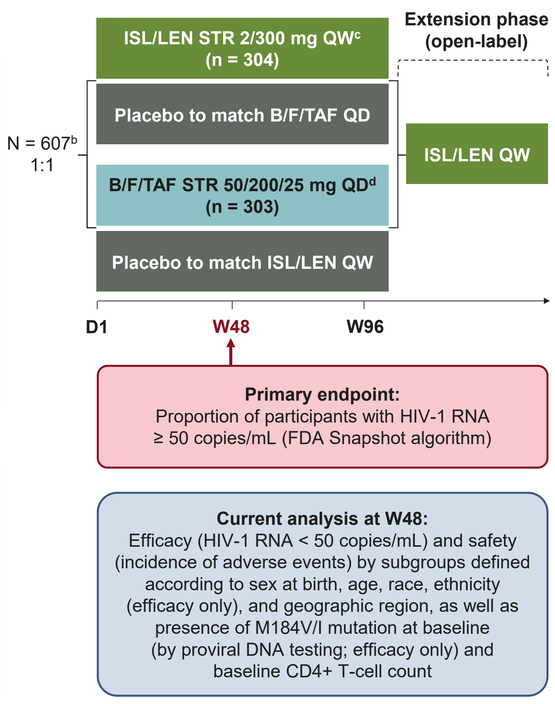
[a]Per US Food and Drug Administration Snapshot algorithm.

Objective

- To present ISLEND-1 Week 48 analyses by subgroups based on baseline demographic and clinical characteristics

Methods

Figure 1. Study Design



[a]Defined as hepatitis B surface antigen positive or hepatitis B core antibody positive and surface antibody negative.
[b]Randomized: N = 609, dosed: N = 607.
[c]Participants received two oral tablets (initiation dose), each containing 0.5 mg ISL and 300 mg LEN on D1 and D2, then one oral tablet of ISL/LEN 2/300 mg QW from D8, without regard to food, plus matching B/F/TAF placebo.
[d]Participants continued B/F/TAF 50/200/25 mg tablet administered orally QD, without regard to food, and received matching ISL/LEN placebo (initiation/loading dose and weekly treatment).
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CD4, cluster of differentiation 4; D, Day; FDA, US Food and Drug Administration; HBV, hepatitis B virus; ISL, islatravir; LEN, lenacapavir; QD, once daily; QW, once weekly; STR, single-tablet regimen; W, Week.

- ISLEND-1 was a Phase 3, double-blind, active-controlled noninferiority study in virologically suppressed people with HIV-1[6] (**Figure 1**)

Results

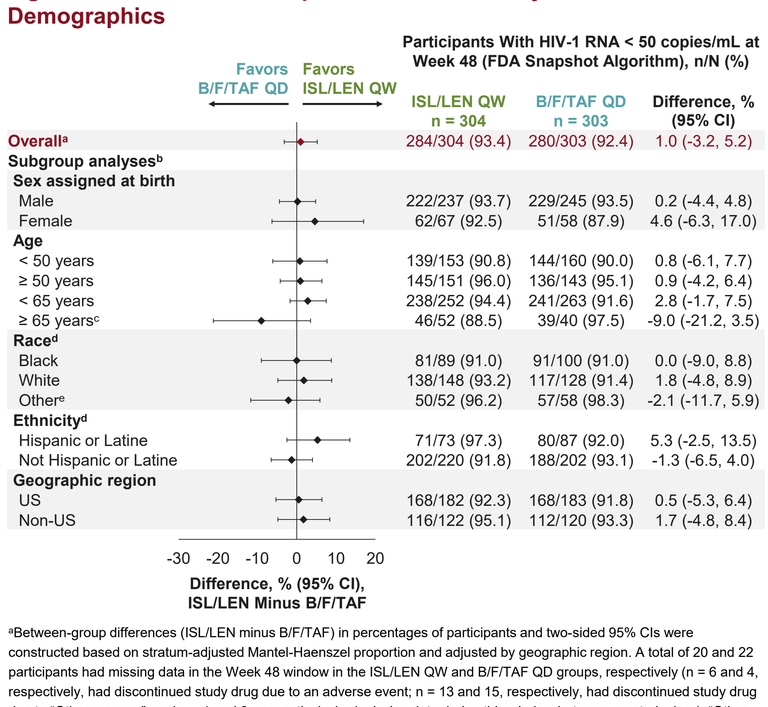
Table 1. Baseline Demographic and Clinical Characteristics

Participants, n (%)		ISL/LEN QW n = 304	B/F/TAF QD n = 303
Sex assigned at birth	Male	237 (78)	245 (81)
	Female	67 (22)	58 (19)
Age	≥ 50 years	151 (50)	143 (47)
	≥ 65 years	52 (17)	40 (13)
Race[a]	Black	89 (29)	100 (33)
	White	148 (49)	128 (42)
	Other[b]	52 (17)	58 (19)
Ethnicity[a]	Hispanic or Latine	73 (24)	87 (29)
	Not Hispanic or Latine	220 (72)	202 (67)
Geographic region	US	182 (60)	183 (60)
	Non-US	122 (40)	120 (40)
M184V/I mutation[c]	Yes	13 (4)	18 (6)
	No	271 (89)	265 (88)
CD4+ T-cell count	< 500 cells/μL	63 (21)	63 (21)
	≥ 500 cells/μL	241 (79)	240 (79)
Duration of HIV from diagnosis, years, median (IQR)		14.2 (7.3, 23.0)	14.2 (7.3, 23.0)
Duration of HIV treatment, years, median (IQR)		12.3 (7.1, 19.3)	13.1 (7.1, 19.1)
Select comorbidities	Dyslipidemia	116 (38)	112 (37)
	Hypertension	109 (36)	104 (34)
	Hyperglycemia/ new-onset diabetes mellitus	34 (11)	48 (16)
	Chronic kidney disease	14 (5)	23 (8)

[a]In some countries, local regulators did not allow the collection of race or ethnicity information; this subgroup is not shown as participant numbers were small, which could lead to functional unblinding. [b]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, and other. [c]Data were missing for 20 (7%) participants in both groups.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CD4, cluster of differentiation 4; ISL/LEN, islatravir/lenacapavir; QD, once daily; QW, once weekly.

- Baseline demographic and clinical characteristics were similar between groups (**Table 1**)
- The study population was diverse, with almost half of participants aged over 50 years, and approximately 20% female, 30% Black, and 26% Hispanic or Latine

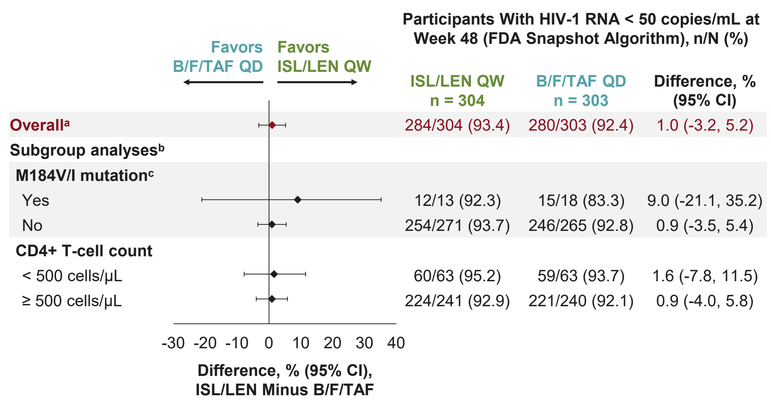
Figure 2. HIV-1 RNA < 50 copies/mL at Week 48 by Baseline Demographics



[a]Between-group differences (ISL/LEN minus B/F/TAF) in percentages of participants and two-sided 95% CIs were constructed based on stratum-adjusted Mantel-Haenszel proportion and adjusted by geographic region. A total of 20 and 22 participants had missing data in the Week 48 window in the ISL/LEN QW and B/F/TAF QD groups, respectively (n = 6 and 4, respectively, had discontinued study drug due to an adverse event; n = 13 and 15, respectively, had discontinued study drug due to "Other reasons"; and n = 1 and 3, respectively, had missing data during this window but were on study drug). "Other reasons" for discontinuing the trial regimen could include withdrawal by the investigator, withdrawal by the participant, loss to follow-up, nonadherence to the trial regimen, and pregnancy. [b]Between-group differences (ISL/LEN minus B/F/TAF) in percentages of participants and 95% CIs were calculated based on an unconditional exact method using two inverted one-sided tests. [c]Lower point estimate for virologic suppression in this subgroup is driven by missing data for six ISL/LEN participants. [d]In some countries, local regulators did not allow collection of race or ethnicity information; this subgroup is not shown as participant numbers were small, which could lead to functional unblinding. [e]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, and other.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; FDA, US Food and Drug Administration; ISL/LEN, islatravir/lenacapavir; QD, once daily; QW, once weekly.

- Rates of virologic suppression were high and generally comparable between the treatment groups across subgroups defined by baseline demographics, including in people assigned female at birth and older adults (**Figure 2**)

Figure 3. HIV-1 RNA < 50 copies/mL at Week 48 by Baseline Clinical Characteristics



[a]Between-group differences (ISL/LEN minus B/F/TAF) in percentages of participants and two-sided 95% CIs were constructed based on stratum-adjusted Mantel-Haenszel proportion and adjusted by geographic region. A total of 20 and 22 participants had missing data in the Week 48 window in the ISL/LEN QW and B/F/TAF QD groups, respectively (n = 6 and 4, respectively, had discontinued study drug due to an adverse event; n = 13 and 15, respectively, had discontinued study drug due to "Other reasons"; and n = 1 and 3, respectively, had missing data during this window but were on study drug). "Other reasons" for discontinuing the trial regimen could include withdrawal by the investigator, withdrawal by the participant, loss to follow-up, nonadherence to the trial regimen, and pregnancy.
[b]Between-group differences (ISL/LEN minus B/F/TAF) in percentages of participants and 95% CIs were calculated based on an unconditional exact method using two inverted one-sided tests.
[c]Data were missing for 20 (7%) participants in both groups.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CD4, cluster of differentiation 4; FDA, US Food and Drug Administration; ISL/LEN, islatravir/lenacapavir; QD, once daily; QW, once weekly.

- Rates of virologic suppression were high and generally comparable between the treatment groups across subgroups defined by baseline clinical characteristics (**Figure 3**)

Table 2. Adverse Events – Overall Incidence at Week 48 by Treatment Group and Subgroup

All Adverse Events, n/N (%)		ISL/LEN QW n = 304	B/F/TAF QD n = 303
All participants		**241/304 (79)**	**238/303 (79)**
Sex assigned at birth	Male	190/237 (80)	190/245 (78)
	Female	51/67 (76)	48/58 (83)
Age	< 50 years	121/153 (79)	130/160 (81)
	≥ 50 years	120/151 (79)	108/143 (76)
	< 65 years	197/252 (78)	205/263 (78)
	≥ 65 years	44/52 (85)	33/40 (83)
Race[a]	Black	68/89 (76)	77/100 (77)
	White	119/148 (80)	105/128 (82)
	Other[b]	42/52 (81)	42/58 (72)
Geographic region	US	143/182 (79)	141/183 (77)
	Non-US	98/122 (80)	97/120 (81)
Baseline CD4+ T-cell count	< 500 cells/μL	47/63 (75)	43/63 (68)
	≥ 500 cells/μL	194/241 (80)	195/240 (81)

[a]In some countries, local regulators did not allow the collection of race or ethnicity information; this subgroup is not shown as participant numbers were small, which could lead to functional unblinding.
[b]Includes Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, and other.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CD4, cluster of differentiation 4; ISL/LEN, islatravir/lenacapavir; n, number of participants with the event; N, number of participants in the subgroup of interest; QD, once daily; QW, once weekly.

- The safety profile was consistent with previously reported data[6] and similar across the subgroups; no new safety concerns were identified (**Table 2**)
- Safety and efficacy findings were consistent with those of the subgroup analysis of the Phase 3 ISLEND-2 study comparing once-weekly ISL/LEN and daily standard of care (Poster P049)

References: **1.** Derrick CB, et al. *Open Forum Infect Dis*. 2018;5:ofy247. **2.** Graham SM, et al. *J Int AIDS Soc*. 2023;26 (Suppl 2):e26099. **3.** Michailidis E, et al. *J Biol Chem*. 2014;289:24533-48. **4.** Salie ZL, et al. *Proc Natl Acad Sci U S A*. 2016;113:9274-9. **5.** Link JO, et al. *Nature*. 2020;584:614-18. **6.** Rockstroh JK, et al. *N Engl J Med*. 2026;395:1299-309.

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Correspondence: Chloe Orkin, c.m.orkin@qmul.ac.uk.

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