Project Brief: MK 8591A-028

Full Title of Study/Programme	A Phase 2 Clinical Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Doravirine/Islatravir in Adolescents with HIV-1 Infection who are Virologically Suppressed, are ≥12 to <18 Years of Age, and Weigh ≥35 kg
Technical Focus Area	Research Pediatric
Rationale	With anticipation of lifelong treatment, long term tolerability and safety of antiretrovirals have become increasingly important for pediatric patients. Accumulating evidence shows simplified 2-drug regimens can achieve efficacy and improve tolerability comparable to that of 3-drug regimens. A 2-drug regimen could mean fewer potential DDIs, and a lesser likelihood of safety or tolerability issues compared to 3-drug regimens. DOR/ISL has the potential to be an ideal 2-drug regimen for adult and pediatric patients for the treatment of HIV-1
Primary Objectives	Primary Objectives: • To evaluate the steady-state plasma pharmacokinetic profile of ISL and DOR as assessed by intensive pharmacokinetic sampling on Day 28 in the Intensive PK Cohort • To evaluate the steady-state intracellular pharmacokinetic profile of ISL-triphosphate in peripheral blood mononuclear cells on Day 28 in the Intensive PK Cohort • To evaluate the safety and tolerability of DOR/ISL as assessed by review of the accumulated safety data through Week 24
Secondary Objectives	• To evaluate the safety and tolerability of DOR/ISL as assessed by review of the accumulated safety data through study duration • To evaluate the antiretroviral activity of DOR/ISL as assessed by the percentage of participants with the following at Weeks 24 and 48: - HIV-1 RNA ≥50 copies/mL - HIV-1 RNA <50 copies/mL • To evaluate the immunologic effect of DOR/ISL as measured by change from baseline in CD4+ T-cell count at Weeks 24 and 48 • To evaluate the development of viral drug resistance to DOR or ISL in participants who receive DOR/ISL
Tertiary Objectives/ Exploratory	• To evaluate the pharmacokinetics of ISL and DOR as assessed by sparse pharmacokinetic sampling through Week 48 • To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study

Endpoint/Outcome	1. Pharmacokinetic Endpoints: • Plasma PK PK samples collected for analysis of ISL and DOR plasma concentrations will be used to calculate the steady-state plasma AUC0-24 and Cmax, and C24 (for DOR only). These results will confirm that adequate exposures of ISL and DOR are achieved in adolescents ≥12 to <18 years of age weighing ≥35 kg and will support dosing recommendations in the pediatric population. As DOR/ISL is anticipated to be chronically dosed, steady-state PK endpoints are the most appropriate endpoints. Intensive plasma PK samples will be collected from the Intensive PK Cohort participants. In addition to these results, data from sparse plasma PK sampling collected from all participants will be used in population PK models for ISL and DOR levels. • PBMC PK PBMC PK samples collected from the Intensive PK Cohort participants (Section 8.6) will be used to evaluate intracellular ISL-TP levels, the active anabolite resulting from ISL dosing. Intracellular PBMC trough levels (C24) are a better predictor of efficacy than the exposure (AUC) and can be used along with in vitro potency values to predict efficacy against both wild-type virus and mutant variants. 2. Safety Endpoints Safety evaluations will include physical examinations (including vital signs) and laboratory tests (haematology, chemistry, and urinalysis). AEs will be evaluated at each visit and assessed according to the study guidelines. Participants may be asked to return for unscheduled visits to perform additional safety monitoring. Efficacy Endpoints The key efficacy endpoint in this study is plasma HIV-1 RNA ≥50 copies/mL. Eligible participants in the adolescent population being studied are virologically suppressed, with HIV-1 RNA 3. Efficacy Endpoints The key efficacy endpoint in this study is plasma HIV-1 RNA ≥50 copies/mL. Eligible participants in the adolescent population being studied are virologically suppressed, with HIV-1 RNA <50 copies/mL at baseline. The assessment of interest is the percentage of participants who are unable to maintain virologic

	suppression after switching to a new antiretroviral regimen. Clinical studies of antiretroviral agents in multiple drug classes have demonstrated that virologic suppression of HIV-1 RNA to <50 copies/mL reflects a clinically relevant standard used across development programs for antiretroviral therapies and in clinical practice [Vandenhende, M. A., et al 2015]. Suppressing HIV-1 RNA to <50 copies/mL preserves the immune system and minimizes the risk of opportunistic infections and disease progression.
Study Design	This is a Phase 2 nonrandomized, noncomparative, multi-site, open-label study to evaluate PK, safety, tolerability, and efficacy of DOR/ISL in adolescents with HIV-1 who have been virologically suppressed for ≥3 months on a stable oral 2-drug or 3-drug cART (±PK booster). Approximately 30 participants will be enrolled to receive DOR/ISL at the adult dose [DOR (100 mg)/ISL (0.75 mg) FDC tablet administered QD] through Week 48. Participants will be required to discontinue use of their current suppressive ART regimen and receive only DOR/ISL as ART during the study. Approximately 10 participants who provide consent for intensive PK sampling (plasma and PBMC) on Day 28 will comprise the Intensive PK Cohort. Results from evaluation of the Intensive PK Cohort will be used for dose confirmation of ISL and DOR. All participants, including those in the Intensive PK Cohort, will undergo sparse plasma PK sampling at prespecified visits during the study. All participants will be evaluated for efficacy of DOR/ISL to maintain virologic suppression based on predefined, clinically significant, and confirmed viremia. Any participants with confirmed viremia, will be assessed for development of viral drug resistance and potential discontinuation from study intervention. Participant safety will be monitored by an eDMC who will perform periodic reviews of safety data throughout the study. Details regarding eDMC will be provided in a charter. At the end of Week 48, there will be a mechanism for all eligible participants to continue receiving study intervention without interruption until it becomes commercially accessible. Scientific Rationale for Study Design: The open-label, nonrandomized, PK-confirmatory study design is consistent with recent published regulatory guidance for conducting clinical studies in the pediatric population [Food and Drug Administration 2019]. Aligned with this guidance, the known clinical and pharmacological profile of DOR/ISL provides sufficient support to safely evaluate DOR/ISL in adolescents living with HIV-1 in parallel with the pivotal Phase 3 clinical studies in adults. Conducting adult and adolescent studies in parallel accelerates the development of antiretrovirals in the pediatric population, providing clinically meaningful information about the use of DOR/ISL for the treatment of HIV-1 in adolescents earlier and more efficiently.
Study Arms	DOR/ ISL (DOR=Doravirine; ISL=Islatravir; QD=once daily)

Study Population	Adolescent participants with HIV-1 who are ≥12 to <18 years of age, weighing ≥35 kg, and have been virologically suppressed for ≥3 months on any stable oral 2-drug or 3-drug cART (± PK booster) and Treatment Naïve, will be enrolled in this study.
Study Sample Size	Virologically suppressed Cohort (10 Intensive PK + 20 Non-Intensive PK participants) Treatment Naïve Cohort (15 participants)
Follow-up/Duration	Each participant will participate in the study for approximately 60 weeks from the time the participant signs the Informed Consent Form through the final contact. After a screening phase of up to 45 days, participants will receive daily study intervention for approximately 48 weeks. Participants who discontinue study intervention will be followed as described in the protocol.
Study/Programme Sites	South African allocation: • Wits RHI Shandukani Research Centre (SRC) (Dr Lee Fairlie) • Perinatal HIV Research Unit (Dr Avi Violari) • Durban Site (Prof Moherhdran Archary) • Rahima Moosa Mother and Child Hospital (Dr Renate Strehlau)
Study/Programme Duration	Start Date: June 2021 Estimated End Date: Jun 2024
Intervention	Islatravir ISL is the first member of a new class of antiretroviral agents, known as NRTTIs, which block HIV-1 reverse transcriptase by novel mechanisms of action. ISL is an inactive nucleoside analog that is converted to the pharmacologically active triphosphate (ISL-TP) form via endogenous intracellular kinases. It acts through multiple mechanisms, including immediate chain termination by blocking translocation and delayed chain termination by preventing nucleotide excision [Michailidis E 2014] ISL is differentiated from other HIV-1 antiretrovirals by its high potency, long half-life, favorable drug resistance profile, and broad pharmacologic distribution. ISL (at the proposed dose of 0.75 mg QD) achieves higher steady-state IQs (the ratio of drug exposure to viral susceptibility [Ctrough/IC50]) against wild-type HIV-1 than any NRTI currently approved for treatment. It also exhibits potent in vitro activity against the most prevalent NRTI resistance-associated mutations, including M184V/I and TAMs. Doravirine DOR, a potent NNRTI with demonstrated efficacy and good tolerability, was first approved for the treatment of HIV-1 infection by the FDA and the EMA in 2018. DOR is differentiated from other NNRTIs by its distinct resistance profile, low likelihood of selection for viral resistance in vivo, and low potential for DDIs. As compared to Efavirenz, DOR had fewer CNS-related AEs in Phase 3 studies. DOR exhibits potent activity against both wild-type HIV-1 virus and frequently transmitted NNRTI-resistance-associated substitutions (e.g., K103N, Y181C, G190A, and E138K). The safety and efficacy profiles of DOR have been well characterized in Phase 3 clinical studies conducted in treatment-naïve adult participants [Orkin, C., et al 2018] [Molina, J. M., et al 2018] and in virologically suppressed adult participants switching from a stable antiretroviral regimen (MK-1439A Protocol 024).

	Doravirine/Islatravir DOR/ISL is an FDC tablet containing DOR (100 mg) and ISL (0.75 mg) administered as a single tablet QD. DOR and ISL represent 2 distinct classes of antiretrovirals that inhibit reverse transcription by different mechanisms. Based on the profiles of each of these drugs and data available to date, the combination DOR/ISL is expected to be safe, well tolerated, and highly efficacious, with a high barrier to resistance. The combination has demonstrated additive antiretroviral activity in vitro and has suppressed emergence of resistance at clinically relevant concentrations. DOR and ISL have been studied in a Phase 1 fixed-sequence, 2-period, multiple-dose, drug interaction clinical study (MK-8591 Protocol 10). This study indicated no clinically meaningful interactions between DOR and ISL. The combination of DOR and ISL (administered as single-entities, ISL+DOR) is being evaluated in an ongoing randomized Phase 2 study (MK-8591 Protocol 011) in approximately 90 treatment-naïve adult participants with HIV-1. Participants were initially assigned to receive either ISL+DOR and 3TC or an FDC of DOR, 3TC, and TDF (DOR/3TC/TDF). Participants receiving ISL+DOR+3TC who achieved HIV-1 RNA discontinue 3TC at Week 24) while continuing DOR+ISL. At Week 48, the percentage of participants with HIV-1 RNA 200 copies/mL cutoff. As such, no participant met the criteria for resistance testing. ISL+DOR, administered with 3TC or alone as a 2-drug regimen, had a favorable safety and tolerability profile through Week 48, comparable to that of DOR/3TC/TDF
Operations	Study Specific
Investigators	• Dr Lee Fairlie, Principal Investigator • Dr Faeezah Patel Dr Elizea Horne
Other Partners & Collaborators	• None
Sponsors/Donors	• Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc. (hereafter referred to as the Sponsor or MSD)
Publications/Key Presentations to Date	• None as yet
Progress Update as at Jun 2021	Screened: 3 • Enrolled: 0
Frequency of Donor Narrative Report	Monthly
Overall Study/Project Contact	Dr Hermien Gous (hgous@wrhi.ac.za)
Briefing Owner and Date	Shini Moaisi 21 Jun 2021