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"Current Status of the Merck LA/ER pipeline"

MERCK LA HIV portfolio is centered around NRTTIs – ISL was the initial foundation.

An ISL lymphocyte effect (decreases in lymphocytes and T-cells) observed in late-stage programs resulted in **Full** or **Partial** FDA Clinical Holds across ISL programs (end of November 2021).

- HIV treatment.
  - Internal Program: **QD oral ISL + DOR** (P3); **QW oral ISL + MK-8507** (P2).
  - Collaboration with Gilead: **QW oral ISL + LEN** (P2); **LAI ISL + LEN** (Preclinical).
- HIV prevention.
  - Internal Program: **QM oral ISL** (P3); **Once-yearly ISL implant** (P1).

Comprehensive assessment of the lymphocyte findings (2022) enabled select HIV treatment programs to restart with lower ISL doses.

- Characterize safety.
  - Lymphocyte and CD4+ T-cell decreases are exposure dependent; Other hematologic cell lines are not affected; and No enhanced incidence of infections.
  - **Lower ISL doses may be less likely to cause reductions.**
- Understand the mechanism.
  - Lymphocyte effect likely related to high intracellular ISL-TP exposures; Observed similar high TP levels with other NRTIs; and Not due to mitochondrial toxicity.
- Find new ISL doses.
  - Developed exposure response models for lymphocytes and CD4+ T-cells.
  - **Identified lower ISL doses for QD and QW HIV treatment programs** that would retain efficacy and mitigate the lymphocyte effect.
  - **Unable to identify ISL doses for oral PrEP or injectable HIV treatment programs.**

Status of ISL programs (as of March 2024).

- Resumed with lower ISL dose.
  - QD oral ISL + DOR (P3) and QW oral ISL + LEN (P2) for HIV treatment.
- **FDA Partial Clinical Hold**.
  - QW oral ISL + MK-8507 (P2) for HIV treatment.
- Discontinued.
  - LAI program for HIV treatment and HIV PrEP programs (QM oral ISL and ISL implant).

Merck pipeline continues to leverage the potent antiviral activity and LA PK of NRTTIs to provide simple options for PWH.

QD oral HIV treatment program.

- Four new P3 studies of ISL/DOR (0.25mg/100mg) using a lower ISL dose (PN051, 052, 053, and 054).
  - Studies among VS PWH are fully enrolled.
    PN051 (OL, 2:1 randomization, DOR/ISL vs baseline ART); PN052 (Blinded, 2:1 randomization, DOR/ISL vs BIC/FTC/TAF); and PN054 (OL, single-arm, de-escalation).
  - Treatment-naïve study is still enrolling.
    PN053 (Blinded, 1:1 randomization, DOR/ISL vs BIC/FTC/TAF).
- Most participants from the original ISL (0.75mg) HIV treatment program had the opportunity to enroll in PN054.

QW oral HIV treatment program.

- ISL+LEN in collaboration with Gilead (P2); ISL+MK-8507 (P2, Partial Clinical Hold).

Ultra-Long-Acting (ULA) injectable HIV treatment.

- GS-1614 (ISL prodrug) formulation in collaboration with Gilead (ongoing preclinical and early development).

Merck remains committed to develop a LA agent for HIV PrEP.

QM oral PrEP program.

- MK-8527 (novel NRTTI) replaces ISL (P2).
- Ongoing P2 randomized, double-blind, placebo-controlled, dose-ranging study to assess safety, tolerability, and PK of QM oral MK-8527 in adults at low risk for HIV-1 infection (NCT06045507).
  - Participants randomized (2:2:2:1) to lower, middle, or high-dose MK-8527 or placebo; study drug or placebo administered QM x 6 doses; then follow-up x 8 weeks.
  - MK-8527 doses studied are not expected to impact lymphocyte and CD4+ T-cell counts.
- Abstracts to be presented at CROI 2024.
  - Discovery and mechanism of MK-8527, a LA HIV-1 NRTTI (poster #638).
  - Safety and PK of MK-8527, a novel NRTTI, in adults without HIV-1 (oral #1836).
  - Single-dose administration of MK-8527, a novel NRTTI, in adults with HIV-1 (oral #115).

Summary.

- Comprehensive assessment of lymphocyte findings and identification of new ISL doses paved the way to resume QD and QW oral ISL programs for HIV treatment.
  - QD oral ISL/DOR (0.25mg/100mg) P3 program restarted in Q12023 – four new clinical studies using a lower ISL dose.
  - QW oral ISL/LEN (2mg/300mg) P2 program restarted in Q12023 – week 24 results to be presented as a CROI 2024 late breaker.
- LAI ISL is no longer being developed for HIV treatment.
  - An ISL prodrug (GS-1614) is being developed under the Merck-Gilead collaboration and has entered P1.
- ISL implant is no longer being developed for HIV prevention.
  - The focus is development of a novel NRTTI (MK-8527) as QM oral PrEP and is in P2.