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"Current Status of the Gilead LA/ER pipeline"

LEN (small molecule Capsid Inhibitor) is the foundation of GILEAD's person-centric LA portfolio.

Favorable characteristics.

- High potency (EC50=100pM); Low dose requirement with an extended dosing interval.
- Multimodal mechanism; First-in-class agent with no overlapping resistance with existing compounds.
- Well-characterized clinical PK, including long half-life.
- Flexible dosing profile (oral or injectable dosing).

LEN as combination therapy for HIV treatment – diverse options across drug classes and routes of administration.

Pipeline.

- Injectable (Pre-IND to P3): Q3M dosing is the immediate focus; Q6M dosing is the longer-term aim.
  - Q6M compounds (pre-IND): GS-1219 (INSTI) and GS-3242 (INSTI).
  - Q3M compounds (P1): GS-6212 (INSTI) and GS-1614 (NRTTI; Merck-Gilead collaboration).
  - Q6M complete regimen (P2)**: LEN + 2bNAbs** (Terapavimab [TAB] and Zinlirvimab [ZAB]).
- Oral (P1 to P2): QW dosing is the immediate focus.
  - QW compounds (P1): GS-1720 (INSTI) and GS-4182 (LEN prodrug).
  - QW complete regimen (P2): **LEN + ISL** (NRTTI; Merck-Gilead collaboration).
  - QD complete regimen (P2): **LEN + BIC** (INSTI).

Clinical development of complete regimens.

- Q6M injectable LEN SC + 2bNAbs IV (TAB + ZAB).
  - P1b study (LEN + 2bNAbs [10mg/kg and 30mg/kg]) in VS PWH with viral susceptibility to TAB and ZAB (n=21).
    *Both dose groups maintained virological suppression at week 26 (Eron J et al Lancet HIV 2024).
  - Small P1b pilot cohort study in VS PWH with viral susceptibility to only one bNAb (n=10).
    *Results to be presented at CROI 2024 (Oral #2258; Eron J et al).
  - Ongoing P2 randomized (2:1) study (LEN + 2bNAbs vs baseline ART) in VS PWH with viral susceptibility to both TAB and ZAB (n=75); Safety and efficacy endpoints at week 26 and 52.
    *Fully enrolled.
- QW oral ISL + LEN (Merck-Gilead collaboration).
  - P2 randomized (1:1) study (ISL + LEN vs QD B/F/TAF) in VS PWH on B/F/TAF (n=100).
    *FDA clinical hold in 2021 due to ISL lymphocyte effect; Study resumed in 2023 using a lower ISL dose (2mg).
    *Week 24 safety and efficacy to be presented at CROI 2024 (late-breaker #208; Colson A et al).
- QD oral BIC + LEN (not LA; aims to address the needs of VS PWH on a complicated regimen).
  - Ongoing P2 randomized (2:2:1) switch study (QD oral BIC + LEN [25mg or 50 mg] vs baseline multi-tablet regimen).
    *Results to be presented at CROI 2024 (poster #1289; Mounzer K et al).
  - Just began P3 randomized (2:1) study (BIC [75mg] + LEN [50 mg] vs baseline multi-tablet regimen).

LEN as Q6M monotherapy for HIV prevention – potential to address the burden/stigma of daily pill-taking and increase global uptake of PrEP.

PURPOSE Program.

- Five studies intentionally designed to enroll populations traditionally left out of clinical and prevention studies: Women, particularly adolescent girls and young women (AGYW); Transgender (TG); and Gender non-binary (GNB).
- Proof of Concept: Capsid inhibitors prevent simian HIV in NHPs; robust safety and PK database in persons with and without HIV.
- Leverages: partnerships; input from people who may benefit from PrEP and the community; person-centric design; and diversity equity and inclusion (DEI).

PURPOSE 1 is fully enrolled (n=5000 cisgender AGYM).

- Large P3 randomized (2:2:1) blinded study of Q6M LEN + oral placebo (2:1 F/TAF or F/TDF) vs QD oral F/TAF + LEN placebo vs QD oral F/TDF + LEN placebo.
- Innovative components:
  - Incidence Phase. AGYM screened for HIV in the community to estimate background HIV (bHIV) incidence; HIV-positive persons will be linked to care, and HIV-negative persons meeting eligibility will be recruited.
  - Controls. External control is bHIV incidence. Internal (active) control is F/TDF + LEN placebo arm.
- Primary analysis: HIV incidence rate per 100 PY (LEN vs bHIV and F/TAF vs bHIV).

PURPOSE 2 is fully enrolled (n=3000 CGMSM, TGW, TGM, and GNB who have sex with men).

- Large P3 randomized (2:1) study of Q6M LEN SC + F/TDF placebo vs QD oral F/TDF + LEN placebo.
- Innovative components: same as PURPOSE 1.
- Primary analysis: HIV incidence rate per 100 PY (LEN vs bHIV).

PURPOSE 3 (n=250): US women.

- Randomized (1:1) study of Q6M LEN SC vs QD oral F/TDF.
- PK, safety, and acceptability.

PURPOSE 4 (n=250): People who inject drugs.

- Randomized (2:1) study of QM LEN SC vs QD oral F/TDF.
- PK, safety, and acceptability.

Summary.

- LEN remains the foundation of Gilead's patient-centric LA portfolio.
- Gilead's HIV treatment program includes diverse combination therapy options across drug classes and routes of administration.
  - Three complete regimens are in P2 clinical trials; multiple compounds are in development (Pre-IND to P1), including a novel INSTII (GS-1720) for QW oral administration (CROI 2022 oral #1903; Fichtenbaum C et al).
- HIV Prevention – the innovative PURPOSE program is evaluating Q6M injectable LEN in various at-risk populations that are traditionally left out of clinical and prevention trials.
  - Two large P3 studies are fully enrolled and will estimate bHIV incidence as well as LEN efficacy among at-risk AGYM, TGW/M, CGMSM, and GNB populations.