CLINICAL EVALUATION OF DRUG INTERACTIONS WITH ORAL LENACAPAVIR AND PROBE DRUGS

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Disclosure: Employee and stockholder of Gilead Sciences.
Lenacapavir (LEN): First-in-class HIV Capsid Inhibitor

EC_{50}, half maximal effective concentration.
LEN Overview

- Favorable in vitro pharmacology profile:
  - Potent antiviral activity (30 – 100 pM), with high selectivity (>140,000)\(^1\)
  - Activity against mutants resistant to existing ARV classes\(^{1,2}\)
- Significant antiviral activity in Phase 1b clinical trial\(^{1,3}\)
  - Up to 2.3 log\(_{10}\) decline in HIV RNA
- Currently in clinical development as component of long-acting regimen for the treatment of HIV-1 infection
  - Presentation ID 2228: Segal-Maurer et al. Potent Antiviral Activity of Lenacapavir in Phase 2/3 in Heavily ART-Experienced PWH

LEN DDI Liability and Study Objectives

- Based on in vitro data, LEN may
  1. Be a substrate for P-gp, CYP3A, and UGT1A1
  2. Inhibit P-gp, BCRP, OATP, and CYP3A, and induce CYP3A
  3. Demonstrate increased absorption at high gastric pH

- Study objectives:
  - Evaluate clinical effects of
    - Strong P-gp, CYP3A and UGT1A1 inhibitors/inducers on LEN exposure
    - LEN coadministration on sensitive P-gp, BCRP, OATP, and CYP3A substrates
    - Increased gastric pH on LEN exposure

BCRP, breast cancer resistance protein; CYP3A, cytochrome P450 3A; DDI, drug-drug interaction; OATP, organic-anion-transporting polypeptides; P-gp, p-glycoprotein; UGT1A1, UDP glucuronosyltransferase 1A1.
Study Design (Part 1): LEN as a Victim of DDIs

Inhibitors were dosed to steady-state and through LEN PK assessment

Probe dosing: VORI 400 mg bid, DRV 800 mg qd, COBI 150 mg qd, ATV 300 mg qd.
Strong CYP3A/P-gp Inhibition Increased LEN Exposure by ~ 2-fold

- Similar fold increase (2.3x [1.8 – 2.9x]) after COBI coadministration
- Deemed not clinically relevant based on available safety data
- LEN can be co-administered with strong CYP3A/P-gp inhibitors, such as DRV/COBI

*Amax increase was comparable*
# P-gp and UGT1A1 More Important For Disposition of LEN Than CYP3A

<table>
<thead>
<tr>
<th>Strong Inhibition of:</th>
<th>CYP3A</th>
<th>CYP3A/P-gp</th>
<th>CYP3A/P-gp/UGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitor:</td>
<td>VORI</td>
<td>COBI</td>
<td>ATV/COBI</td>
</tr>
<tr>
<td>LEN AUC % increase*</td>
<td>30 (2–67)</td>
<td>130 (80–190)</td>
<td>300 (200–420)</td>
</tr>
</tbody>
</table>

- Minimal change after selective CYP3A inhibition (VORI)
- P-gp/CYP3A inhibition (COBI) implicates P-gp transport-limited LEN absorption
- Moderate DDI after P-gp/CYP3A/UGT1A1 inhibition (ATV/COBI): glucuronidation is the primary LEN elimination pathway

*\(C_{max}\) increases were comparable
Study Design (Part 2): LEN as a Victim of DDIs

- RIF and EFV were dosed to steady-state and through LEN PK assessment
- Single dose famotidine (FAM) administered 2 hr prior to LEN dramatically increases gastric pH

*2 hours post FAM dose
Probe dosing: RIF 600 mg qd PM, EFV 600 mg qd PM, FAM single dose 40 mg.
85% Decrease in LEN AUC by Strong CYP3A/P-gp/UGT Induction

- LEN + RIF coadministration not advised
- EFV (moderate inducer) results pending
Study Design (Part 3): LEN as a perpetrator of DDIs

Healthy Volunteers
n=30

Day 1
PIT
ROS
TAF
MDZ

Day 4
PIT
ROS
TAF
MDZ

Day 7
PIT
ROS
TAF
MDZ

Day 10
PIT
ROS
TAF
MDZ

Day 11
PIT
ROS
TAF
MDZ

Day 15
PIT
ROS
TAF
MDZ

Day 18
PIT
ROS
TAF
MDZ

Day 21
PIT
ROS
TAF
MDZ

Day 24
PIT
ROS
TAF
MDZ

LEN 600 mg bid x 2d, then q3d

Probe
Pitavastatin (PIT)
Rosuvastatin (ROS)
Tenofovir alafenamide (TAF)
Midazolam (MDZ)

Sensitive Substrate
OATP
BCRP/OATP
P-gp
CYP3A

♦ LEN administration was continued through probe PK evaluation

Substrate dosing: PIT 2 mg, ROS 5 mg, TAF 25 mg, MDZ 2.5 mg.
LEN 600 mg bid for 2 days, then q3d provides for supra-therapeutic exposure; conservative DDI liability assessment
LEN is a Moderate Inhibitor of CYP3A: 3.3x (3.1–3.6x) Increase in MDZ AUC

- Caution is advised with LEN coadministration with sensitive CYP3A substrates
- Minimal increase in TAF, ROS and PIT AUC* indicates that LEN can be administered with sensitive P-gp, BCRP or OATP substrates

*AUC↑:
- TAF = 1.5x (1.4–1.7x);
- ROS = 1.3x (1.2–1.4x);
- PIT = 1.1x (1.0–1.2x)
LEN Clinical DDI Profile

<table>
<thead>
<tr>
<th>Substrate</th>
<th>CYP3A</th>
<th>UGT1A1</th>
<th>P-gp</th>
<th>BCRP</th>
<th>OATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>Yes — Minor (VORI)</td>
<td>Yes — Sensitive (ATV/COBI)</td>
<td>Yes (COBI, DRV/co)</td>
<td>N.A.*</td>
<td>N.A.*</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>Yes — Moderate</td>
<td>N.A.*</td>
<td>Yes — Weak</td>
<td>Yes — Weak</td>
<td>No</td>
</tr>
</tbody>
</table>

- Potent inducer (RIF) decreased LEN by 85%: potent inducers disallowed
- Moderate inducer data (EFV): data pending, currently disallowed
- No effect of FAM on LEN PK (data not shown): Acid reducing agents (H2RAs/PPIs) allowed

*Not applicable; Study deemed unnecessary based on pre-clinical data
LEN DDI Clinical Recommendations

- Increased LEN exposure after coadministration with strong CYP3A/P-gp inhibitors is not clinically relevant; supports coadministration without dose modification.

- In the absence of additional data, coadministration of LEN and strong UGT1A1 inhibitors is not recommended.
  - Potent inducers of CYP/P-gp/UGT should be avoided.

- LEN can be coadministered with gastric acid reducers.

- Caution is advised if LEN is coadministered with sensitive CYP3A substrates, but not P-gp, BCRP nor OATP substrates.
Acknowledgments

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