Doravirine Efficacy Exposure–Response Analysis at Week 48 and Implications
and
Doravirine Pharmacokinetics After Switching from Efavirenz Therapy in Healthy Volunteers

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Disclosures

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- Ka Lai Yee, Rosa I Sanchez, Rachael Liu, Li Fan, Ilias Triantafyllou, Marian Iwamoto, Xia Xu, Hedy Teppler, Sauzanne Khalilieh are current employees of Merck & Co., Inc., Kenilworth, NJ, USA.

- Patrice Auger, Charles Tomek, and Mike Di Spirito have nothing to disclose.
Doravirine (MK-1439): Novel NNRTI with Potential for Improved Efficacy and Safety

- Common NNRTIs associated with suboptimal efficacy and/or safety profiles
  - Efavirenz: frequent CNS adverse events\(^1\)
  - Rilpivirine: treatment-naïve indication only for RNA ≤100,000 c/mL in both US and EU\(^2,3\)

- Doravirine, a novel NNRTI in development for the treatment of HIV-1 infection in combination with other ART.
  - High \textit{in vitro} potency vs broad panel of isolates including wild-type virus and common NNRTI-resistant variants (K103N, Y181C, K103N/Y181C)\(^4\)

- \textbf{PK properties of doravirine include}\(^5,6\):
  - Rapid onset (\(T_{\text{max}}\) 1-5 hours) and moderate half-life (11-19 hours)
  - Dose proportional AUC and \(C_{\text{max}}\) over the clinically relevant dose range
  - Steady state achieved in 4-5 days of once-daily dosing
  - Dosed without regard to food

- Primarily metabolized by CYP3A4\(^5,6\), but is not an inducer or inhibitor\(^7\)

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2. Rilpivirine US PC.
3. Rilpivirine EU SPC.
Phase 2 (P007) Study Design and Analysis Methods

- Randomized, two-part dose-ranging study of doravirine vs efavirenz in combination with TRUVADA™ (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg), designed to examine safety, tolerability, PK, and efficacy.
  - **Part 1:**
    - ART-naïve adults with HIV-1 infection, having vRNA ≥1,000 cc/mL and CD4 counts ≥100 cells/µL were eligible to take part in the study.
    - Patients received 1 of 4 doses of doravirine (25, 50, 100, or 200 mg once daily) or efavirenz 600 mg nightly.
    - All patients also received TRUVADA throughout.
  - **Part 2:**
    - Patients switched to doravirine 100 mg daily at the next scheduled visit.
      - Nine patients receiving 25, 50, or 200 mg switched at Week 36.
      - Other patients switched at or after Week 48.
    - For this study, patients were assumed to retain their initial dose and exposure levels.

- **The PK of doravirine based on:**
  - Sparsely sampled plasma concentrations through Week 24.
  - Data pooled with densely sampled Phase 1 PK data in a population PK model to obtain individual post hoc estimates of steady state PK parameters.

- Exposure–response relationships were explored based on vRNA results at Week 48.
Doravirine, in combination with TRUVADA™, was efficacious in treating ART-naïve HIV-1–infected patients over 25-200 mg dose range compared with efavirenz at Week 48.¹

Doravirine was generally well tolerated. The most common AEs related to study treatment were dizziness, abnormal dreams, diarrhea, nausea, and fatigue.
vRNA Exposure Response at Week 48

- Individual PK estimates and Week 48 vRNA were matched
  - No apparent trend between PK ($C_{\text{trough}}$, $AUC$, or $C_{\text{max}}$) and vRNA at Week 48
  - No difference in PK/PD relationship between high and low viral load patients
Proportion of Patients with Undetectable vRNA (<40 copies/mL) and Doravirine Exposure: Stratification by Baseline vRNA

- **Individual $C_{\text{trough}}$ and AUC estimates plotted against proportion of patients with undetectable vRNA (<40 copies/mL)**
  - PK estimates binned into equal sized bins
  - No apparent trend between PK and the proportion of patients with undetectable vRNA across all patients and stratified by high (>100,000 copies/mL) or low (≤100,000 copies/mL) baseline viral load
Baseline vRNA or SS $C_{\text{trough}}$ as a Predictor for Achieving vRNA Levels <40 cells/mL

- Even distribution of patients with detectable vRNA across all quadrants of high/low baseline viral load and SS $C_{\text{trough}}$ values further suggest no trend between detectable vRNA and SS $C_{\text{trough}}$ for both patients with both high and low baseline viral load.
Conclusions

• No evidence of an exposure–response relationship for vRNA or the proportion of patients achieving undetectable vRNA at Week 48 for SS doravirine $C_{\text{trough}}$, AUC, or $C_{\text{max}}$.

• No trends with respect to exposure and vRNA or achieving undetectable vRNA after 48 weeks of treatment for patients when stratified by high or low baseline VL.

• Data implies the attainment of a plateau over the 25-200 mg once daily dose range.

• Doravirine 25-200 mg daily for 48 weeks also showed good safety and tolerability profile

• Based on the overall benefit/risk assessment which includes consideration of potential drug interactions, activity against common mutant HIV-1 strains, and forgiveness of missed doses, these data support selection of 100 mg once daily for evaluation in Phase 3 studies.
Effects of Switching From Efavirenz to Doravirine Treatment on Doravirine PK

- A proportion of patients with HIV who are unable to tolerate the most common side effects of efavirenz-based regimens may be switched to alternative NNRTIs, including doravirine.

- Doravirine exposure is reduced when co-administered with multiple doses of rifampin\(^1\), a strong CYP3A4 inducer.
  - Transient reduction in doravirine exposure is anticipated following a switch from efavirenz, a moderate CYP3A4 inducer.

- To support a planned Phase 2 study in which subjects with HIV will switch from efavirenz-based to doravirine-based treatment, a study was conducted to assess the impact of switching from efavirenz to doravirine on doravirine PK in healthy volunteers

Study Design

Objective:
• To assess the impact of switching from treatment with efavirenz to treatment with doravirine on the single- and multiple-dose PK of doravirine.

Three treatments in a fixed-sequence design:
• Period 1: 100 mg doravirine QD in the morning for 5 days followed by a 7-day washout
• Period 2: 600 mg efavirenz QD at bedtime for 14 days
• Period 3: 100 mg doravirine QD in the morning for 14 days, with no washout between Periods 2 and 3

PK assessments
• Doravirine PK without efavirenz pretreatment
• Doravirine PK after switching from efavirenz to doravirine
• Efavirenz concentrations after cessation of efavirenz

Safety
• AEs monitored throughout the study.
• Physical examination, vital signs, 12-lead ECG and clinical laboratory tests monitored at selected intervals.
Doravirine Plasma Concentration-Time Profiles

Subjects

- Seventeen males (age 21-53 years) and 3 females (age 43-53 years) enrolled in the study.
- Three discontinued the study before completion:
  - Two subjects in Period 2 (efavirenz pretreatment) due to AEs (papular rash)
  - One for personal reasons.

Single-dose of 100 mg doravirine

Multiple-dose of 100 mg doravirine

SD, standard deviation.

*Values are displayed as arithmetic means on a linear scale (±SD).
## Doravirine Plasma PK without Efavirenz and Following Cessation of Efavirenz Treatment

<table>
<thead>
<tr>
<th>Doravirine PK parameter</th>
<th>Single-dose (SD) of 100 mg doravirine</th>
<th>Multiple-dose (MD) of 100 mg doravirine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD doravirine (n=20)</td>
<td>Day 1 after Cessation: SD doravirine + efavirenz/SD dose doravirine (n=17)</td>
</tr>
<tr>
<td>GM (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AUC(_{0-24h}^a)</strong> ((\mu\text{M} \cdot \text{hr}))</td>
<td>28.0 (24.9, 31.6)</td>
<td>10.7 (9.00, 12.80)</td>
</tr>
<tr>
<td><strong>C(_{\text{max}}^a)</strong> (nM)</td>
<td>2080 (1810, 2380)</td>
<td>1350 (1160, 1570)</td>
</tr>
<tr>
<td><strong>C(_{24h}^a)</strong> (nM)</td>
<td>625 (528, 740)</td>
<td>93.3 (56.5, 154)</td>
</tr>
</tbody>
</table>

GM, geometric mean; CI, confidence interval; GMR, geometric least-squares mean ratio.

\(^a\)Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural-log-transformed values.
Doravirine and Efavirenz Plasma Concentrations After Cessation of Efavirenz Treatment

- Doravirine $C_{24h}$ reduced by 85% on the first day after cessation of efavirenz treatment, and gradually recovered, but was still reduced by approximately 50% after 14 days of doravirine dosing.
- Efavirenz geometric least-square mean concentrations decreased steadily from 3180 ng/mL on Day 1 to 95.7 ng/mL on Day 15, but remained detectable in all subjects for 9 days following cessation of efavirenz dosing.

*Day represents Hour 24 on the day. Efavirenz concentrations for Subject AN 0008 were not included in the $C_{efv}$ analysis since this subject is a slow metabolizer (CYP2B6*6/*6).
Conclusions

• Doravirine exposure is transiently decreased when doravirine treatment is initiated immediately following cessation of efavirenz therapy
  • Doravirine $C_{\text{trough}}$ exceeded $C_{24h}$ PK targets based on efficacy against the wild type virus in in vitro studies (78 nM; data on file)
  • Based on intersubject variability in $C_{24h}$ values for the 25 mg dose in a Phase 2 study, efficacy based on VL suppression at Week 48, was observed in subjects with trough levels as low as 107 nM.\(^1\)

• The clinical relevance of this transient interaction will be further evaluated in a Phase 2 study switching virologically suppressed patients with HIV infection continuing on combination ART from efavirenz to doravirine.

\(C_{24h}\), plasma concentration at 24 hours; VL, viral load.