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Doravirine Efficacy Exposure–Response Analysis at Week 48 and Implications[1] and Doravirine Pharmacokinetics After Switching from Efavirenz Therapy in Healthy Volunteers[2]

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Poster viewing session 3
Wed, May 27th at 4:30 PM
Poster No.: 5 (Exposure-Response) and 54 (HV Switch PK)

Disclosures

- This research was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

- 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 *in vitro* potency vs broad panel of isolates including wild-type virus and common NNRTI-resistant variants (K103N, Y181C, K103N/Y181C)[4]
- **PK properties of doravirine include[5,6]:**
  - Rapid onset (T_{max} 1-5 hours) and moderate half-life (11-19 hours)
  - Dose proportional AUC and C_{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]**

1. US DHHS Guidelines, 2013.
2. Rilpivirine US PC.
3. Rilpivirine EU SPC.
4. Lai M, 52nd ICAAC, 2012.
5. Anderson MS, et al. Antivir Ther. 2014 Dec 3. [Epub ahead of print].
6. Yee KL, et al. ICAAC 2014. September 5-9, 2014. Washington DC. Abstract H-647b.
7. Anderson M, et al. ICAAC 2013, Paper H-1462.

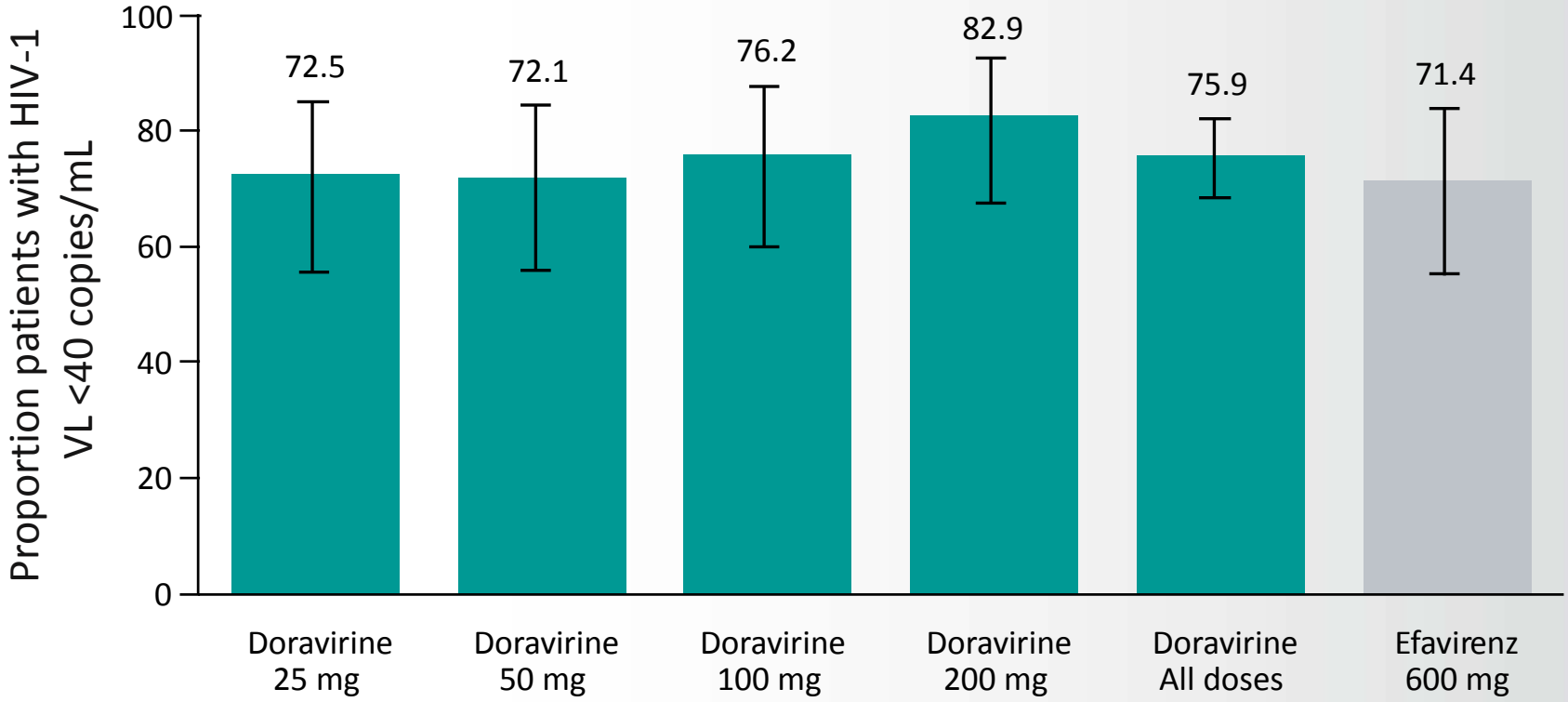
Phase 2 (P007) Study Design and Analysis Methods

- **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.**

Proportion of Patients Achieving HIV-1 VL <40 copies/mL at 48 Weeks

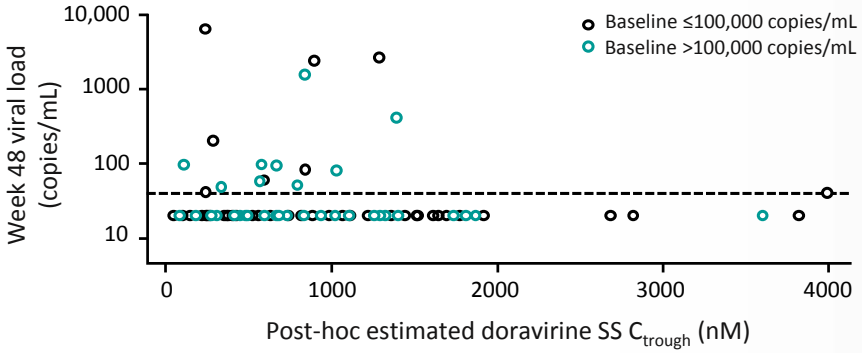


- **Doravirine , in combination with TRUVADA™, was efficacious in treating ART-naïve HIV-1–infected patients over 25-200 mg dose range compared with efavirenz at Week 48.[1]**

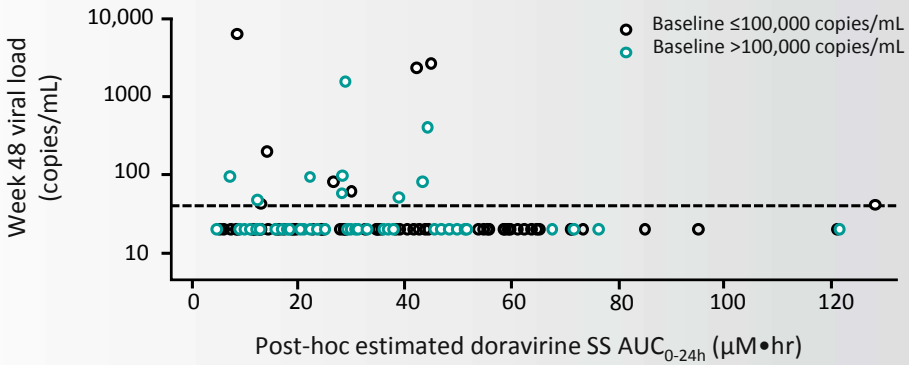
- **Doravirine was generally well tolerated. The most common AEs related to study treatment were dizziness, abnormal dreams, diarrhea, nausea, and fatigue.**

vRNA Exposure Response at Week 48

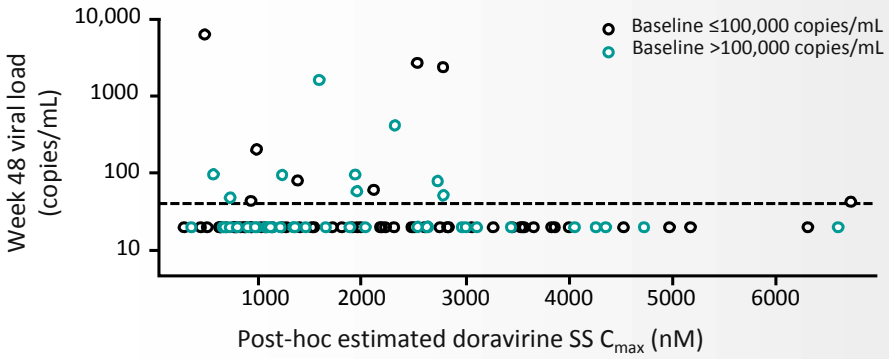
C_{trough}



$AUC_{0\text{-}24h}$

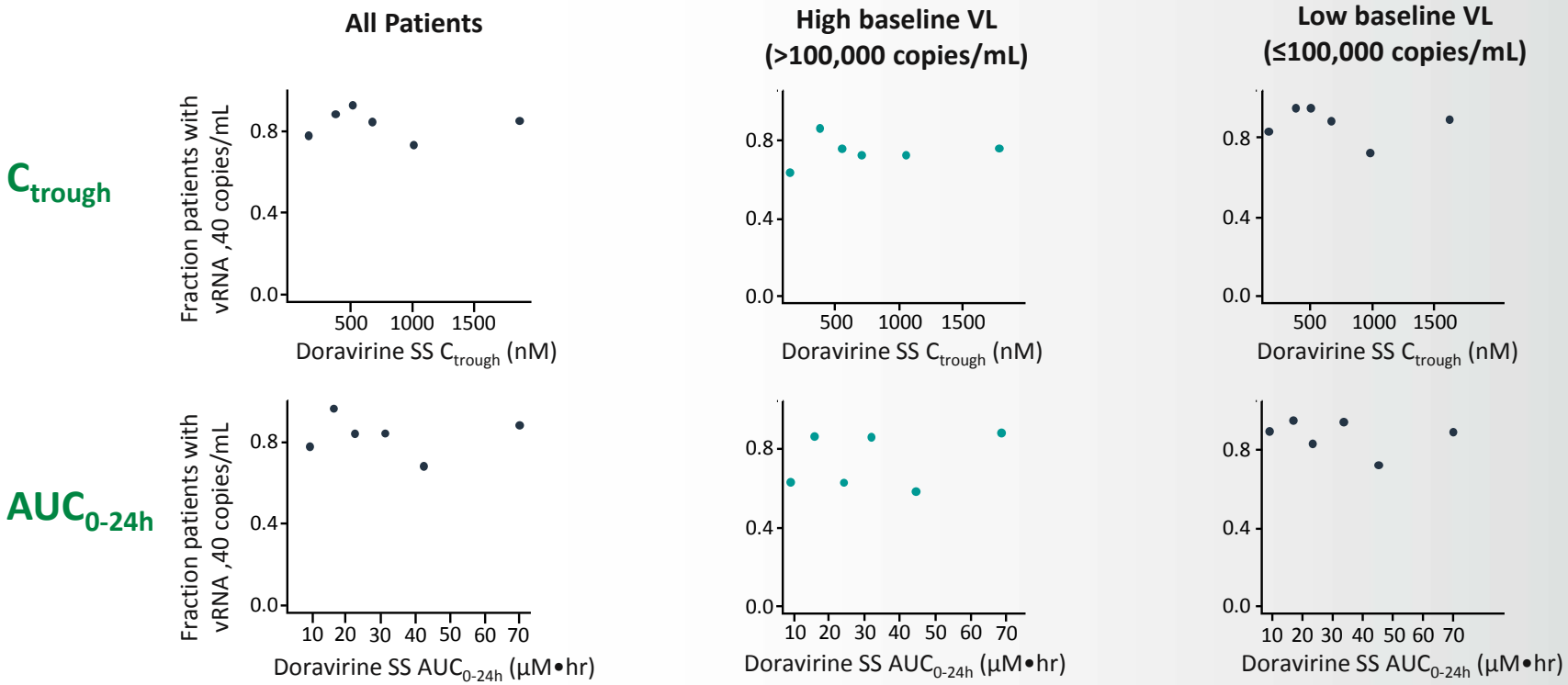


C_{max}



- **Individual PK estimates and Week 48 vRNA were matched**
  - No apparent trend between PK ($C_{trough,}$ AUC, or Cmax) and vRNA at Week 48
  - No difference in PK/PD relationship between high and low viral load patients

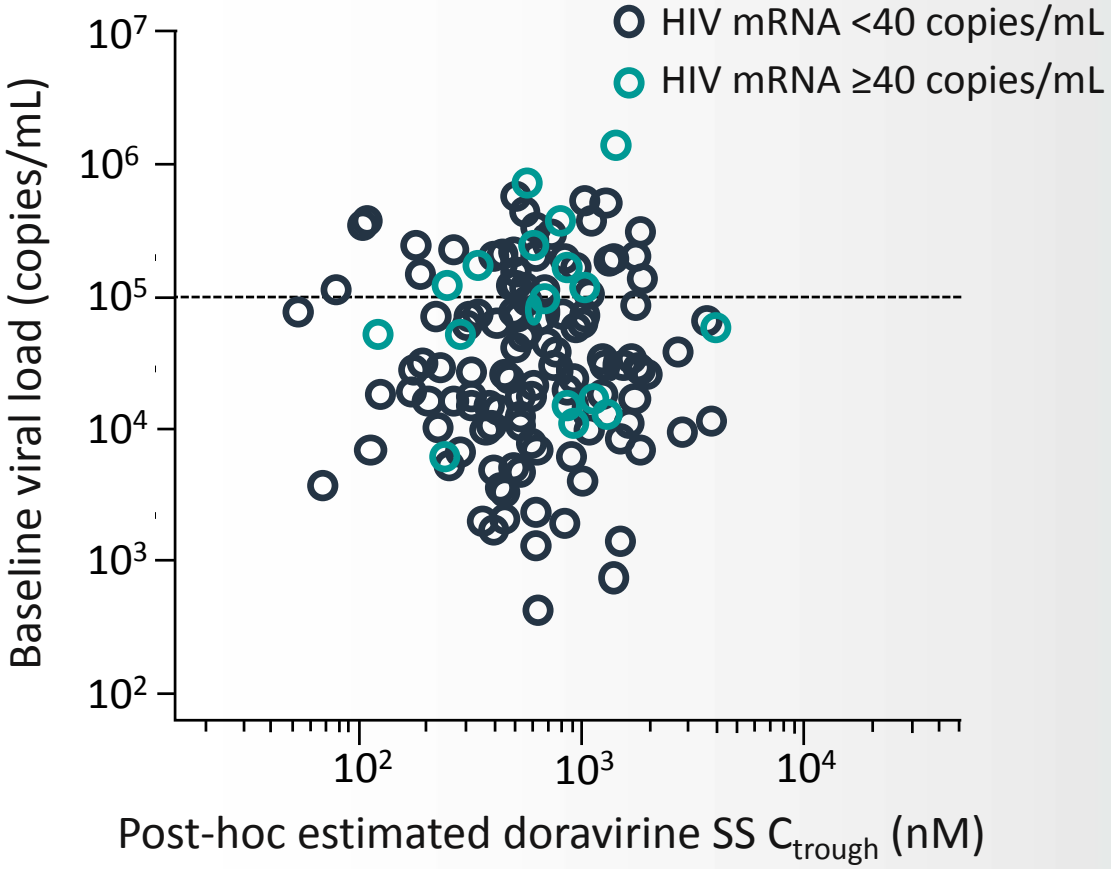
Proportion of Patients with Undetectable vRNA (<40 copies/mL) and Doravirine Exposure: Stratification by Baseline vRNA



- **Individual C_{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

uVL, undetectable viral load.

Baseline vRNA or SS C_{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_{trough} values further suggest no trend between detectable vRNA and SS C_{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_{trough}, AUC, or C_{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**

1. Yee KL, et al. CROI 2015. Feb 23-26, 2015, Seattle, WA.

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

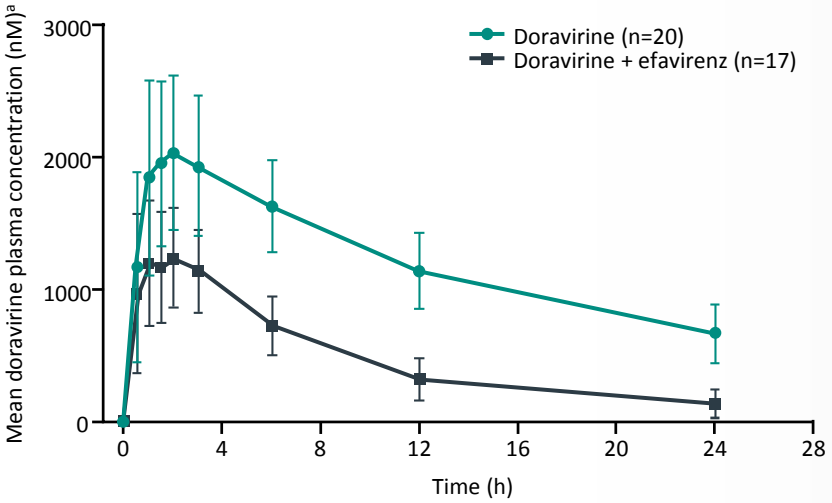
- AEs monitored throughout the study.
- Physical examination, vital signs, 12-lead ECG and clinical laboratory tests monitored at selected intervals.

Doravirine Plasma Concentration-Time Profiles

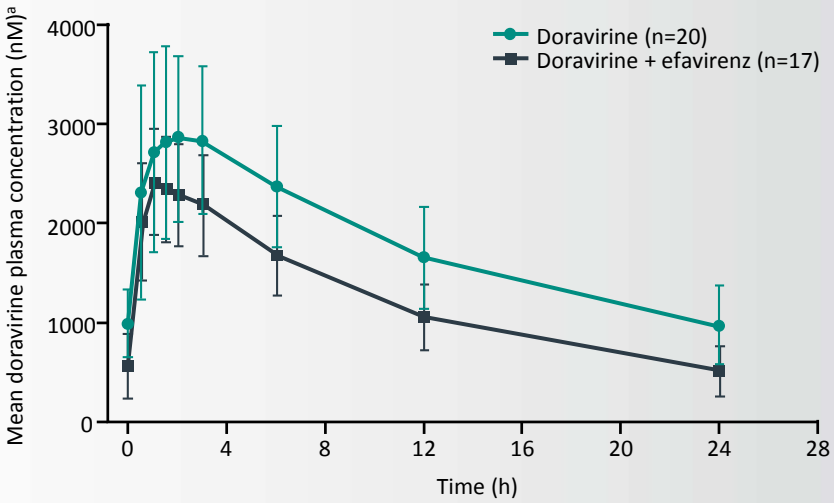
Subjects

- **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



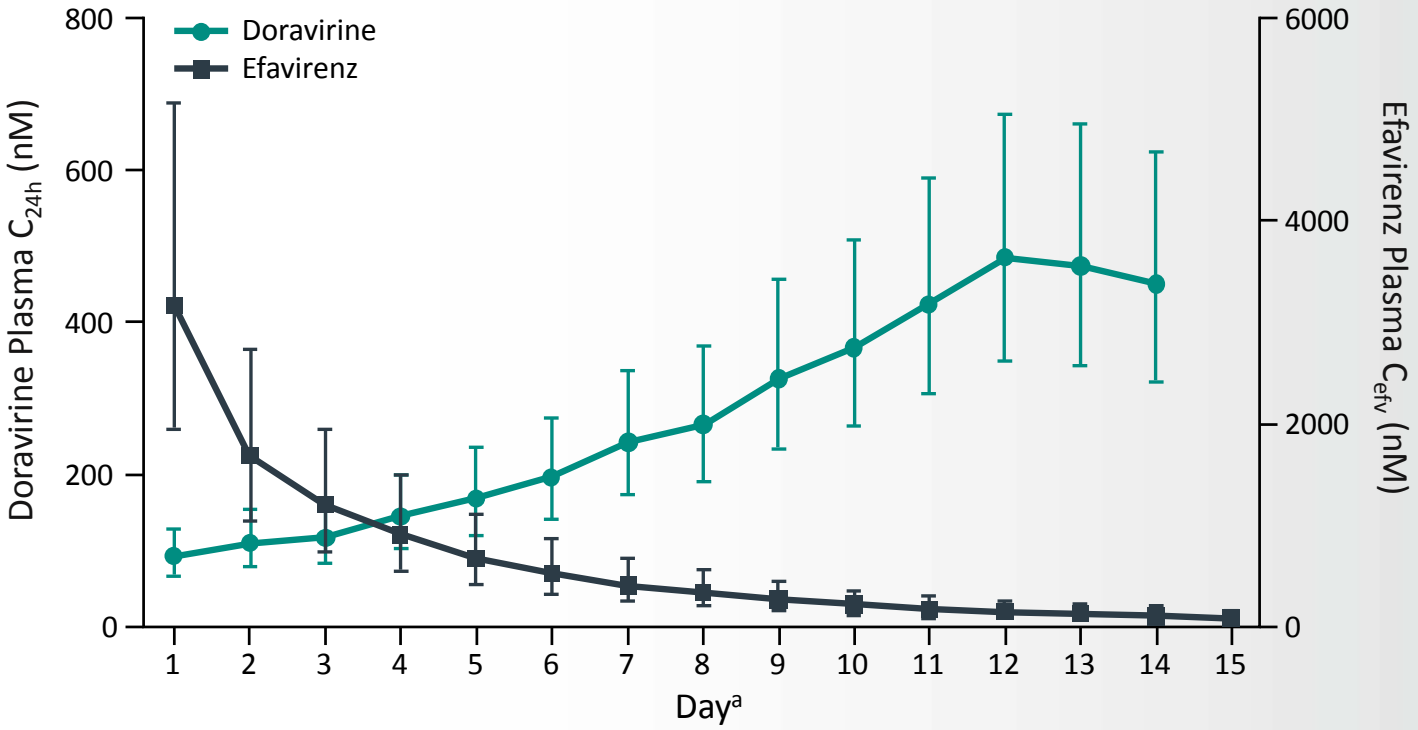
SD, standard deviation.
[a]Values are displayed as arithmetic means on a linear scale (±SD).

Doravirine Plasma PK without Efavirenz and Following Cessation of Efavirenz Treatment

	Single-dose (SD) of 100 mg doravirine			Multiple-dose (MD) of 100 mg doravirine		
Doravirine PK parameter GM (95% CI)	SD doravirine (n=20)	Day 1 after Cessation: SD doravirine + efavirenz (n=17)	SD doravirine + efavirenz/SD dose doravirine	MD doravirine (n=19)	Day 14 after Cessation: MD doravirine + efavirenz (n=17)	MD doravirine + efavirenz/ MD doravirine
$AUC_{0\text{-}24h}$[a] (µM•hr)	28.0 (24.9, 31.6)	10.7 (9.00, 12.80)	0.38 (0.33, 0.45)	41.1 (35.3, 47.9)	28.0 (23.9, 33.0)	0.68 (0.58, 0.80)
C_{max}[a] (nM)	2080 (1810, 2380)	1350 (1160, 1570)	0.65 (0.58, 0.73)	2880 (2470, 3360)	2490 (2230, 2780)	0.86 (0.77, 0.97)
C_{24h}[a] (nM)	625 (528, 740)	93.3 (56.5, 154)	0.15 (0.10, 0.23)	902 (730, 1120)	449 (331, 610)	0.50 (0.39, 0.64)

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.

[a]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_{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.

1. Yee KL, et al. ICAAC 2014. September 5-9, 2014. Washington, DC. Abstract H-647b.