AIDS 2015
Vancouver, BC
Abstract TUAB0104

Efficacy and Safety of Doravirine 100mg QD vs Efavirenz 600mg QD with TDF/FTC in ART-Naive HIV-Infected Patients: Week 24 Results

Jose M. Gatell[1], Francois Raffi[2], Andreas Plettenberg[3], Don Smith[4], Joaquin Portilla[5], Christian Hoffmann[6], Keikawus Arasteh[7], Melanie Thompson[8], Debbie P. Hagins[9], Javier O. Morales-Ramirez[10], Xia Xu[11], Hedy Teppler[11] for the P007 Study Team

[1]Hospital Clinic/IDIBAPS, Univ of Barcelona, Barcelona, Spain; [2]COREVIH Pays de Loire, France; [3] ifi-Institute for Infections, Hamburg, Germany; [4] Albion Centre, Sydney, Australia; [5] Univ Miguel Hernandez, Alicante, Spain; [6] ICH Study Center, Hamburg, Germany; [7] EPIMED/Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany; [8] AIDS Research Consortium of Atlanta, Atlanta, GA; [9] Chatham County Health Dept, Savannah, GA; [10] Clinical Research Puerto Rico, San Juan, PR; [11] Merck & Co., Inc., Kenilworth, NJ

Acknowledgements

We thank all the patients who participated in this study.

The contributions of the investigators and their staff are likewise gratefully recognized.

Primary Investigators (by country): *Australia - M. Bloch, N. Roth, D. Baker, R. Moore, D. Smith, D. Cooper; Belgium - J-C. Goffard, J-C. Legrand; Canada - B. Conway, J-G. Baril, S. Walmsley; France - J. Reynes, L. Cotte, Y. Yazdanpanah, J-M. Molina, F. Raffi; Germany - J. Rockstroh, A. Plettenberg, M. Stoll, S. Esser, K. Arasteh, A. Baumgarten, D. Schürmann, C. Hoffmann, A. Trein; Netherlands - B. Rijnders; Russia - N. Zakharova, E. Smirnov, A. Yakovlev, V. Prokrovski; Romania - G. Coltan, A. Streinu-Cercel, S. Rugina, S. Erscoiu; Spain - J. Arribas López, B. Clotet Sala, J. Berenguer Berenguer, J. Gatell Artigas, J. Portilla Sogorb; Puerto Rico - J. O. Morales-Ramirez, I. Melendez-Rivera; United States - U. F. Bredeek, D. Hagins, T. Jefferson, M. Mogyoros, D. J. Prelutsky, A. Scarsella, J. Slim, G. Sussman, M. Thompson, F. Felizarta, R. Dretler, P. Salvato, K. Abriola, O. Osiyemi, E. DeJesus, M. Ramgopal, W. Robbins, J. Montero, J. Rodriguez.*

This study is sponsored by MSD, a subsidiary of Merck & Co., Inc.

Disclosures

- Dr. Gatell has received research grants or honoraria for lectures or for Advisory Boards from MSD, Abbvie, Janssen, Gilead, ViiV and BMS.

Background

- 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[1,2]
  - Neither is recommended as first-line treatment in current DHHS guidelines[1]
- Doravirine (DOR, aka MK-1439), a novel NNRTI
  - High *in vitro* potency vs broad panel of isolates including common NNRTI-resistant variants[3]
  - Primary metabolism by CYP3A4; not an inducer or inhibitor[4]
  - Once daily dosing, can be dosed without regard to food
  - No interactions expected with proton pump inhibitors
- At 25, 50, 100 and 200mg QD, DOR showed rates of virologic suppression similar to EFV 600mg QD; 100mg was selected for ongoing evaluation[5,6]

1. US DHHS Guidelines, Apr 2015.
2. Rilpivirine EU PC.
3. M Lai , AAC 2014;58:1652.
4. M Anderson, Antiviral Ther 2014.
5. J Morales-Ramirez, CROI 2014 [Abstr 92LB].
6. J Gatell, J Int AIDS Soc. 2014;17:19532.

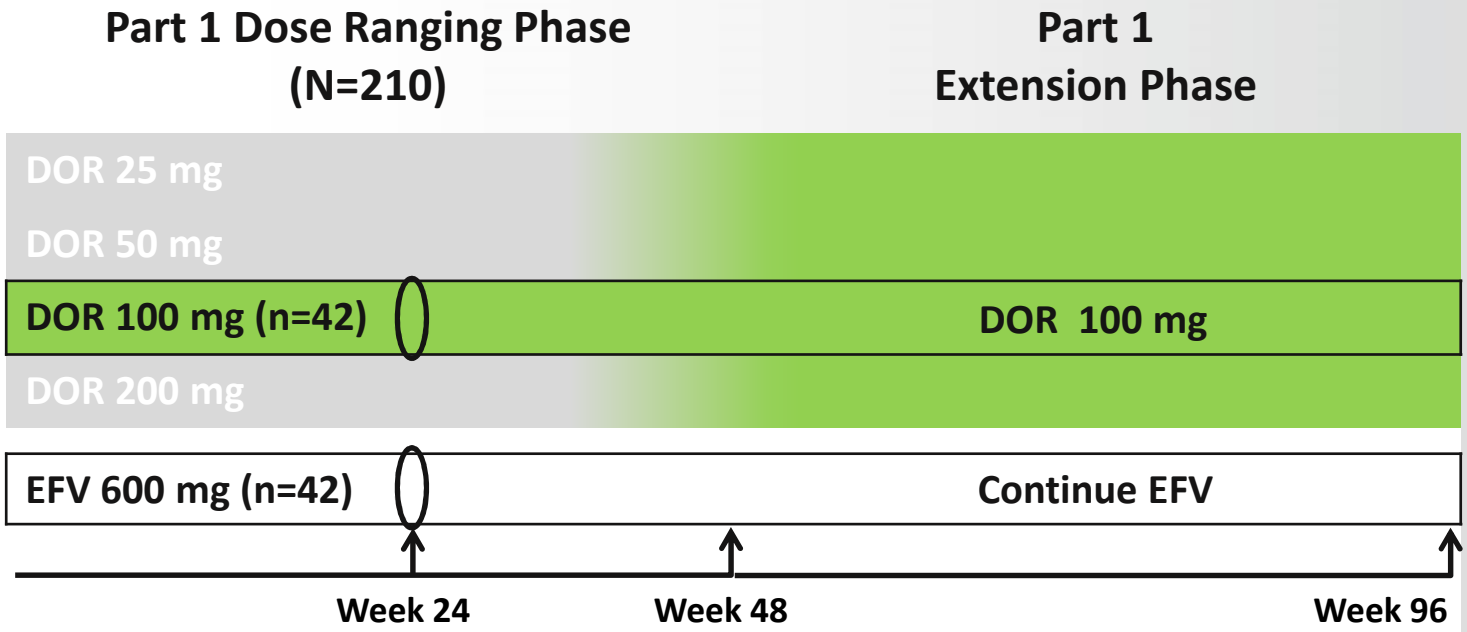
Protocol 007: Study Schema

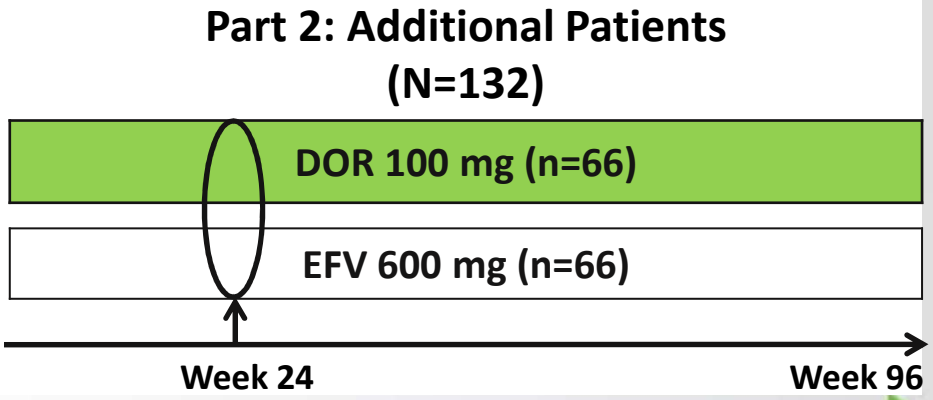
AIDS 2015
Vancouver, BC
Abstract TUAB0104

Patients:
HIV-1+
ART-naïve

HIV RNA
≥ 1,000 c/ml

CD4 count
≥ 100 cells/µL





Note: blinding maintained through Week 96 study visit

Protocol 007: Current Analysis, Methods

AIDS 2015
Vancouver, BC
Abstract TUAB0104

- **Parts 1 and 2 combined, Week 24**
  - DOR 100 mg vs EFV 600 mg; N=108 per group
- **Efficacy endpoints**
  - Virologic response: % with HIV RNA <40 c/mL (primary), % with HIV RNA <200 c/mL (secondary)
    - Non-completer = Failure (NC=F) approach for missing data
  - Immunologic response: Change from baseline in CD4 cell count
    - Observed Failure (OF) approach for missing data
  - Virologic response by screening HIV RNA (< vs ≥ 100K c/mL)
    - OF approach for missing data: missing values imputed as failure for (1) discontinuation due to lack of efficacy, and (2) discontinuation for non-treatment related reasons, if final vRNA is >40 copies/mL.
- **Safety endpoints**
  - Proportion of patients with pre-specified CNS AEs
    - Primary safety endpoint, hypothesis testing with >80% power
  - Clinical adverse events
  - Laboratory parameters – predefined limits of change, DAIDS toxicity criteria

AIDS 2015
Vancouver, BC
Abstract TUAB0104

Baseline Patient Characteristics

Parts 1 & 2 Combined

	Doravirine 100 mg (N=108)	Efavirenz 600 mg (N=108)
% Male	91.7	93.5
Age (years), median (range)	35 (19 – 67)	34 (20 – 57)
% White	79.6	79.6
% with AIDS	3.7	6.5
HIV RNA (log_{10} c/mL), median (range)	4.6 (2.6 – 6.5)	4.6 (3.0 – 6.7)
% with HIV RNA >100,000 c/mL, at screening*	35.2	37.0
CD4 Count (cells/µL), median (range)	402 (92 – 1110)	430 (118 – 1121)
% with CD4 count ≤ 200 cells/µL	6.5	9.3
% with Clade B viral subtype	69.4	79.6

*Patients stratified at entry by viral load ≤ or > 100,000 c/mL

Patient Status, Week 24

Parts 1 & 2 Combined

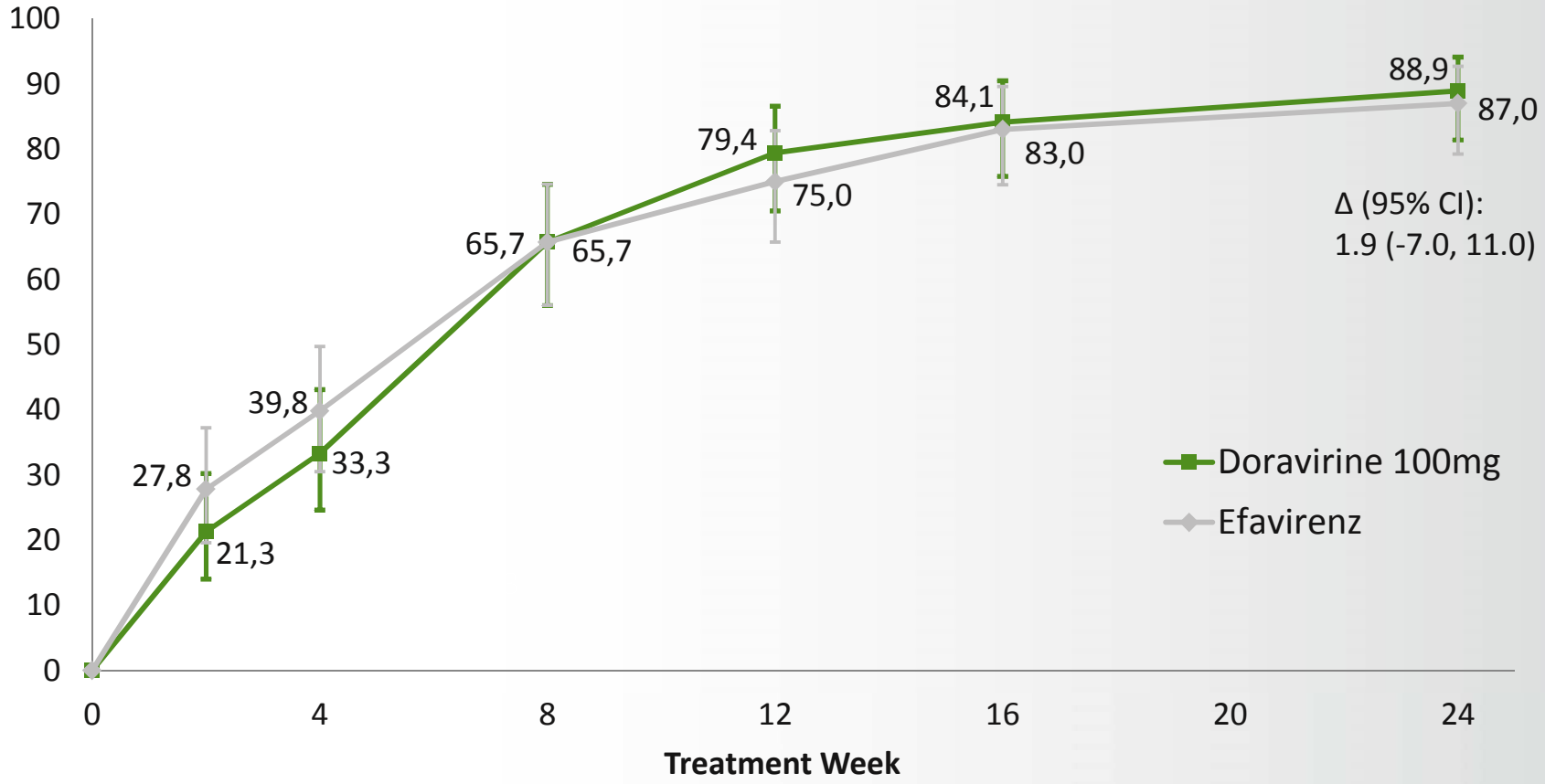
	Doravirine 100 mg	Efavirenz 600 mg
Patients randomized, n	108	109
Patients treated, n	108	108
Patients discontinued, %	4.6	11.9
Adverse event	0.9	5.5
Lost to follow-up	1.9	2.8
Noncompliance with study drug	0.9	0.0
Physician decision	0.0	0.9
Withdrawal by subject	0.9	2.8

Note: Denominator for % calculation is the number of patients randomized.

AIDS 2015
Vancouver, BC
Abstract TUAB0104

Patients with HIV RNA <200 c/mL, % (95% CI)

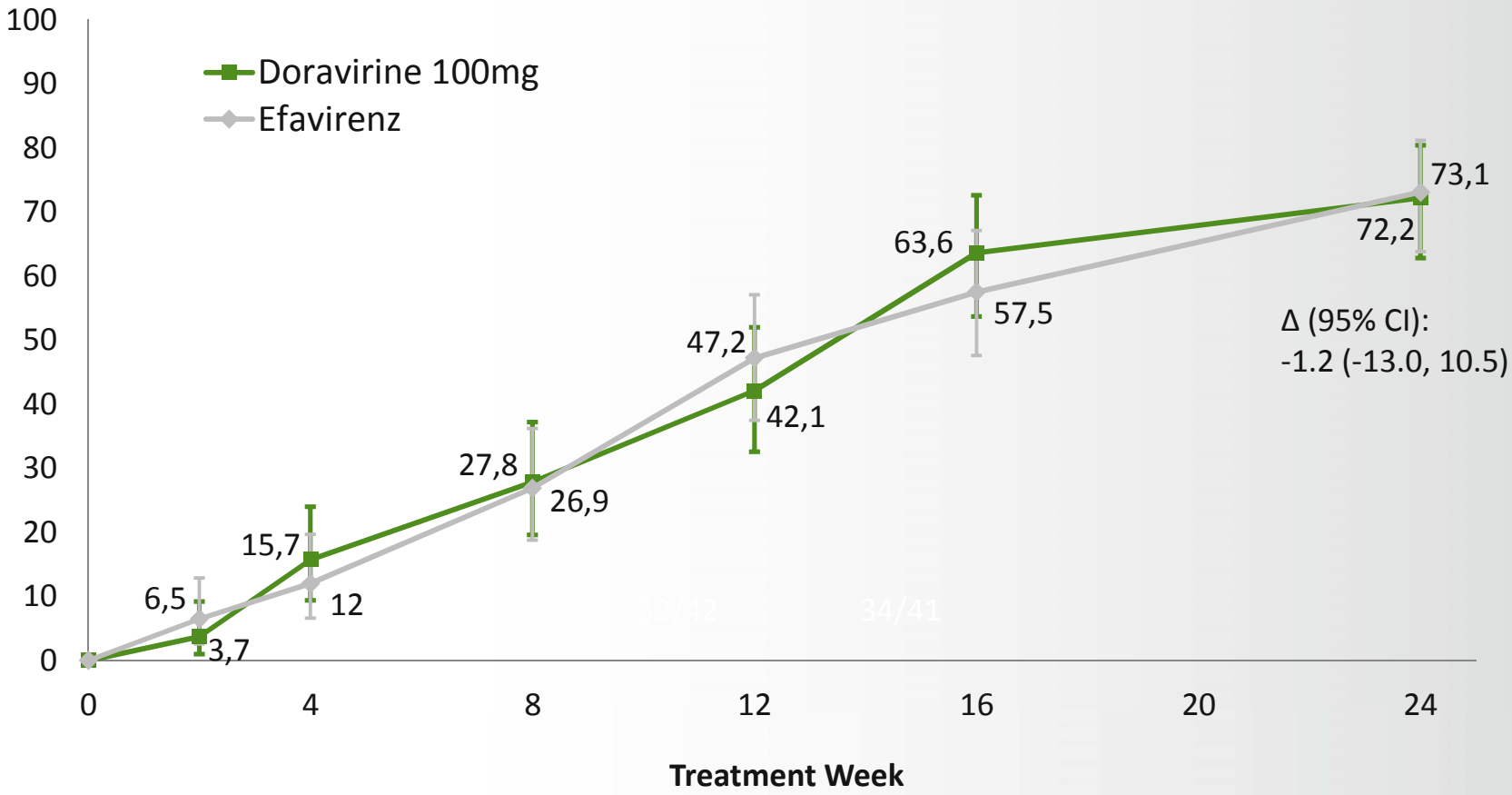
Non-completer = Failure Approach



AIDS 2015
Vancouver, BC
Abstract TUAB0104

Patients with HIV RNA <40 c/mL, % (95% CI)

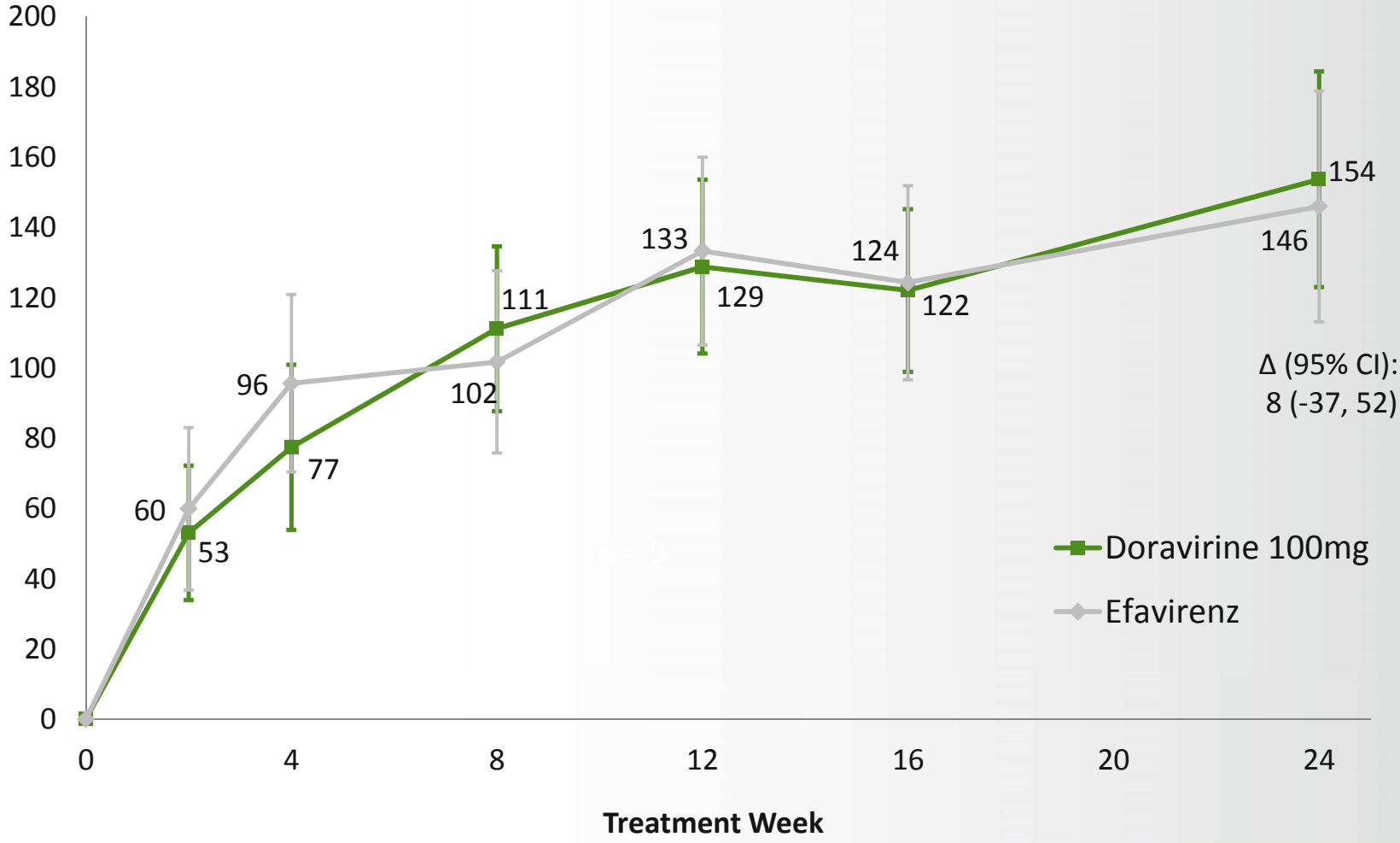
Non-completer = Failure Approach



AIDS 2015
Vancouver, BC
Abstract TUAB0104

Change in CD4 Count (cells/µL), Mean (95% CI)

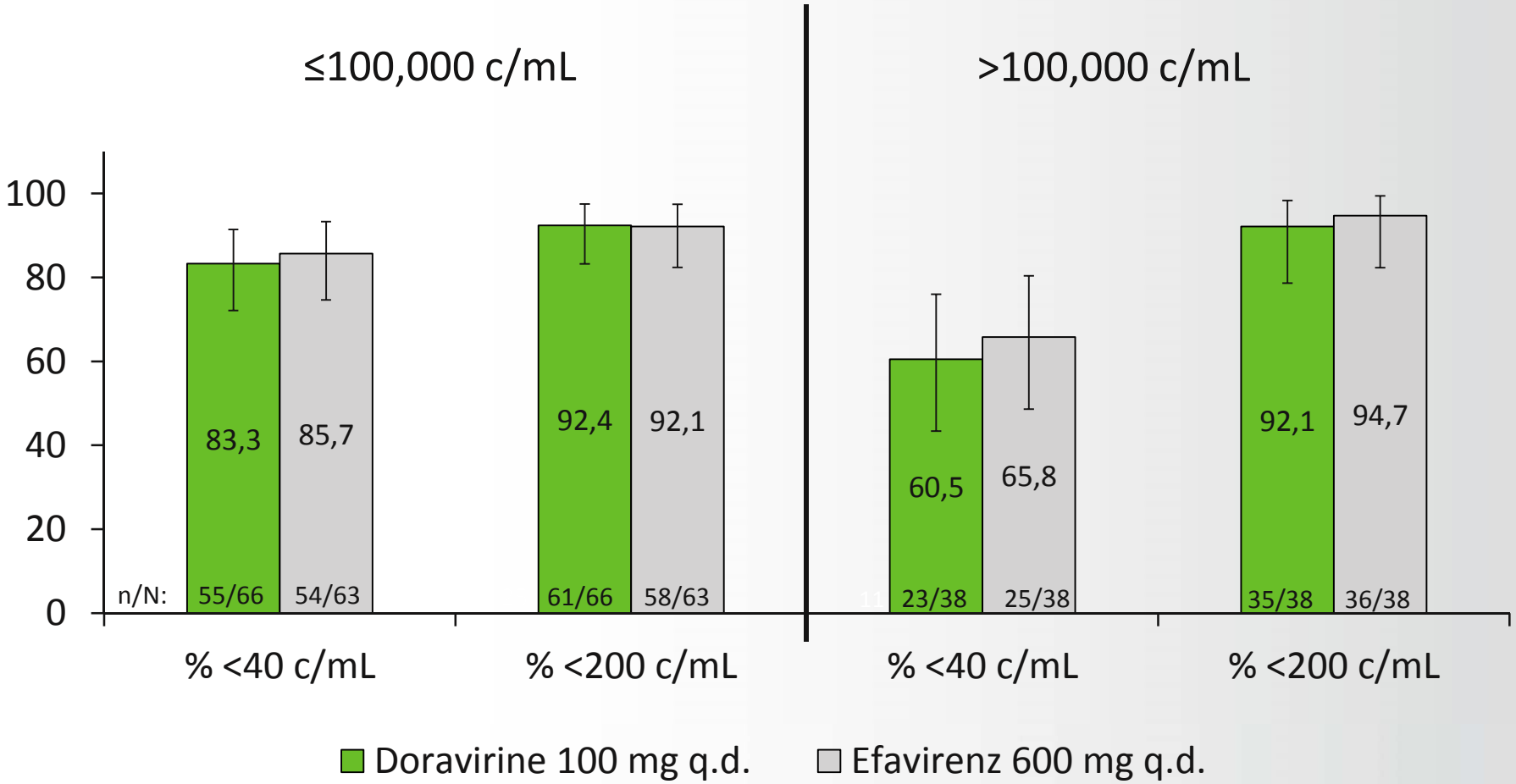
Observed Failure Approach



Virologic Response by Screening RNA

Week 24 (Observed Failure Approach*)

AIDS 2015
Vancouver, BC
Abstract TUAB0104



*Excludes: Patients who discontinued due to non-treatment related reasons but with last RNA <40 c/mL, or due to AE, or who lack data in week 24 window.

AIDS 2015
Vancouver, BC
Abstract TUAB0104

Protocol-defined Virologic Failures by Week 24

	Doravirine 100 mg (N=108)	Efavirenz 600 mg (N=108)
Virologic failure ≥40 c/mL, n (%)		
Non-response†	17 (15.7)	10 (9.3)
Rebound‡	0	1 (0.9)
Virologic failure ≥200 c/mL, n (%)		
Non-response†	4 (3.7)	0
Rebound‡	0	1 (0.9)
Resistance testing performed*	1	1
NNRTI mutations detected	0	0
NRTI mutations detected	0	0

† Non-response: patient did not achieve vRNA <40 (or <200) c/mL by Week 24.
‡ Rebound: after initial response of vRNA <40 (or <200) c/mL, patient had 2 consecutive measurements ≥40 (or ≥200) c/mL at least 1 week apart, at or after Week 24. (Rebound after Week 24 not included here.)
* vRNA > 500 copies/mL required for resistance testing.

Clinical Adverse Events

AIDS 2015
Vancouver, BC
Abstract TUAB0104

% of patients with:	Doravirine 100 mg (N=108)	Efavirenz (N=108)	Difference [DOR – EFV] (95% CI)
One or more adverse events (AE)	75.9	84.3	-8.3 (-19.1, 2.4)
Serious AE[†]	0.9	4.6	-3.7 (-9.6, 0.9)
Discontinued due to AE	0.9	5.6	-4.6 (-10.8, 0.1)
Drug-related[‡] AE	27.8	55.6	-27.8 (-39.9, -14.8)
Diarrhea	0.9	6.5	---
Nausea	7.4	5.6	---
Dizziness	6.5	25.0	---
Headache	3.7	5.6	---
Abnormal dreams	5.6	14.8	---
Insomnia	5.6	2.8	---
Nightmares	4.6	8.3	---
Sleep disorder	3.7	6.5	---

[†] One serious AE (depression) in the EFV group was considered drug-related.
[‡] Determined by investigator to be related to study therapy; specific AEs with >5% incidence are listed.

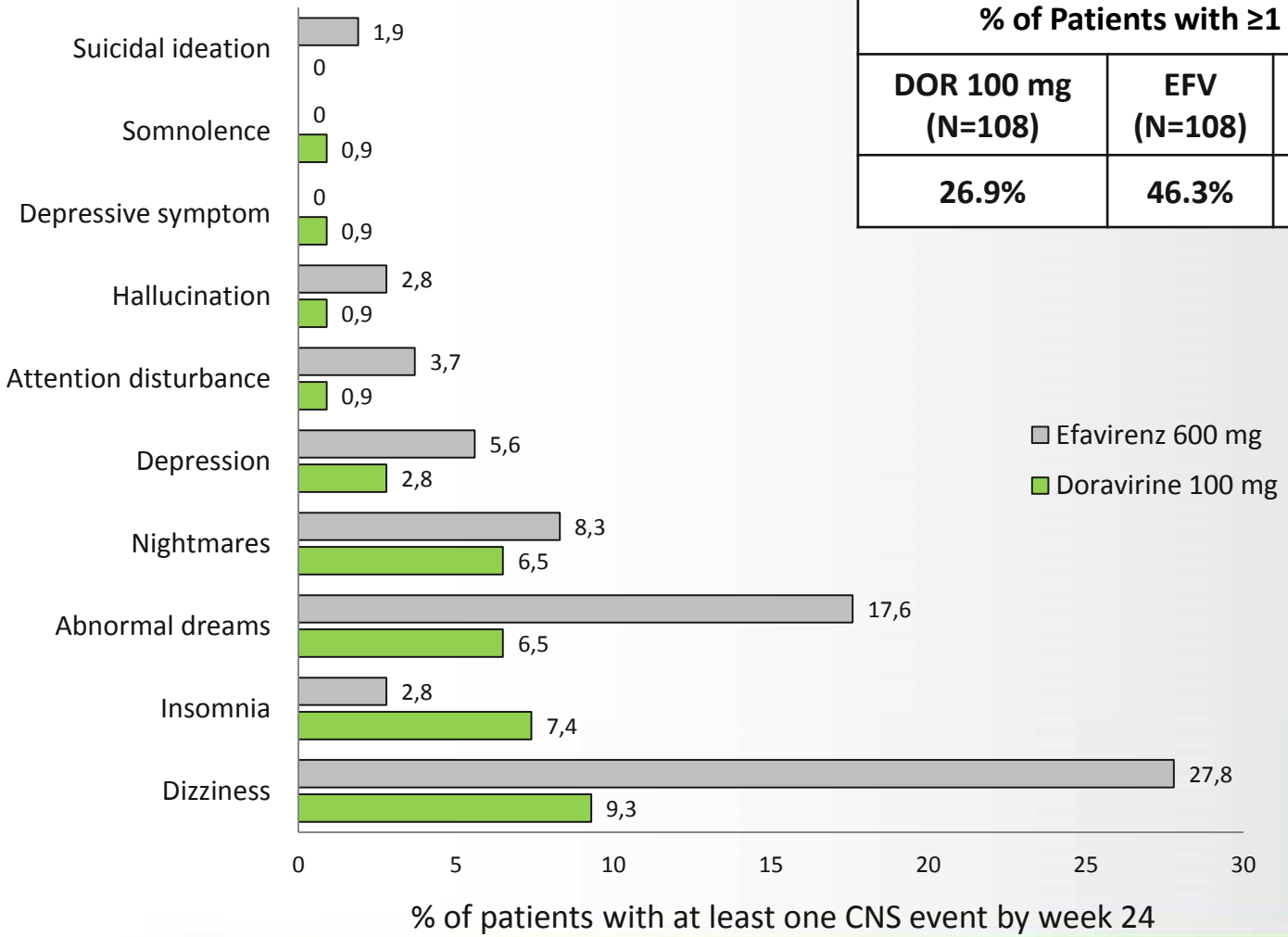
Specific AEs causing discontinuation (number of patients): DOR – hallucination (1); EFV – dysaesthesia (1), hallucinations (2), drug eruption (1), dizziness (1), disturbance in attention (1).

Primary Safety Comparison: CNS Events, All Causality

AIDS 2015
Vancouver, BC
Abstract TUAB0104

Significantly fewer patients on DOR had ≥1 CNS event by week 24 (p<0.001)

% of Patients with ≥1 CNS Event		
DOR 100 mg (N=108)	EFV (N=108)	Δ (95% CI)
26.9%	46.3%	-19.4 (-31.7, -6.6)



Common† Lab Abnormalities (%)

Laboratory Test	Doravirine 100 mg (N=108)	Efavirenz (N=108)	Difference [DOR – EFV] (95% CI)
LDL-cholesterol, fasting			
Grade 1 (130 – 159 mg/dL)	1.0	12.6	-11.6 (-19.6, -5.6)
Total cholesterol, fasting			
Grade 1 (200 – 239 mg/dL)	3.8	17.3	-13.5 (-22.4, -5.5)
Grade 2 (240 – 300 mg/dL)	0.0	3.8	-3.8 (-9.5, -0.2)
Glucose, fasting			
Grade 1 (110 – 125 mg/dL)	6.4	6.6	-0.2 (-8.1, 7.6)
Bilirubin, total			
Grade 1 (1.1 – 1.5 x ULN)	3.7	0.9	2.8 (-1.7, 8.4)
Aspartate aminotransferase			
Grade 1 (1.25 -- 2.5 x ULN)	6.5	8.3	-1.8 (-9.4, 5.7)
Alanine aminotransferase			
Grade 1 (1.25 – 2.5 x ULN)	4.7	9.3	-4.6 (-12.2, 2.5)
Alkaline phosphatase			
Grade 1 (1.25 – 2.5 x ULN)	1.9	5.6	-3.7 (-10.0, 1.7)
Lipase			
Grade 1 (1.1 – 1.5 x ULN)	11.2	9.3	2.0 (-6.5, 10.5)
Grade 2 (1.6 – 3.0 x ULN)	4.7	7.4	-2.7 (-9.9, 4.1)

† occurred in at least 4 patients in one or more treatment groups, with indicated grade (based on DAIDS toxicity criteria) and was also an increase from baseline.

All Lab Abnormalities ≥ Grade 2 (%)

Laboratory Test	Grade (criteria)	Doravirine 100 mg (N=108)	Efavirenz (N=108)
Platelet count	2 (50 – 99.9 x 10^3/µL)	0.9	0.9
LDL-cholesterol, fasting	2 (160 – 189 mg/dL)	1.0	1.9
	3 (≥190 mg/dL)	0	1.0
Total cholesterol, fasting	2 (240 – 300 mg/dL)	0	3.8
	3 (>300 mg/dL)	0	1.0
Triglycerides, fasting	2 (500 – 750 mg/dL)	0	1.9
Glucose, fasting	2 (126 – 250 mg/dL)	2.1	1.1
Aspartate aminotransferase	2 (2.6 – 5.0 x ULN)	0.9	2.8
	3 (5.1 – 10.0 x ULN)	0.9	0
	4 (>10.0 x ULN)	0	0.9
Alanine aminotransferase	2 (2.6 – 5.0 x ULN)	0	0.9
	3 (5.1 – 10.0 x ULN)	0.9	0.9
Lipase	2 (1.6–3.0 x ULN)	4.7	7.4
	3 (3.1 – 5.0 x ULN)	2.8	2.8
	4 (>5.0 x ULN)	0.9	1.9

Conclusions

In ART-naïve subjects with HIV-1 infection, doravirine 100 mg q.d. in combination with TDF/FTC:

- Demonstrates antiretroviral activity and immunological effect similar to efavirenz with TDF/FTC at week 24
- Is safe and well tolerated at week 24 compared to efavirenz with TDF/FTC
- Has significantly fewer and less severe treatment-emergent CNS adverse events by week 24 than efavirenz with TDF/FTC