Week 48 Resistance Analyses of the Once-daily, Single-tablet Regimen Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) in Adults Living with HIV-1 from the AMBER and EMERALD Phase 3 Trials

P294

Erkki Lathouwers[1], Eric Y. Wong[2], Kimberley Brown[1], Bryan Baugh[3], Anne Ghys[1], John Jezorwski[4], El Ghazi Mohsine[1], Erika Van Landuyt[1], Magda Opsomer[1], Sandra De Meyer[1]

[1]Janssen Pharmaceutica NV, Beerse, Belgium; [2]Janssen Scientific Affairs, LLC, Titusville, NJ, USA; [3]Janssen Research & Development LLC, Raritan, NJ, USA; [4]Janssen Research & Development, Pennington, NJ, USA

INTRODUCTION

- Boosted darunavir (DRV) containing regimens have demonstrated a high, durable virologic response, a high genetic barrier to resistance, and long-term safety in a broad range of patients,[1–4] and are included in international HIV-1 treatment guidelines
  - DRV is also recommended for rapid initiation and in situations when resistance test results are not available.[5–7]
- In Phase 3 randomised trials, darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg had non-inferior efficacy and favourable renal and bone safety versus the control arms:
  - D/C + F/TDF in antiretroviral treatment (ART)-naïve adults (AMBER; NCT02431247)
    - Primary outcome: 91.4% vs 88.4%, respectively, with viral load [VL] <50 copies/mL at Week 48 (FDA-snapshot)[8]
  - Boosted protease inhibitor (PI) + F/TDF in ART-experienced, virologically-suppressed adults (EMERALD; NCT02269917)
    - Primary outcome: 2.5% vs 2.1%, respectively, had protocol-defined virologic rebound (PDVR; confirmed VL ≥50 copies/mL) cumulative through Week 48
    - Secondary outcomes: Week 48 VL <50 copies/mL: 94.9% vs 93.7%; VL ≥50 copies/mL: 0.8% vs 0.5%; FDA Snapshot.[9]
- Week 48 resistance analyses of AMBER and EMERALD are reported.

METHODS

AMBER and EMERALD Studies

- AMBER (double-blind) included ART-naïve adults with a screening plasma VL ≥1000 copies/mL, $CD4^+$ cell count >50 cells/mm^3 and genotypic sensitivity to DRV, emtricitabine (FTC) and TFV.[8]
- EMERALD (open-label) included ART-experienced, virologically-suppressed adults:
  - VL <50 copies/mL for ≥2 months before screening, allowing one VL blip[9]
  - ART history:
    - Previous ART virologic failure (VF) allowed, with no history of VF on DRV-based regimens and absence of DRV RAMs[10] if historical genotypes were available
    - No restriction on FTC or TFV RAMs or any other RAMs.

Virology Assessments

- For both studies (AMBER and EMERALD):
  - Plasma HIV-1 RNA was quantified at screening, baseline, Weeks 2, 4, 8, and 12, and every 12 weeks thereafter
  - Standard resistance testing was done when HIV-1 RNA was ≥400 copies/mL (resistance assay cut-off).
- For AMBER (ART-naïve patients):
  - Genotypic resistance testing was performed using GenoSure® MG (HIV-1 protease [PR]/reverse transcriptase [RT] genotype assay; Monogram Biosciences, South San Francisco, CA, USA) at screening
  - PhenoSense® GT (combined HIV-1 PR/RT genotype/phenotype) was used for genotypic and phenotypic testing post-baseline in patients with protocol-defined virologic failure (PDVF) with VL ≥400 copies/mL at failure (confirmed or unconfirmed) or at later time points,[8] where PDVF was defined as virologic nonresponse, virologic rebound and/or VL ≥400 copies/mL at study endpoint or discontinuation
  - Deep sequencing was performed using NGS GenoSure® MG (Illumina MiSeq; codon variants >1%) on samples from one patient.
- For EMERALD (virologically-suppressed, ART-experienced patients):
  - GenoSure® MG was used for post-baseline genotypic resistance testing of patients with PDVR (confirmed VL ≥50 copies/mL) and a VL ≥400 copies/mL at failure (confirmed or unconfirmed) or at later time points, including those who discontinued with a last single VL ≥400 copies/mL
  - HIV-1 proviral DNA was analysed retrospectively using GenoSure Archive® on baseline samples (VL <50 copies/mL) for patients with PDVR or prior VF.

RESULTS

AMBER: ART-naïve Patients

Baseline Resistance

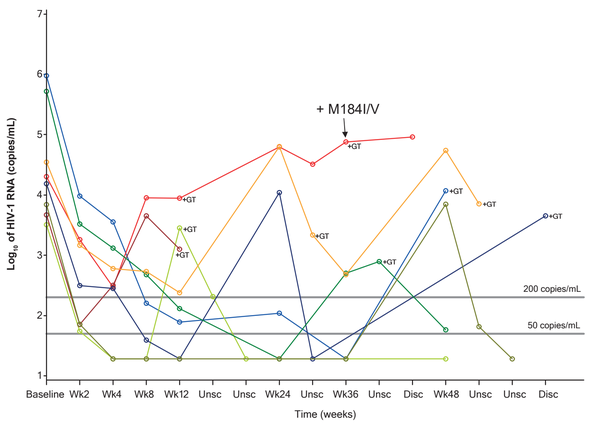
- The majority of all patients in both treatment arms were infected with HIV-1 subtype B (71%).
- As depicted by the protocol at screening, all patients in AMBER had genotypic sensitivity to DRV, FTC and TFV
  - Overall, few patients had ≥1 primary PI RAMs (2%; [15/723]) and ≥1 DRV RAMs (1% [7/723]; six V11I, one L33F)
  - 5% (34/723) had N(t)RTI RAMs; no RAMs related to FTC or TFV were detected
  - 16% (118/723) had NNRTI RAMs.
- There was no effect of HIV-1 subtype (B, non-B), presence of baseline primary PI and/or DRV RAMs, or N(t)RTI RAMs on VL <50 copies/mL at Week 48 (FDA Snapshot).

Post-baseline Resistance

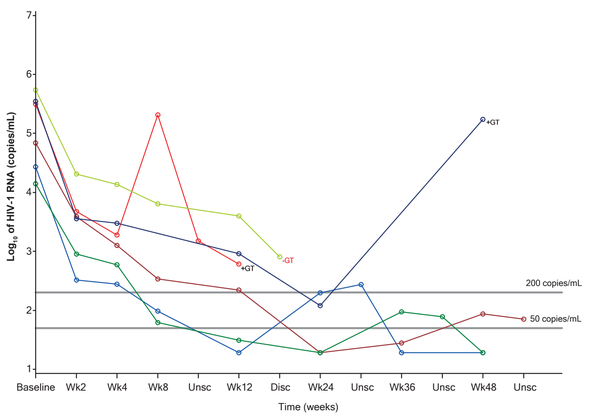
- Through 48 weeks, eight (D/C/F/TAF) and six (control) patients had PDVF (**Figure 1**); paired screening and post-baseline on-treatment genotypes were available for seven and two patients, respectively (**Table 1**).
- No DRV, primary PI, or TFV RAMs emerged in any patient (**Table 1**).
- One PDVF receiving D/C/F/TAF had the NRTI RAM M184I/V at Week 36, conferring phenotypic resistance to FTC (fold change [FC] in EC_{50}=56) and lamivudine (FC=143) (**Table 1**)
  - M184V was detected pre-treatment at screening by deep sequencing as a minority variant (9%); at Week 12 only the wild type genotype was detected, and at Week 36, M184I (32%) and M184V (67%)
  - This patient had transmitted NNRTI resistance (efavirenz [FC=7]/nevirapine [FC=39]) as K103N at screening, and discontinued after Week 48 (due to treatment noncompliance, also evident from low observed DRV plasma concentrations).
- All other patients had HIV-1 virus that remained susceptible to all drugs in the treatment regimens.

Figure 1. AMBER: Individual Viral Load Profiles for Patients with PDVF; Intent-to-treat Population.

A) D/C/F/TAF (8/362 patients, 2% with PDVF)



B) D/C + F/TDF (6/363 patients, 2% with PDVF)



+GT marks time point of genotype/phenotype; a red -GT indicates no genotype could be generated.
One patient receiving D/C/F/TAF had the NRTI RAM M184I/V at Week 36
Disc = discontinuation; PDVF = protocol-defined virologic failure; Unsc = unscheduled

Table 1. AMBER and EMERALD: Post-baseline Resistance Through Week 48.

						Patients with ≥1 RAM[11] post-baseline, n (%)	
Study	ART	Patients, N	Patients with PDVF, n (%)	PDVF patients with post-baseline genotype data, n (%)	Reverse transcriptase FTC or TFV	Protease Primary PI or DRV
AMBER	D/C/F/TAF	362	8 (2)	7 (2)	M184I/V; n=1	0
	D/C + F/TDF	363	6 (2)	2 (1)	0	0
EMERALD	D/C/F/TAF	763	19 (2)	1[‡] (<1)	0	0
	bPI* + F/TDF	378	8 (2)	3[§] (1)	0	0
Total	D/C/F/TAF	1125	27 (2)	8 (1)	1 (<1)	0

*At screening, 266 patients were on boosted DRV (n=202 DRV/ritonavir; n=64 DRV/cobicistat), 82 on boosted atazanavir (ATV; n=81 ATV/ritonavir; n=1 ATV/cobicistat), and 30 on lopinavir (LPV)/ritonavir; ‡One rebounder in the D/C/F/TAF arm had an N(t)RTI RAM, D67D/N; §One rebounder in the control arm had an NNRTI RAM, E138E/G, conferring resistance to rilpivirine; These mutations were not related to any of the study drugs and were probably related to previous ART use
PDVF = protocol-defined virologic failure

EMERALD: Virologically-suppressed ART-experienced Patients

Antiretroviral Experience

- For the 1141 patients, previous ART (including screening ART and PI booster counted as a separate antiretroviral [ARV]) included: ≥5 ARVs (58%), ≥8 ARVs (27%); ≥2 PIs (41%), ≥3 N(t)RTIs (42%), ≥1 NNRTI (30%) and ≥1 integrase inhibitor (INI) (6%).
- Overall, 15% (n=169) of patients had a previous ARV VF; 7% on a PI, 11% on an N(t)RTI, 6% on an NNRTI and 1% on an INI.

Archived Baseline Resistance

- HIV-1 proviral DNA from baseline samples was analysed for patients with prior VF (n=169) or with PDVR (n=27).
- Overall, of the 140 patients with previous VF and geno-archive data, 6 (4%: 4 D/C/F/TAF and 2 bPI + F/TDF) had DRV RAMs, 5 (4%) had TFV RAMs, and 53 (38%) had FTC RAMs, mainly at reverse transcriptase position M184 (35%) (**Table 2**)
  - Genotypic susceptibility data showed 61% were susceptible to all NNRTIs, 51% to all N(t)RTIs, 83% to all PIs (100% to DRV) and 89% to all INIs
    - Two patients showed possible resistance to dolutegravir and full resistance to raltegravir and elvitegravir (INI RAMs: G140S, Q148H and G140A, Q148R) on the genotype report (**Table 2**). Both patients had previously virologically failed on raltegravir
  - All of these patients with archived DRV, FTC and TFV RAMs achieved VL <50 copies/mL at Week 48 or at last on-treatment VL.
- In addition 24 (17 D/C/F/TAF and 7 control) patients with PDVR had baseline geno-archive data. None had archived RAMs to DRV, FTC and TFV.

Table 2. Prevalence of Baseline RAMs[12] in HIV-1 Proviral DNA from Patients with Previous VF in EMERALD.

	D/C/F/TAF N=763	bPI* + F/TDF N=378	Total N=1141
Patients with previous VF, N	116	53	169
Patient with previous VF and geno-archive[‡] data at baseline, N[§]	98	42	140
Genotypic susceptibility, n (%):			
All NNRTIs	56 (57)	29 (69)	85 (61)
All N(t)RTIs	53 (54)	19 (45)	72 (51)
FTC	62 (63)	21 (50)	83 (59)
TFV	76 (78)	30 (71)	106 (76)
All PIs	80 (82)	36 (86)	116 (83)
Boosted ATV	91 (93)	40 (95)	131 (94)
Boosted DRV	98 (100)	42 (100)	140 (100)
Boosted LPV	94 (96)	40 (95)	134 (96)
All INIs	86 (88)	39 (93)	125 (89)
Dolutegravir	97 (99)	41 (98)	138 (99)
Elvitegravir	89 (91)	40 (95)	129 (92)
Raltegravir	86 (88)	39 (93)	125 (89)
≥1 DRV RAMs, n (%)	4[¶] (3)	2 (5)	6 (4)
I84I/V	4 (4)	0	4 (3)
L33L/F	0	1 (2)	1 (1)
L76L/V	1 (1)	0	1 (1)
T74T/P	0	1 (2)	1 (1)
≥1 primary PI RAMs, n (%)	20 (20)	7 (17)	27 (19)
≥1 N(t)RTI RAMs, n (%)	46 (47)	23 (55)	69 (49)
≥1 TFV RAMs, n (%)	4 (4)	1 (2)	5 (4)
K65K/R	4 (4)	0	4 (3)
K70K/D/E/N	0	1 (2)	1 (1)
≥1 FTC RAMs, n (%)	35 (36)	18 (43)	53 (38)
K65K/R	4 (4)	0	4 (3)
M184M/I/V	31 (32)	18 (43)	49 (35)
≥1 NNRTI RAMs, n (%)	44 (45)	14 (33)	58 (41)
≥1 Primary INI RAMs, n (%)	5 (5)	1 (2)	6 (4)

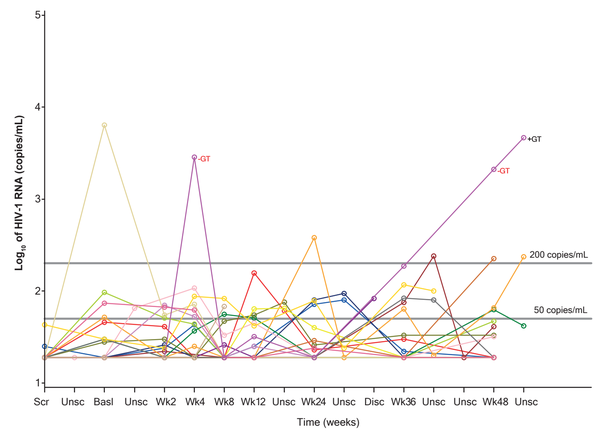
Observed mutations were concatenated
*266 patients were on boosted DRV (n=202 DRV/ritonavir; n=64 DRV/cobicistat) at screening and 112 on boosted ATV or boosted LPV; †GenoSure Archive®; §Denominator for the prevalence of baseline RAMs; ¶In one patient 2 DRV RAMs were observed (I84I/V and L76L/V)

Post-baseline Resistance

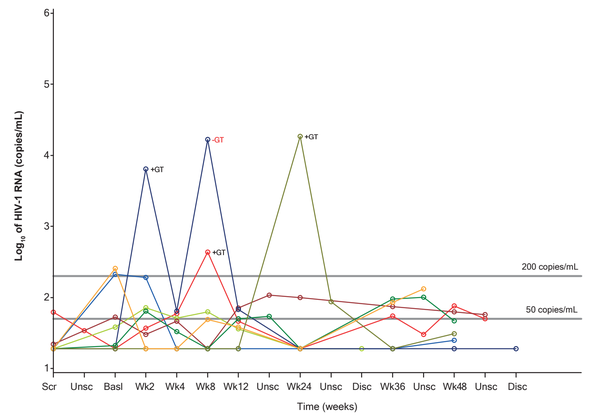
- There were few PDVRs throughout 48 weeks (19/783 D/C/F/TAF arm and 8/378 control arm) (**Figure 2**), most of whom had low VL values (only 3 and 0 with VL ≥200 copies/mL, respectively), so only one (D/C/F/TAF arm) and three (control arm) rebounders had post-baseline genotypes.
- No DRV, primary PI, TFV or FTC RAMs were observed (**Table 1**), and all patients had HIV-1 virus susceptible to all drugs in the regimens.

Figure 2. EMERALD: Individual Viral Load Profiles for Patients with PDVR (≥50 copies/mL); Intent-to-treat Population.

A) D/C/F/TAF (19/763 patients, 2% with PDVR)



B) bPI + F/TDF (8/378 patients, 2% with PDVR)



+GT marks time point of genotype/phenotype; a red -GT indicates no genotype could be generated
Basl = baseline; Disc = discontinuation; PDVR = protocol-defined virologic rebound;
Scr = screening; Unsc = unscheduled

CONCLUSIONS

- Through Week 48 in AMBER and EMERALD (1125 patients receiving D/C/F/TAF and 629 patients receiving boosted DRV in combination with F/TDF), no treatment-emergent DRV, primary PI or TFV RAMs were observed
  - In only one patient, an FTC RAM (M184I/V) was identified post-VF (AMBER; D/C/F/TAF arm).
- Archived RAMs to DRV, FTC and TFV and a relatively high frequency of baseline ARV resistance were observed in patients with prior VF in EMERALD, but this did not preclude virologic response to D/C/F/TAF.
- D/C/F/TAF provides a convenient treatment option by combining the efficacy and high genetic barrier to resistance of DRV with the safety advantages of TAF, all in a single-tablet regimen for ART-naïve and -experienced adults living with HIV-1.

REFERENCES

1. Orkin C, et al. HIV Med 2013;14:49–59.
2. Cahn P, et al. AIDS 2011;25:929–39.
3. Flynn P, et al. PIDJ 2014;33:940–5.
4. Lathouwers E, et al. HIV Clin Trials 2017;18:196–204.
5. DHHS guidelines. Updated May 30, 2018.
6. EACS Guidelines, Version 9.0. October 2017.
7. Saag MS, et al. JAMA 2018;320:379–96.
8. Eron JJ, et al. AIDS 2018;32:1431–42.
9. Orkin C, et al. Lancet HIV 2018;5:e23–e34.
10. Wensing AM, et al. Top Antivir Med 2014;22:642–50.
11. Wensing AM, et al. Top Antivir Med 2015;23:132–41.
12. Wensing AM, et al. Top Antivir Med 2017;24:132–3.

ACKNOWLEDGEMENTS AND DISCLOSURES

We thank the participants of this study, the Janssen study teams and the site staff.

The authors would also like to thank other Janssen staff members for their important contributions to the data collection and/or poster presentation.

All authors are full-time employees of Janssen and potential stockholders of Johnson and Johnson.

This study was sponsored by Janssen. Medical writing support was provided by Ian Woolveridge and Jackie Phillipson from Zoetic Science, Macclesfield, UK, an Ashfield Company. Support for medical writing assistance was provided by Janssen.

Presented at the HIV Glasgow Drug Therapy Meeting; Glasgow, UK, 28–31 October 2018

janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

V2