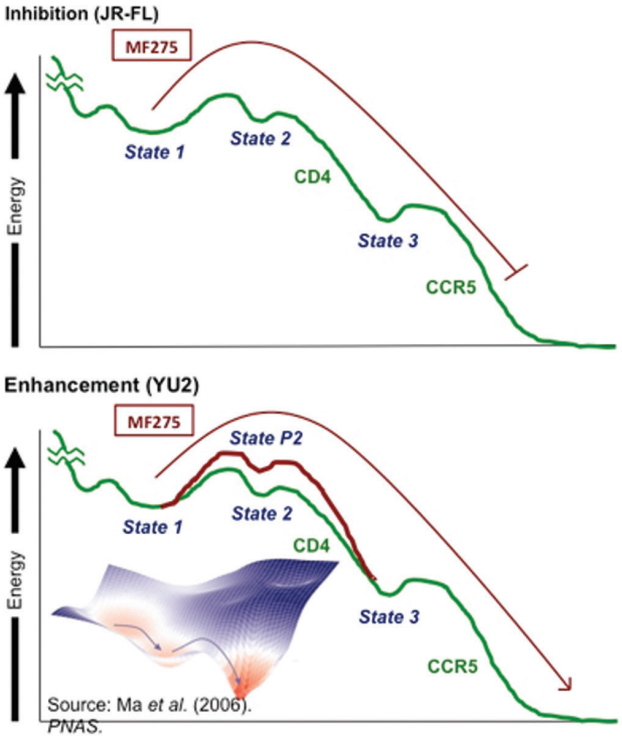

Figure 2. Proposed mechanisms for MF275 inhibition and activation. In Envs with baseline conformations more prone to inhibition (e.g. JR-FL), MF275 triggers transition from State 1 to States 2 and 3. Upon CCR5 binding, however, MF275 acts as a steric blockade to 6HB formation, removable with washout. In Envs more prone to activation (e.g. YU2), MF275 triggers transition from State 1 to States P2 and 3, which are parallel to but conformationally distinct from those induced by CD4 or CD4-mimetics. These activated intermediates are metastable, even with washout of MF275, and can mediate CD4-independent infection in the presence of CCR5.

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541. Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1 Treatment Naïve Patients: Week 48 Results in Subgroups Based on Baseline Viral Load, CD4$^+$ Count, and WHO Clinical Staging

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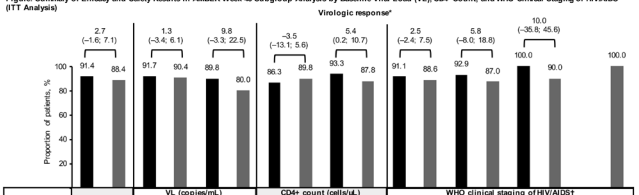
Background. Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg is a once-daily, single-tablet regimen approved in Europe and under regulatory review in the United States for the treatment of HIV-1 infection. In the pivotal AMBER trial in antiretroviral treatment (ART)-naïve, HIV-1–infected adults, D/C/F/TAF achieved a high virologic response rate at Week 48 that was non-inferior to control (D/C+F/tenofovir disoproxil fumarate); favorable renal/bone outcomes were seen with D/C/F/TAF vs. control. These results were consistent across age, gender, and race subgroups. Here we report Week 48 results in subgroups based on viral load (VL), CD4$^+$ count, and WHO clinical staging of HIV/AIDS at baseline.

Methods. The phase 3, randomized (1:1), blinded, noninferiority AMBER trial enrolled ART-naïve, HIV-1–infected adults. The primary endpoint was the proportion of patients with virologic response (VL <50 copies/mL; FDA snapshot) at Week 48. Adverse events (AEs) and laboratory parameters were monitored throughout the study. Results were evaluated in subgroups based on VL (≤ vs. >100,000 copies/mL), CD4$^+$ count (< vs. ≥350 cells/μL), and WHO clinical stage (1 vs. 2 vs. 3 vs. 4) at baseline.

Results. Of the 725 patients randomized and treated, the majority had VL ≤100,000 copies/mL (82% of patients), CD4$^+$ count ≥350 cells/μL (72%), and WHO clinical stage 1 (84%) at baseline. Overall virologic response rates were 91.4% with D/C/F/TAF and 88.4% with control; results were similar across baseline VL, CD4$^+$ count, and WHO clinical stage subgroups (figure). Overall rates of serious AEs, grade 3–4 AEs, and AE-related discontinuations were similar for D/C/F/TAF (n = 17 [4.7%], n = 19 [5.2%], and n = 7 [1.9%], respectively) and control (n = 21 [5.8%], n = 22 [6.1%], and n = 16 [4.4%]), as well as across subgroups (table).

Conclusion. D/C/F/TAF achieved high (91.4%), noninferior virologic response rates vs. control (88.4%) in ART-naïve, HIV-1–infected adults. Consistent and robust efficacy and safety results were found with D/C/F/TAF vs. control based on VL, CD4$^+$ count, and WHO clinical stage at baseline.

Figure. Summary of Efficacy and Safety Results in AMBER Week 48 Subgroup Analysis by Baseline Viral Load (VL), CD4$^+$ Count, and WHO Clinical Staging of HIV/AIDS (ITT Analysis)



Safety parameter, %	Overall		VL (copies/mL) ≤100,000		VL (copies/mL) >100,000		CD4+ count (cells/μL) <350		CD4+ count (cells/μL) ≥350		WHO clinical staging of HIV/AIDS† Stage 1		Stage 2		Stage 3		Stage 4	
	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control
N	362	363	303	293	59	70	95	108	267	255	314	298	42	54	6	10	0	1
Serious AE	4.7	5.8	5.3	6.1	1.7	4.3	2.1	5.6	5.6	5.9	3.8	5.7	9.5	5.6	16.7	10.0	–	0
Grade 3-4 AE‡	5.2	6.1	5.6	6.5	3.4	4.3	6.3	4.6	4.9	6.7	4.5	6.0	9.5	5.6	16.7	10.0	–	0
Discont due to AE	1.9	4.4	2.3	4.4	0	4.3	0	1.9	2.6	5.5	1.9	4.0	2.4	5.6	0	10.0	–	0

VL, viral load; WHO, World Health Organization; ITT, intention-to-treat; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; AE, adverse event; discont, discontinuation; c, copies; CI, confidence interval. *Virologic response was VL <50 c/mL (FDA snapshot). Difference (95% CI) between treatment arms is shown with brackets. Overall population: stratum-adjusted Mantel-Haenszel test where stratification factors are HIV-1 RNA level (≤100,000 or >100,000 c/mL) and CD4+ cell count (<200 or ≥200 cells/μL). †Stage 1 = asymptomatic, stage 2 = mild symptoms, stage 3 = advanced symptoms, stage 4 = severe symptoms. ‡With ≥1 worst grade 3-4 AE.

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This abstract has been withdrawn at the author's request.

543. An Integrated Safety Analysis Comparing Once-Daily Doravirine (DOR) to Darunavir+Ritonavir (DRV+r) and Efavirenz (EFV) in HIV-1-Infected, Antiretroviral Therapy (ART)-Naïve Adults

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Background. DOR is a novel NNRTI that has shown noninferior efficacy to DRV+r- and EFV-based regimens in phase 3 trials (DRIVE-FORWARD [NCT02275780] and DRIVE-AHEAD [NCT02403674]). A prespecified integrated analysis of those trials plus a completed phase 2 trial (P007; NCT01632345) was performed to evaluate the overall safety and tolerability of DOR.

Methods. In this integrated analysis, DOR (100 mg QD) arms from P007, DRIVE-FORWARD, and DRIVE-AHEAD were compared with DRV+r in DRIVE-FORWARD and EFV in P007 and DRIVE-AHEAD for treatment of HIV-1 in ART-naïve adults. The NRTI background included FTC/TDF in P007, ABC/3TC or FTC/TDF in DRIVE-FORWARD, and 3TC/TDF for DOR and FTC/TDF for EFV in DRIVE-AHEAD. The primary safety endpoint was the proportion of participants discontinuing due to adverse events (AEs) through Week 48.

Results. A total of 1,710 treated participants were included in the analysis (table). Similar proportions of DOR– and DRV+r-treated participants, and fewer of those treated with DOR than with EFV discontinued due to AEs (2.5% vs. 3.1%, DOR vs. DRV+r; 2.5% vs. 6.6%, DOR vs. EFV). Drug-related AEs (DRAEs) were similar for DOR (30.9%) and DRV+r (32.1%), and higher for EFV (61.4%). The most common DRAEs (≥10% any group, any grade) were dizziness (4.9%, 1.8%, and 30.7%) diarrhea (4.0%, 12.8%, and 5.7%), and abnormal dreams (3.2%, 0.3%, and 10.6%) for DOR, DRV+r, and EFV, respectively. Higher rates of central nervous system (CNS) AEs were reported for DOR when EFV was the comparator, while similar low rates of CNS AEs were reported for DOR when DRV+r was the comparator. In two prespecified analyses combining the DOR 100-mg arms and EFV arms from P007 and DRIVE-AHEAD, 2.8% vs. 6.1% discontinued due to AEs on the DOR- and EFV-treated arms, respectively, for a treatment difference of −3.4% (95% CI: −6.2, −0.8; $P = 0.012$); 25.0% vs. 55.9% of participants experienced ≥1 neuropsychiatric AE in DOR and EFV arms, respectively.

Conclusion. At Week 48, DOR was generally safe and well tolerated in ART-naïve adults with HIV-1. Statistically significantly lower proportions of DOR- than EFV-treated participants discontinued due to AEs supported by a lower proportion that discontinued due to DRAEs. Those on DOR had fewer CNS AEs compared with those on EFV, and less diarrhea than those on DRV+r.

Table. AE Summary, Weeks 0-48[a]

	DOR (n=855) n (%)	DRV+r (n=383) n (%)	EFV (n=472) n (%)
With ≥1 AE	701 (82.0)	300 (78.3)	427 (90.5)
With DRAE[b]	264 (30.9)	123 (32.1)	290 (61.4)
With SAE	39 (4.6)	23 (6.0)	30 (6.4)
With serious DRAE[c]	2 (0.2)	1 (0.3)	6 (1.3)
Deaths	1 (0.1)	0 (0.0)	2 (0.4)
Discontinued[d] due to an AE	21 (2.5)	12 (3.1)	31 (6.6)
Discontinued due to a DRAE	14 (1.6)	8 (2.1)	27 (5.7)
Discontinued due to a SAE	5 (0.6)	2 (0.5)	4 (0.8)
Discontinued due to a serious DRAE	1 (0.1)	1 (0.3)	3 (0.6)

[a]Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication. [b]Determined by the investigator to be related to the drug. [c]DOR: nausea/vomiting (n=1), asthenia/insomnia/nightmare (n=1); DRV+r: peripheral edema (n=1); EFV: dizziness, suicidal ideation, hypertriglyceridemia, rash generalized, rash macular, rash maculo-papular (n=1 each). [d]Study medication withdrawn.

SAE, serious AE.

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544. Pharmacokinetic Profile of Ibalizumab From a Phase 3 Trial

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Background. Ibalizumab (IBA) is a long-acting humanized monoclonal antibody that binds domain 2 of the CD4 receptor and blocks HIV-1 infection of host cells. TMB-301 was a 24-week, Phase 3 clinical trial conducted in 40 heavily treatment-experienced patients with multidrug-resistant (MDR) HIV-1 investigating the safety, efficacy and tolerability of IBA. Patients received a 2,000 mg IBA loading dose followed by 800 mg every 2 weeks by intravenous infusion plus an optimized background regimen. Viral load <50 and <200 HIV RNA copies/mL was achieved in 43% and 50% of patients, respectively, at Week 25. We determined the pharmacokinetic profile of IBA, i.e., serum concentrations, CD4 receptor occupancy (RO), and CD4 receptor density (RD), in these patients with MDR HIV-1.

Methods. Pre- and post-dose blood samples collected at various time points during trial were used to determine IBA serum concentrations, CD4 RO and RD at trough. IBA serum concentrations were measured using a validated ELISA. IBA bound to CD4+ T cells (RO) and cell surface CD4 levels (RD) were measured simultaneously by flow cytometry using the Molecules of Equivalent Soluble Fluorescence approach.

Results. The maximum IBA serum concentrations were observed immediately after the end of the 2,000 mg infusion with mean (SD) of 567 (235) μg/mL. Steady state was reached at Week 4 after the loading dose. The mean IBA concentrations were >30 μg/mL throughout the dosing period. Both C_{peak} and C_{trough} (Day 7 and Week 25 IBA concentrations) were decreased with increased body weight. The median C_{trough} in the high body weight group (≥85 kg) was 0.23 μg/mL. The mean RO was >85% throughout the dosing period. The 2,000 mg loading dose helped to reach >85% RO after the initial dose and maintain high levels of RO throughout the dosing period. Elevation in RO was generally associated with increased IBA serum concentrations; concentrations ≥0.13 μg/mL supported ≥85% CD4 RO. After IBA administration, down-modulation of surface CD4 receptors by up to 20% was observed. There was no apparent association between IBA serum concentration and RD probably due to high inter-individual variation.

Conclusion. Dosing regimen of 2,000 mg loading dose followed by 800 mg every 2 weeks was sufficient to support high levels of RO and to maintain the drug concentration above the therapeutic level.

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