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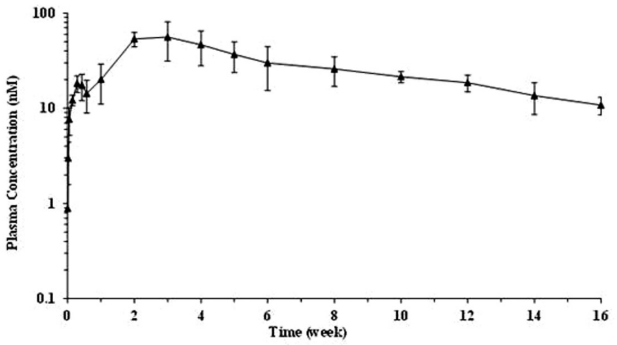
Background. GS-CA2, an analog of GS-CA1, is a novel and selective inhibitor of HIV-1 capsid function. Safety and pharmacokinetics (PK) of GS-CA2 is currently being evaluated in healthy human subjects. Herein, we present the anti-HIV activity and nonclinical PK of GS-CA2, demonstrating its potential as a first-in-class long-acting antiretroviral agent.

Methods. GS-CA2 antiviral activity was evaluated in MT-4 cells and in human peripheral blood mononuclear cells (PBMCs) acutely infected with HIV-1 (IIIb) and clinical HIV-1 isolates, respectively. Standard in vitro methods were used to characterize compound lipophilicity (LogD), solubility and relative binding to cell culture and plasma proteins. Metabolic stability was assessed in cryopreserved hepatocytes. GS-CA2 PK parameters following intravenous and subcutaneous (SC) administration were assessed in rat and dog. GS-CA2 plasma concentrations were determined by HPLC-MS/MS.

Results. GS-CA2 showed potent and selective anti-HIV activity in MT-4 cells (EC_{50} = 0.1 nM; CC_{50} = 26.6 μM). In PBMCs, GS-CA2 displayed a mean EC_{50} of 0.05 nM (0.02–0.16 nM) against 23 HIV-1 clinical isolates representing all major subtypes. GS-CA2 is highly lipophilic (LogD of 3.7) with low aqueous solubility (<0.01 mg/mL) and low predicted clearance (CL) in human hepatocytes (0.01 L/h/kg). In rat and dog, GS-CA2 demonstrated low CL (<4% of liver blood flow). GS-CA2 PK in rat and dog exhibited sustained and slow drug release following a single SC administration. Factors including species, formulation, concentration, dose, volume, and number of injections were examined for the effect on systemic exposure over time. GS-CA2 plasma concentrations in dogs (Figure 1) were maintained above the human plasma protein binding-adjusted EC_{95} (4 nM) for the entire study duration (16 weeks).

Conclusion. GS-CA2 is a selective and first-in-class HIV capsid inhibitor with picomolar potency and potential to be clinically effective against a broad range of HIV-1 strains. In animals following a single SC injection, GS-CA2 maintained therapeutically relevant concentrations for >3 months. These nonclinical data support clinical development of GS-CA2 as a novel long-acting antiretroviral agent suitable for the treatment of HIV-1 infection.

Figure 1. Plasma Concentration-Time Profile of GS-CA2 Following a Single Subcutaneous Administration to Dogs at 6 mg/kg



Disclosures. **J. Zheng**, Gilead Sciences, Inc.: Employee, Salary. **S. R. Yant**, Gilead Sciences, Inc.: Employee, Salary. **S. Ahmadyar**, Gilead Sciences, Inc.: Employee, Salary. **T. Y. Chan**, Gilead Sciences, Inc.: Employee, Salary. **A. Chiu**, Gilead Sciences, Inc.: Employee, Salary. **T. Cihlar**, Gilead Sciences, Inc.: Employee, Salary. **J. O. Link**, Gilead Sciences, Inc.: Employee, Salary. **B. Lu**, Gilead Sciences, Inc.: Employee, Salary. **J. Mwangi**, Gilead Sciences, Inc.: Employee, Salary. **W. Rowe**, Gilead Sciences, Inc.: Employee, Salary. **S. D. Schroeder**, Gilead Sciences, Inc.: Employee, Salary. **G. J. Stepan**, Gilead Sciences, Inc.: Employee, Salary. **K. W. Wang**, Gilead Sciences, Inc.: Employee, Salary. **R. Subramanian**, Gilead Sciences, Inc.: Employee, Salary. **W. C. Tse**, Gilead Sciences, Inc.: Employee, Salary.

540. Investigating the Mechanism of a Unique Human Immunodeficiency Virus-1 (HIV-1) Entry Inhibitor, MF275

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Background. HIV-1 entry into cells is mediated by sequential binding of target cell CD4 and CCR5 or CXCR4 to the metastable envelope (Env) trimer of gp120-gp41 heterodimers (Figure 1). We determined that MF275, a single diastereomer of the small molecule entry inhibitor PF-68742, is necessary and sufficient to inhibit entry of a subset of HIV-1 strains. We investigated the mechanism of MF275.

Methods. Recombinant luciferase-expressing HIV-1 pseudotyped by wild-type or mutant HIV-1 Envs was incubated with MF275, other entry inhibitors, and/or antibodies. The virus-inhibitor mixture was added to CD4+ CCR5+ or CD4− CCR5+ target cells and luciferase activity measured.

Results. Unlike other entry inhibitors, MF275 not only reversibly inhibited the infection of CD4+ CCR5+ cells by some HIV-1 strains, but also irreversibly enhanced the infection of CD4− CCR5+ cells by others. In both cases, the strain susceptibility profiles were unique from those of CD4-mimetics, BMS-378806, and maraviroc. Furthermore, MF275 activity was not affected by mutations conferring resistance to other entry inhibitors and vice versa. In line with its activating activity, MF275 sensitized susceptible Envs to neutralization by a variety of broadly neutralizing antibodies against different epitopes. Changes in the gp120 C5 and gp41 FP regions conferred resistance to MF275 inhibition but not activation. Furthermore, sensitivity to other entry inhibitors in the presence of MF275 indicated that inhibition and activation target different conformational intermediates along the entry pathway, with the former targeting the prehairpin intermediate.

Conclusion. MF275 is unique among HIV-1 entry inhibitors. Depending on the conformation of the target Env, which appears related to the gp120-gp41 interface, MF275 mediates inhibition or activation via distinct mechanisms (Figure 2). Further characterization of the MF275 mechanisms and binding site/s will advance understanding of the HIV-1 entry pathway as well as assist optimization of its clinical utility as an antiretroviral in multi-class drug resistance and potentially as an adjunct to vaccines.

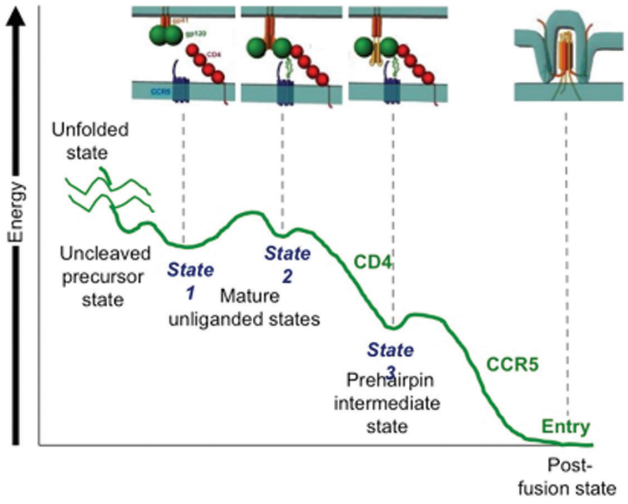

Figure 1. The HIV-1 entry pathway. In its mature unliganded form, Env is in equilibrium between two conformational intermediates: State 1 and a higher energy State 2 more prone to CD4 receptor binding. CD4 receptor binding to gp120 triggers transition to State 3 or the prehairpin intermediate state, characterized by exposure of the gp41 complementary HR1 and HR2 domains. CCR5 or CXCR4 coreceptor binding to gp120 triggers association of the HR1 and HR2 domains to form the 6-helix bundle (6HB), mediating fusion of the target cell and viral membranes.

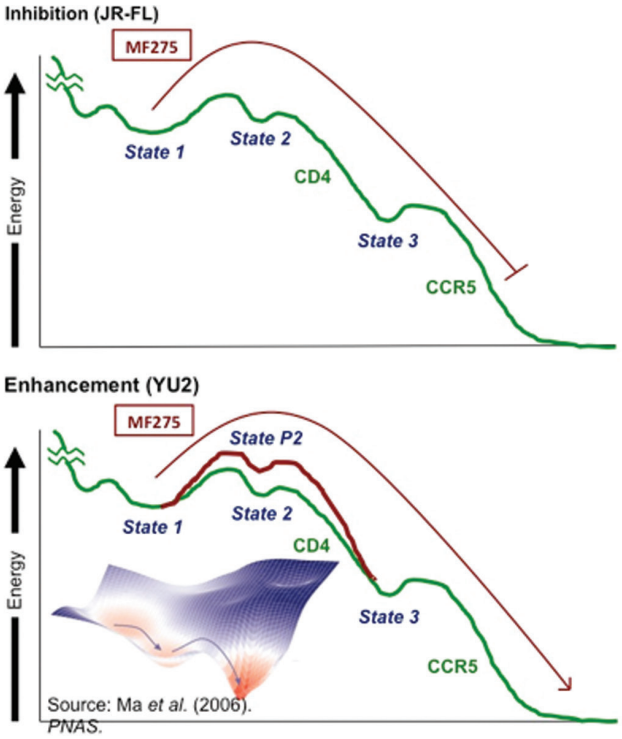

Figure 2. Proposed mechanisms for MF275 inhibition and activation. In Envs with baseline conformations more prone to inhibition (e.g. JR-FL), MF275 triggers transition from State 1 to States 2 and 3. Upon CCR5 binding, however, MF275 acts as a steric blockade to 6HB formation, removable with washout. 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.

Disclosures. **All authors:** No reported disclosures.

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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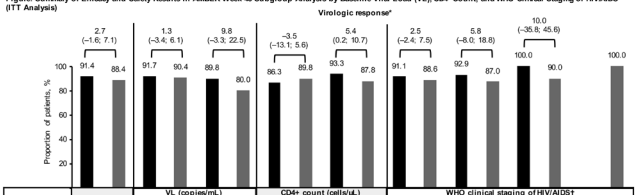
Background. Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg is a once-daily, single-tablet regimen approved in Europe and under regulatory review in the United States for the treatment of HIV-1 infection. In the pivotal AMBER trial in antiretroviral treatment (ART)-naïve, 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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