Weight Changes by Gastrointestinal Adverse Events Among Treatment-naïve (AMBER) and Virologically Suppressed (EMERALD) Patients Receiving Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Over 96 Weeks

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INTRODUCTION

- Guidelines from the US Department of Health and Human Services recognize that greater weight gain has been observed among patients initiating antiretroviral therapy (ART) with an integrase inhibitor (INI)–based regimen than with a boosted protease inhibitor (bPI)–based regimen[1]
- The mechanisms by which INI-based regimens may contribute to greater weight gain are unknown; however, one hypothesis is improved gastrointestinal (GI) tolerability compared to other classes of ART medication[2]
- Historically, bPI-based regimens have been associated with poor GI tolerability, in part due to ritonavir[1,3,4]; however, more recent bPI-based regimens, such as darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF), include a different pharmacokinetic boosting agent that has a favorable GI tolerability profile[5,6]
- When evaluated over 96 weeks in two phase 3 studies, AMBER (treatment-naïve patients) and EMERALD (treatment-experienced, virologically suppressed patients), D/C/F/TAF demonstrated GI tolerability that was generally consistent with that of commonly used INI-based regimens[7-16]
- This post hoc analysis explored GI tolerability with D/C/F/TAF and potential associations with changes in weight

OBJECTIVE

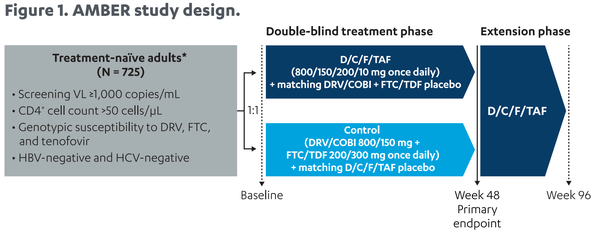
- To evaluate changes in weight over 96 weeks among patients in AMBER and EMERALD receiving D/C/F/TAF with versus without *any* or *related* GI adverse events (AEs)

METHODS

Study Designs

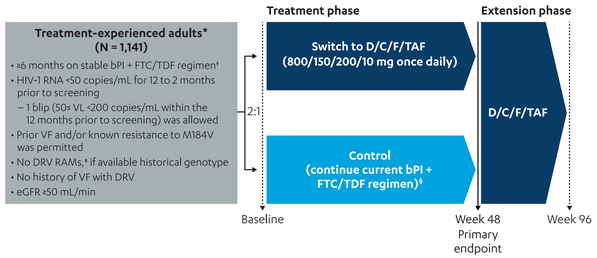
- The AMBER (ClinicalTrials.gov Identifier: NCT02431247) and EMERALD (NCT02269917) study designs[7-10] are summarized in **Figures 1** and **2**

Figure 1. AMBER study design.



VL, viral load; DRV, darunavir; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; COBI, cobicistat; TDF, tenofovir disoproxil fumarate.
*Patients were stratified by VL (≤ or >100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/µL) at screening prior to randomization.

Figure 2. EMERALD study design.



HIV-1, human immunodeficiency virus–1; VF, virologic failure; RAM, resistance-associated mutation; eGFR, estimated glomerular filtration rate; IAS-USA, International Antiviral Society–USA; ATV, atazanavir; rtv, ritonavir; LPV, lopinavir.
*Patients were stratified by bPI at screening prior to randomization. Prior experience with multiple antiretroviral drugs was allowed, and there was no restriction on the number of non-DRV prior VFs.
†Prior use of boosted DRV was allowed.
‡IAS-USA DRV RAMs.
§bPI was ATV with rtv or COBI, DRV with rtv or COBI, or LPV with rtv.

Analyses

- In this post hoc analysis, change in weight from baseline was assessed at Week 96
- GI AEs were defined as any term within the *Medical Dictionary for Regulatory Activities* (MedDRA) v21 system organ class of GI disorders
- Related GI AEs were those assessed by the investigator to be very likely, probably, or possibly related to the study drug
- Descriptive statistics were used to summarize the data

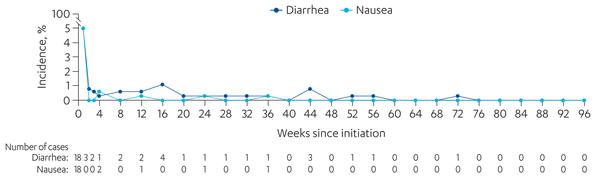
RESULTS

Overview of GI AEs

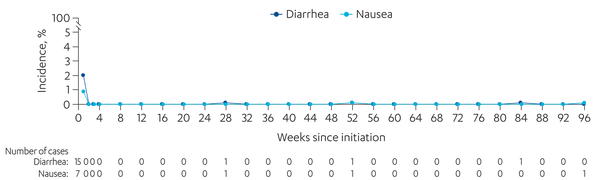
- Of those patients receiving D/C/F/TAF in AMBER and EMERALD, 175/362 (48%) and 278/763 (36%), respectively, experienced any GI AE
  - Most of these were deemed unrelated to D/C/F/TAF, as only 67 (19%) patients in AMBER and 49 (6%) patients in EMERALD had a D/C/F/TAF-related GI AE
- Among any GI AEs in AMBER and EMERALD, the most common were diarrhea, nausea, vomiting, and abdominal pain
- Across studies, the incidences of D/C/F/TAF-related diarrhea and nausea were low and tended to present early and rapidly decrease thereafter (**Figure 3**)
  - All D/C/F/TAF-related diarrhea and nausea events were grade 1 or 2 in severity and none were serious

Figure 3. Incidence of D/C/F/TAF-related diarrhea and nausea over time.

A. AMBER



B. EMERALD



Weight

- In AMBER, the median (interquartile range [IQR]) baseline weight for patients with versus without any GI AEs was 74.5 (66.5; 85.0) kg versus 74.5 (66.1; 85.9) kg (**Table 1**)
- In EMERALD, the median (IQR) baseline weight for patients with versus without any GI AEs was 76.9 (68.0; 87.0) kg versus 78.2 (68.7; 90.4) kg (**Table 2**)
- Across both studies, median increases in weight from baseline through Week 96 ranged from 2.0 to 2.3 kg for patients who experienced any GI AEs versus 1.6 kg for patients who did not experience any GI AEs (**Tables 1** and **2**)
  - Median percent change in weight from baseline ranged from 3.0% to 3.5% for patients who had any GI AEs versus 2.0% for patients who did not have any GI AEs

Table 1. Baseline and Change in Weight Over 96 Weeks for Patients With Versus Without GI AEs Receiving D/C/F/TAF in AMBER*

Weight, median (IQR)	Overall		Related	
	With any GI AEs (n = 155)	Without any GI AEs (n = 163)	With any related GI AEs (n = 57)	Without any related GI AEs (n = 261)
Baseline, kg	74.5 (66.5; 85.0)	74.5 (66.1; 85.9)	73.2 (65.1; 83.0)	75.0 (67.0; 85.7)
Absolute change at Week 96, kg	2.3 (−0.7; 5.0)	1.6 (−0.2; 4.7)	2.6 (−0.1; 5.0)	1.8 (−0.3; 5.0)
Percent change at Week 96	3.5 (−1.0; 6.8)	2.0 (−0.2; 5.6)	3.6 (−0.1; 6.9)	2.3 (−0.5; 6.1)

*n values indicate the number of patients with available weight data at baseline and Week 96.

Table 2. Baseline and Change in Weight Over 96 Weeks for Patients With Versus Without GI AEs Receiving D/C/F/TAF in EMERALD*

Weight, median (IQR)	Overall		Related	
	With any GI AEs (n = 258)	Without any GI AEs (n = 441)	With any related GI AEs (n = 44)	Without any related GI AEs (n = 655)
Baseline, kg	76.9 (68.0; 87.0)	78.2 (68.7; 90.4)	74.2 (63.1; 85.7)	78.0 (68.9; 89.5)
Absolute change at Week 96, kg	2.0 (−0.4; 4.8)	1.6 (−1.0; 4.4)	2.1 (−1.2; 4.4)	1.7 (−0.8; 4.6)
Percent change at Week 96	3.0 (−0.5; 6.1)	2.0 (−1.2; 5.9)	3.5 (−1.4; 6.6)	2.3 (−1.0; 5.9)

*n values indicate the number of patients with available weight data at baseline and Week 96.

CONCLUSIONS

- **Among treatment-naïve and virologically suppressed patients receiving cobicistat-boosted darunavir, similar numerical changes in weight were observed over 96 weeks, regardless of whether patients experienced GI AEs**
- **In both patient populations, D/C/F/TAF was associated with low incidences of diarrhea and nausea, which tended to present early and were most typically of short duration and mild to moderate severity**
- **These findings suggest that GI tolerability does not drive differences in ART-related weight gain between bPI- and INI-based regimens and that INI-related weight gain is likely related to some other phenomenon. Future studies are needed to explore alternative mechanisms for INI-related weight gain**

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ACKNOWLEDGMENTS

Medical writing support was provided by Melanie Chen, PharmD, and Caryn Gordon, PharmD, of Cello Health Communications/MedErgy, and was funded by Janssen Scientific Affairs, LLC.

DISCLOSURES

This study was sponsored by Janssen Scientific Affairs, LLC.
KD, NB, BB, EVL, SS, DL, JC, and DA are employees of Janssen and may be stockholders of Johnson & Johnson.
KD, NB, BB, EVL, JC, and DA contributed to the analysis and interpretation of the data. SS and DL contributed to the statistical analysis and interpretation of the data. All authors contributed to the drafting of this poster and approved the final version.
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POSTER PRESENTED AT THE AMERICAN CONFERENCE FOR THE TREATMENT OF HIV (ACTHIV); MAY 20-22, 2021; VIRTUAL CONFERENCE.