FINAL CLINICAL STUDY REPORT AMENDMENT

Study Title:	An Observational, Drug Utilization Study of Viread in Children and Adolescents with HIV-1 Infection
Name of Test Drug:	Tenofovir disoproxil fumarate
Dose and Formulation:	245mg, film-coated tablet
Sponsor:	Gilead Sciences International, Ltd.Cambridge, United Kingdom CB21 6GT
Study No.:	GS-EU-104-0433
Report Date:	21 December 2017
Amendment Date(s):	Amendment 1: 18 April 2018

Rationale: Herein is a summary of amendments made to the clinical study report dated 21 December 2017, as requested by the PRAC Rapporteur during the assessment of the final CSR. Amendments to Section 10.2.2 have been implemented to reflect the secondary objectives pertaining to dosing of TDF, with a description of missing data for weight or dose. Updates include an explicit clarification that dose information for pediatric patients treated with TDF-FDC regimens in the EPPICC cohort was collected and reported where the information was available, as per the study secondary objective, subpart 1. Further, the numbers of patients with missing dose or weight values were added, and an aggregated summary of patients receiving a licensed or unlicensed TDF dose for pre- and post-Viread approval was included as per the Rapporteur's tabular example.

Lastly, clarification to the statement, "Before and after the approval for Viread®, the proportion of patients receiving a TDF dose consistent with the licensed Viread® dose increased from 73% to 88%" were in patients 12 to <18 years of age and ≥35kg. Classification of dosing was calculated from patients reporting dose and weight in both the pre- and post-approval period for the pediatric indication for Viread. When dose or weight was not available or collected, these patients were excluded from dose appropriateness calculations.

CSR Section No. and Title:	Section 10.2.2 Descriptive Data
Revised Text:	TDF-FDC was prescribed to males and females equally, similar to results seen in the Viread population. Black Africans were predominantly in treatment with TDF-FDC, also in line with data from the Viread group (Table 1a). There were no notable differences or shifts in the modes of infection or prevalence of HBV or HCV compared to the previous Supplementary report or the second Viread interim report data. As reported previously, there was one death in a patient receiving TDF-FDC and it was unknown whether TDF-FDC administration was causally associated with the fatality. Upon stratifying cohort features by initial FDC treatment regimen (Table 1b), there were no clear demographic trends defined by the presence of a specific TDF-FDC. Truvada and Atripla were the most commonly prescribed regimens in EPPICC cohorts. Among children who initiated TDF-FDC therapy, the median age was greater and the IQR narrower (13.8 years [IQR 12.0, 15.3]) than those exposed to Viread (10.5 years [IQR 7.7, 13.6]). The median age at commencement of ART was also older at 4.1 years (0.9, 10.3) compared to those with Viread exposure (2.1 years [0.5, 6.0]), Table 2a. These children were also more treatment experienced than the Viread group with a median duration of ART prior to TDF-FDC at 8.4 years (IQR 3.2, 12.2) compared to 6.6 years (IQR 2.3, 10.0) in Viread exposed groups. The median age at initiation of these regimens was 13.4 years (IQR 11.9, 15.2 years) for Truvada and 13.7 years (IQR 12.1, 15.3 years) for Atripla. Overall, the median age of initial FDC exposure was during age 13.7, whereas patients on Viread were younger at treatment initiation (median age 10.5 years). A larger proportion of younger patients aged two to eleven initiated TDF-FDC in the pre-approval period (29%, n=134)) compared to the post-approval period (18%, n=51)). TDF-FDC dose by age and weight were collected in the EPPICC cohort, where available. In this age group 52% (n=97) were given a TDF-FDC dose consistent with what became the licensed dose for Viread by weight, and 22% (n=41) were given a dosage of TDF-FDC inconsistent to the approved dose for Viread. Among pediatric patients 12 to <18 years, 79% were >35kg and on a 245 mg dose of TDF. Before and after the approval for Viread, the proportion of patients receiving a TDF dose consistent with the licensed Viread dose increased from 73% to 88% among those patients with available initial dose data. There were 332 TDF-FDC patients between 12 and <18 years and only 7 were on a dose of TDF not consistent with the licensed Viread dose. Of patients in the 2 to <12 year group, 2 (1%) patients were missing a TDF-FDC dose in the pre-approval period, compared with 3 patients (6%) in the post-approval period (overall 3% were missing TDF-FDC dose information). In the 12 to <18 year

group, 89 (27%) patients in the pre-approval period were missing TDF-FDC dose information, and 47 (17%) patients in the post-approval period did not have TDF-FDC dosing available (18% missing overall).

A summary of patients who received licensed or unlicensed doses of TDF initiating TDF-FDC pre- and post-approval for the pediatric indication for Viread for the treatment of HIV is included in the synthetic table below:

		Treatment status (n (%))	
	Initiated TDF-FDC prior to Viread® approval for pediatric indication (n=466)	**Initiated TDF-FDC after Viread® approval for pediatric indication (n=279)**	**Total (n=745)**
Missing weight or dose	**182 (39)**	**80 (29)**	**262 (35)**
Licensed Viread® dose*	**242 (52)**	**186 (67)**	**428 (58)**
Unlicensed Viread® dose	**42 (9)**	**13 (5)**	**55 (7)**

Overall more patients received a licensed TDF/Viread dose when they initiated a TDF-FDC regimen after the approval of Viread (67% vs 52%). Less than 10% of patients with both weight and dose information received an unlicensed dose for TDF in a TDF-FDC regimen. As these data are observational and secondary data, weight or dose was not collected or unreported by EPPICC cohorts in approximately 35% of patients.

Within the TDF-FDC patient group, spanning both the pre and post Viread approval periods, the majority of patients (58%, n=435)) had been previously exposed to between one and three other ART regimens. The proportion of treatment naïve patients was stable at 18% across both time periods. In comparison, 11% of patients initiating Viread were treatment naïve. On notable difference is that patients were more likely to be prescribed an NNRTI (53%) and protease inhibitor (29%) at the start of TDF-FDC than those commencing Viread where 62% were co-prescribed a protease inhibitor and 28% were prescribed an NNRTI. Only 18% of patients of patients on a TDF-FDC were previously prescribed Viread. Among Viread exposed patients (Table 2a), 69% of Viread patients initiated treatment with a VL greater than 400 copies per mL and for TDF-FDC patients this was true for 39% of patients. In the post-approval period 21% initiated TDF-FDC with a VL > 400 copies per mL whereas in the Viread post-approval cohort, 61% had a starting VL over 400 copies per mL,

	suggesting Viread patients may be sicker at the time of TDF treatment initiation. The median initiating VL in the post-approval TDF-FDC group is 1.7 log10 copies/mL. With the Viread post-approval group, the median initiating VL was greater at 3.4 log10 copies/mL. However, at 12 months after initiating TDF-FDC treatment the median VL was 1.6 log10 copies/mL (IQR 1.3, 1.7) and comparable to the Viread post-one year results of 1.7 log 10 copies/mL (IQR 1.6, 2.2). The temporal differences seen in the initiating viral loads may be reflective of shifts in HIV treatment guidance toward empiric therapy.

GILEAD SCIENCES INTERNATIONAL, LTD.

SIGN-OFF FOR CLINICAL STUDY REPORT AMENDMENT

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I have read this clinical study report amendmentand, to the best of my knowledge, it accurately reflects the results and conduct of Gilead Sciences International, Ltd., Study GS-EU-104-0433.

Gilead Sciences International, Ltd., Study Director: PPD
Director, Pharmacovigilance and Epidemiology

Signature Date