Clinical, Clinical Virology, Clinical Pharmacology, and Cross-Discipline Team Leader Review

Date	March 7, 2024
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Subject	Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology, and Virology Review
NDAs/Supplements	NDA 211994/S-018 & S-019
Applicant	ViiV Healthcare Company
Date of Submission	June 6, 2023
Priority or Standard	Standard
PDUFA Goal Date	April 6, 2024
Proprietary Name	Dovato
Established or Proper Name	dolutegravir and lamivudine
Dosage Form(s)	Oral tablets: 50 mg of dolutegravir and 300 mg of lamivudine
Applicant Proposed Indication(s)/Population(s)	Adolescents from 12 to less than 18 years of age who weigh at least 25 kg, and are treatment naïve or virologically suppressed and replacing a current antiretroviral regimen
Applicant Proposed Dosing Regimen(s)	Same as approved dosing regimen, no changes proposed
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Same as proposed: Adolescents from 12 to less than 18 years of age who weigh at least 25 kg, and are treatment naïve or virologically suppressed and replacing a current antiretroviral regimen
Recommended Dosing Regimen(s)	Same as approved
Approved Dose Form	Fixed dose combination tablet
Approved Dosing Regimen(s)	DOVATO, a two-drug combination of dolutegravir (integrase strand transfer inhibitor [INSTI]) and lamivudine (nucleoside analogue reverse transcriptase

	inhibitor [NRTI]) is indicated as a complete regimen for the treatment of HIV- 1 infection in adults with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV- 1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of DOVATO.
Applicant Proposed Dosing Regimen(s)	Same as approved, no changes to dosage regimen

1.0 Introduction

This supplemental New Drug Application (sNDA) review summarizes the data submitted by the Applicant (ViiV Healthcare) to support labeling changes for DOVATO to expand treatment to adolescent patients aged ≥12 years to less than 18 years of age, who weigh at least 25 kg. The sNDA includes the Week 48 Clinical Study Report and associated data sets for study 205861(DANCE): An open label, single arm study to evaluate the Week 48 efficacy and safety of a two-drug regimen of dolutegravir/lamivudine (DTG/3TC) as a fixed dose combination (FDC), in antiretroviral therapy (ART)-naïve HIV-1-infected adolescents, ≥12 to <18 years of age who weigh at least 25 kg. The DANCE study along with evidence from adequate and well-controlled trials in adults, GEMINI-1 and GEMINI-2 (treatment-naïve adults) and TANGO (virologically suppressed adults), support the use of DTG/3TC in treatment-naïve and virologically suppressed (HIV-1 RNA less than 50 copies per /mL) adolescents on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of DOVATO.

The review of the data from the DANCE study fulfills PREA PMR 3590-3: Conduct an open-label, single-arm study to evaluate the week 48 efficacy and safety of dolutegravir and lamivudine (DTG/3TC) as a fixed-dose combination (FDC), in antiretroviral therapy (ART)-naïve HIV-1-infected adolescents from 12 years to less than 18 years of age who weigh at least 40 kg.

Throughout this review the product will be referred to as DOVATO or DTG/3TC FDC.

2.0 Background

Dolutegravir (DTG) is an HIV-1 integrase strand transfer inhibitor (INSTI), and lamivudine (3TC) is a nucleoside reverse transcriptase inhibitor (NRTI). DTG and

3TC are approved products, both individually and as part of other fixed-dose combination (FDC) products. DOVATO (DTG/3TC FDC) is indicated as a complete regimen for treatment of HIV-1 infection in adults with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of DOVATO. This combination was the first two-drug regimen approved as a complete therapeutic regimen for treatment-naïve patients.

The basis for approval of the two-drug regimen DTG/3TC for treatment-naïve patients with HIV-1 infection was noninferiority to the three-drug regimen DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) established at Week 48 in the Phase 3 trials GEMINI-1 and GEMINI-2.

The basis for expanding the indication to include certain virologically suppressed patients was noninferiority to a tenofovir alafenamide (TAF)-containing regimen established at Week 48 in the Phase 3 trial, TANGO.

During the initial review cycle, a PREA PMR was issued to conduct a trial in adolescent patients 12 years and older weighing at least 40 kg to evaluate and obtain 96 week efficacy data in this patient population. Of note, the original PREA PMR issued on April 8, 2019 was amended on March 7, 2022 (PMR 3590-3 below) to allow for 48 week data rather than the original requested 96 week data as follows:

> PMR 3590-3: Conduct an open-label, single-arm study to evaluate the week 48 efficacy and safety of dolutegravir and lamivudine (DTG/3TC) as a fixed-dose combination (FDC), in antiretroviral therapy (ART)-naïve HIV-1-infected adolescents from 12 years to less than 18 years of age who weigh at least 40 kg.

The DANCE study (205861) was conducted in fulfillment of the PREA PMR. The current sNDA submission contains the Applicant's supporting data to expand the use in adolescent patients 12 years and older weighing at least 25 kg and who are treatment naïve or virologically suppressed. Additional evidence used in support of this application comes from previously reviewed adequate and well-controlled trials in adults, GEMINI-1, GEMINI-2 (treatment-naïve adults) and TANGO (virologically suppressed adults).

A safety update report was submitted on August 3, 2023 which included data from Study 205861 up to the data cut-off of May 16, 2023.The data originally submitted in the sNDA included a safety cut-off date February 4, 2022.

3.0 Product Quality

No new Product Quality information was submitted during the review of this sNDA.

4.0 Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology information was submitted during the review of this sNDA.

5.0 Clinical/Statistical- Efficacy

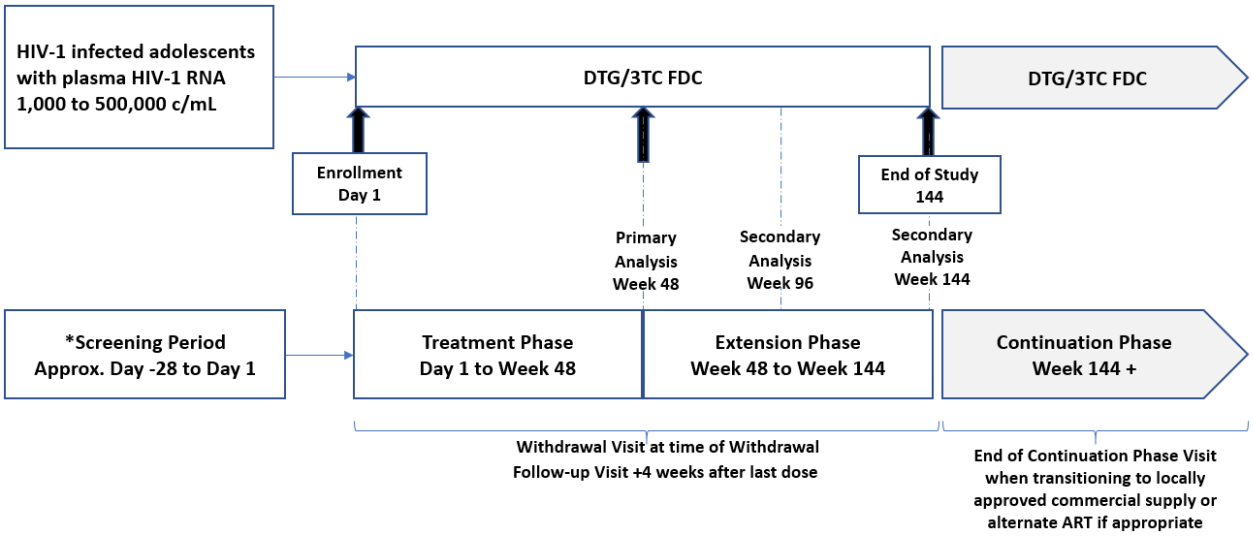
5.1 Study Design

The DANCE study is an ongoing multicenter, multinational, open label single arm study to evaluate the week 48 efficacy and safety of DOVATO, a two-drug regimen of dolutegravir/lamivudine (DTG/3TC) as a fixed dose combination (FDC), in antiretroviral therapy (ART)-naïve HIV-1-infected adolescents, ≥12 to <18 years of age who weigh at least 25 kg.

The DANCE study design is presented in **Figure 1**. This review describes and focuses on the data from the primary analysis at week 48. The 96 week extension phase CSR was also included in the sNDA; however, the proposed labeling and review is based on the primary endpoint of 48 weeks. Pharmacokinetic (PK) data were collected up to the week 48 timepoint; no additional PK data were collected beyond the week 48 visit. This study design is aligned with the regulatory requirements of the issued PMR.

This study was not powered to test an efficacy hypothesis and was designed to collect PK, safety and descriptive efficacy data based on the open label design.

Figure 1. Overview of Study Design for Study 208561 (DANCE)



*** Retesting of an exclusionary lab result (except for exclusionary HIV-1 resistance), is allowed during the screening window (does not require re-screening). In cases of central laboratory assay failure or shipment failure, the screening period may be extended to 35 days to accommodate sample analysis and reporting. Approval of the Medical Monitor is required.**

Source: Applicant's Clinical Study Report for Study 208561, Week 48 CSR page 19 Abbreviations: DTG/3TC FDC=DOVATO

The study enrolled treatment-naive adolescents with plasma HIV-1 RNA between 1,000 and ≤500,000 copies/mL. All enrolled participants received an open-label, two-drug regimen of DTG/3TC (DOVATO) FDC for 48 weeks. Participants who successfully completed 48 weeks of treatment had the opportunity to enter the study Extension Phase for an additional 96 weeks, but as mentioned above this review is limited to the Week 48 data. The phases of the study are outlined below:

- Screening Phase (approximately Day -28 to Day 1)
- Treatment Phase (Day 1 to Week 48) (focus of this review)
- Extension Phase (Week 48 to Week 144)
- Continuation Phase (After Week 144)

GCP noncompliance, site 238608 closure

At the time of this report, GCP noncompliance issues were identified at 1 site in Kenya that resulted in the site closure. The important noncompliance issues included oversight issues inclusive of lack of documentation, manipulation of signatures, and laboratory samples sent without appropriate export license approval.

Based on the findings, this site was closed and all participants were transitioned to standard of care treatment.

The DANCE study was an open label design with an objective endpoint (HIV-1 RNA less than 50 copies/mL at Week 48) measured by a central laboratory. The noncompliance issues noted above would not likely impact the primary efficacy endpoint. The GCP noncompliance was reported to the Division prior to the submission of this sNDA.

The Applicant completed an internal review of the site data and concluded no concerns or trends indicating falsification of the clinical trial data. The study analysis plan was updated to sensor this non-compliance site from the primary efficacy analyses by removing participant data associated with the site as follows:

- Sensitivity analysis 1: primary population with removal of participants with no Week 48 data as a result of site closure.
- Sensitivity analysis 2: primary population with removal of all participants from this site.

The differing analysis populations are highlighted in **Table 1** below as a result of the site closure. For the purposes of this review the efficacy analysis was conducted using ITT-E Sensitivity 1 population, N=30 (excluded participants with no week 48 data). The safety review will utilize the ITT-E patient population, N=32. These two populations are highlighted in red in Table 1.

Table 1. Summary of Analysis Populations (all screened)

Population	No Treatment	DTG/3TC FDC	Total
All Subjects Screened	28	32	60
Enrolled	-	32	32
Safety	-	32	32
Safety Sensitivity 1	-	30	30
Safety Sensitivity 2	-	25	25
ITT-E	-	32	32
ITT-E Extension Phase	-	27	27
ITT-E Sensitivity 1	-	30	30
ITT-E Sensitivity 2	-	25	25
ITT-E Extension Phase Sensitivity 1	-	24	24
ITT-E Extension Phase Sensitivity 2	-	23	23
Per-Protocol	-	32	32
CVW[a]	-	0	0
PK	-	32	32
Sparse and Trough PK	-	32	32
Intensive PK	-	12	12

Data Source: Table 1.1.
The definitions of analysis populations are provided in Section 4.8.2.
a. Includes all CVWs through the data cut-off for database freeze (04 February 2022).
Source: Applicant's Clinical Study Report for Study 208561, Week 48 CSR Table 5 Abbreviations: DTG/3TC FDC=DOVATO

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5.2 Disposition

The DANCE study was a multicenter, multinational study, wherein, a total of nine sites in 3 countries enrolled 1 or more participants. A total of sixty participants were screened as outlined in Table 2 below, of which 28 were screen failures. History of resistance at baseline accounted for the majority of screen failures. Thirty-two participants were enrolled and received at least one dose of study drug. As outlined in **Table 3** below, of the 30 participants in the ITT-E Sensitivity 1 population (efficacy population), 27 (90%) completed the trial through Week 48 and 3 (10%) withdrew before the week 48 analysis. In the safety population, ITT-E (N=32), 27 (84%) participants completed the trial through Week 48 and 5 (16%) withdrew before week 48.

Table 2. Summary of participants screened by country (All Participants)

Number of participants, n (%)	No Treatment (N=28)	DTG/3TC FDC (N=32)	Total (N=60)
Kenya (2 centers)	7 (25)	10 (31)	17 (28)
South Africa (3 centers)	5 (18)	3 (9)	8 (13)
Thailand (4 centers)	16 (57)	19 (59)	35 (58)

Data Source: Table 1.2.
Note: The 'No Treatment' column represents screening failures.
Source: Applicant's Clinical Study Report for Study 208561, Week 48 CSR Table 6 Abbreviations: DTG/3TC FDC=DOVATO

Table 3. Summary of participant status

Number of Participants, n (%)	ITT-E DTG/3TC FDC (N=32)	ITT-E Sensitivity 1 Population DTG/3TC FDC (N=30)	ITT-E Sensitivity 2 Population DTG/3TC FDC (N=25)
Ongoing	0	0	0
Completed	27 (84)	27 (90)	23 (92)
Withdrawn	5 (16)	3 (10)	2 (8)

Source: Applicant's Clinical Study Report for Study 208561, Week 48 CSR Table 4 Abbreviations: DTG/3TC FDC=DOVATO

5.3 Baseline Demographics

The median age was 17 years (range 13-17 years). The clinical reviewer analyses found that four participants (based on year of birth) were 18 years of age at time of enrollment. The Applicant reported that only the year of birth was recorded in the eCRF (electronic case report forms) and calculation of age uses 30 June in place of true day and month of birth for all participants. Based on this updated age calculation four participants were counted as 17-year olds. The age difference between the reviewer findings and Applicant's submission was approximately 6 months for these 4 participants and should have neglibile impact on the PK, safety and efficacy outcomes of this study. More males (21/32; 66%) compared to (11/32; 34%) females were enrolled. As expected, based on the enrollment sites locations in Thailand and Kenya, all of the participants in the DANCE study were Southeast Asian (19/32; 59%) or Black (13/32;41%), and no Hispanics or Latinos were enrolled in this study. Additional demographic data are outlined in Table 4 below.

Table 4.Summary of demographics and baseline characteristics

	DTG/3TC FDC (N=32) (%)
Age (years)	
Median	17
Min, Max	13, 17
Sex, n(%)	
Female	11 (34)
Male	21 (66)
Race, n(%)	
Asian	19(59)
Black	13(41)
Ethnicity, n(%)	
Hispanic or Latino	0(0)
Not Hispanic or Latino	100(0)
Height (cm)	
Median	165
Min, Max	144,178
Weight (kg)	
Median	54

Min, Max	(30, 97)
BMI (kg/m^2)	
Median	20
Min, Max	14,31
Plasma HIV-1 RNA (copies/mL), n (%)	
<1000	2(6)
1000 to < 10,000	6(19)
10,000 to <100,000	15(47)
100,000 to <500,000	9(28)
≥ 500,000	0(0)
CD 4+ (10^6/L) n (%)	
Median	373
Min, Max	20, 1122
CD4 Cell Count Categories (10^6/L), n (%)	
<50	2(6)
50 to <200	2(6)
200 to <350	10(31)
350 to <500	8(25)
>500	9(28)
Missing	1(3)

Source: Clinical Reviewer's Analysis of ADLS, ADLB, and ADVS datasets (DANCE); JMP 16.1.0

5.4 Extent of exposure and Protocol Deviations

The mean time on study was approximately 80 weeks.

A total of 18/32 participants (56%) had a protocol deviation. The most common protocol deviation (10/32 participants) was due to "investigational product bottle not returned at clinic visit and pill count not obtained."

There were no protocol deviations that lead to exclusion of participants from the efficacy analysis.

5.5 Efficacy Results

This section focuses on the Week 48 virologic response rates. No formal statistical testing was conducted; descriptive statistics were used.

The primary efficacy endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (snapshot analysis). The secondary endpoint was the proportion with plasma HIV RNA <200 copies/mL. The ITT-E sensitivity 1 population was used in support of the primary efficacy endpoint and consisted of 30 participants. Twenty-six of thirty 26/30 (86%) participants met the primary efficacy endpoint. Two participants did not meet the primary endpoint and had HIV-1 RNA levels >50 copies/mL at week 48. Two additional participants did not have virologic data in the Week 48 window and discontinued prior to Week 48 due to a grade 3 AE

of glomerular filtration rate and withdrawal of consent at Week 16. These findings are highlighted in Table 6.

Table 5.HIV-1 RNA levels at week 48 for the different analysis populations

Endpoints	ITT-E sensitivity 1 N=30	ITT-E N=32	ITT-E sensitivity 2 N=25
HIV-1 RNA <50 copies/mL at Week 48	26/30 (87)	26/32 (81)	23/25 (92)
HIV-1 RNA <200 copies/mL at Week 48	27/30 (90)	27/32 (84)	23/25 (92)

Source: Clinical reviewer's ADLB datasets (DANCE);JMP 16.1.0

The GCP noncompliance resulting in study closure did not impact the overall results No clinically relevant differences in efficacy outcomes between the sensitivity-1 (N=30; excluded only 2/7 participants from closed site) and sensitivity-2 (N=25; excluded all participants from closed site) populations, were observed.

Overall, these efficacy results, though descriptive, are consistent with the results of the adult treatment naïve studies, GEMINI 1 and GEMIN-2; where at week 48 ninety-one (91%) to ninety three percent (93%) of participants had HIV-1 RNA levels <50 copies/mL. (DOVATO USPI)

The clinical virology section summarizes the details for the one participant who met confirmed virologic withdrawal criteria for resistance testing.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted PK data from the DANCE study and a population PK (PopPK) analysis report based on pooled data from the DANCE study and virologically suppressed adults in Study 204862 (TANGO).

The proposed adolescent dosing is identical to those approved with individual products, TIVICAY (DTG), EPIVIR (3TC), and the components in a three-drug combination product, TRIUMEQ (DTG/3TC/abacavir [ABC]). The Clinical Pharmacology review focused on across-study comparisons of DTG and 3TC exposures in adolescents receiving DOVATO with those observed in adults and pediatric populations receiving products containing DTG and 3TC (EPIVIR, DOVATO, TIVICAY, and TRIUMEQ).

The noncompartmental analysis (NCA) estimated intensive PK parameters for DTG and 3TC in the DANCE study are summarized in **Table 8**. **Table 9** and **Table 10** provide cross-study comparisons of adolescent exposures to historical adult (treatment-naïve and virologically suppressed) and pediatric data for DTG and 3TC, respectively. In adolescents receiving DOVATO, the PK parameters (AUC_{0-24}, C_{max},

and C_{24}) for DTG and 3TC at steady-state are higher relative to historical adult values. The observed differences in exposures of DTG and 3TC were not considered clinically significant given that 1) the exposures were still within the observed ranges in adults and pediatric patients at the recommended dosage receiving individual components of DOVATO; and 2) no additional safety signals were identified and the observed safety profile in adolescent subjects was similar to those observed in adults.

The Applicant performed PopPK analysis with combined data from treatment-naïve adolescents in the DANCE study and treatment-experienced virologically suppressed adults in the TANGO study. The results are consistent with the NCA analyses and support the approval.

6.2. Pharmacokinetics Results and Exposure Comparison

Table 6 Steady-State PK Parameters of DTG and 3TC in Adolescents 12 to <18 Years Old and ≥25 kg (Intensive PK)

PK Parameter	DOVATO one tablet once daily	
	Dolutegravir (50 mg)	Lamivudine (300 mg)
N	12	12
$AUC_{(0-24)}$ (ng*h/mL)	74.0 (23.2)	12.3 (17.7)
C_{max} (ng/mL)	5.35 (25.0)	2.78 (27.8)
C_{24} (ng/mL)	1.64 (25.4)	0.053 (33.4)
t_{max} (h)	2.00 (1.00, 3.00)	1.00 (1.00, 3.00)
$t_{1/2}$ (h)	12.9 (15.4)	4.82 (13.3)
lambda-z (1/h)	0.0537 (15.3)	0.144 (13.3)

Note-

- Values expressed as geometric mean (CV%) except for t_{max} which are presented as median (range).
- AUC_{0-24} (AUC_T): Area under concentration-time curve in one dosing interval; C_{24}: Observed concentration at the end of the dosing interval;
- Source: Study 205861 Week-48 Report, Table 33

Table 7 Comparison of DTG Exposures in DANCE Study vs. Historical Data in Adults and Pediatric Participants Receiving Products Containing DTG at Recommended Dosing

Formulation	Population		DTG Daily Dose	$AUC_{(0-24)}$ mcg·h/mL	C_{max} mcg/mL	C_{24} mcg/mL
Adolescents (12–< 18 years and ≥25 kg (DANCE))						
DTG/3TC	ART-naïve	Intensive PK (n=12)#	50 mg	74.0 (23.2)	5.35 (25.0)	1.64 (25.4)
		PopPK (n=32)&	50 mg	78.2 (91.6)	6.71 (69.5)	1.46 (154)

Adults						
DTG	ART-naïve	PopPK (n=449)*	50 mg	53.6 (26.9)	3.67 (19.7)	1.11 (46.3)
DTG/3TC	virologically suppressed	PopPK (n=361)@	50 mg	59.2 (90.2)	5.08 (83.1)	1.23 (156)
		Intensive PK (n=30)$	50 mg	60.5 (45.3)	4.56 (35.1)	1.27 (91.3)
Pediatric						
DTG/ABC /3TC	25 to <40 kg	Intensive PK (n=7)^	50 mg	71.8 (14)	6.25 (21)	0.98 (28)
	20 to <25 kg	Intensive PK (n=7)^	30 mg	84.4 (26)	7.29 (17)	1.35 (95)
	14 to <20 kg	Intensive PK (n=7)^	25 mg	71.4 (23)	7.04 (17)	0.79 (44)
	10 to <14 kg	Intensive PK (n=7)^	20 mg	91.0 (36)	8.85 (21)	1.22 (77)
	6 to <10 kg	Intensive PK (n=7)^	15 mg	75.9 (34)	7.40 (28)	0.91 (68)

PK parameters presented as geometric mean (%CV).
Data sources: # DANCE Study Report; & DANCE PopPK Report, Table-11; * USPIs of DOVATO, TIVICAY, and TRIUMEQ, and SPRING PopPK Study Report; @ TANGO PopPK Report, Table-9; $ TANGO Study Reprot Table-76; ^ TRIUMEQ PD USPI

Table 8 Comparison of 3TC Exposures in DANCE Study vs. Historical Data in Adults and Pediatric Participants Receiving Products Containing 3TC at Recommended Dosing

Formulation	Population		3TC Daily Dose	$AUC_{(0-24)}$ mcg·h/mL	C_{max} mcg/mL	C_{24} mcg/mL
Adolescents (12–< 18 years and ≥25 kg (DANCE))						
DTG/3TC	ART-naïve	Intensive PK (n=12)#	300 mg	12.3 (17.7)	2.78 (27.8)	0.053 (33.4)
		PopPK (n=32)&	300 mg	14.7 (112)	2.95 (82.8)	0.106 (312)
Adults						
3TC	Healthy	NCA (n=60)*	300 mg	8.87 (21)	2.04 (26)	0.042 (38)
DTG/3TC	Virologically suppressed	PopPK (n=361)@	300 mg	14.1 (102)	2.50 (90.7)	0.089 (229)
		Intensive PK (n=30)$	300 mg	13.7 (42.2)	2.58 (32.6)	0.098 (200)
Pediatric						
DTG/ABC /3TC	25 to <40 kg	Intensive PK (n=7)^	300 mg	21.7 (26)	4.15 (29)	0.084 (35)
	20 to <25 kg	Intensive PK (n=7)^	180 mg	14.5 (17)	2.99 (32)	0.060 (18)
	14 to <20 kg	Intensive PK (n=7)^	150 mg	13.0 (16)	2.92 (23)	0.058 (37)

	10 to <14 kg	Intensive PK (n=7)^	120 mg	14.2 (24)	3.55 (19)	0.046 (48)
	6 to <10 kg	Intensive PK (n=7)^	90 mg	10.7 (46)	2.29 (40)	0.055 (39)

Values presented as geometric mean (%CV) except for the results of Phase 1 study EPV10001 in healthy volunteers (n=60), for which arithmetic mean (CV%) values were reported.
Data sources: # DANCE Study Report; & DANCE PopPK Report, Table-21; * DOVATO USPI and Clin Pharm Review (DARRTS date 8/02/2002); @ TANGO PopPK Report Table 16; $ TANGO Study Report Table-76; ^ TRIUMEQ PD USPI

6.3. Study 205861 (DANCE) Summary

PK assessment:

Intensive PK (n=12) were collected between days 5-10 following the sampling schedule as described below.

Day	Sample Times Relative to Dose
5 to 10	Pre-dose[a], 0.5, 1.0, 1.5, 2, 3, 4, 6, 10, and 24[b] hours post dose

a. Pre-dose samples will be collected immediately before the dose (i.e. within 15 minutes) which will be taken under observation at the clinic.
b. Participants in the intensive PK sampling group must return to the site the next morning for the 24-hour post dose blood sample collection.

C_{trough} samples were collected for all subjects (n=32) at week-8, -16, -36, and -48 visits, immediately prior to dosing. Sparse blood samples were collected in all subjects at the following specified time frames with flexibilities, as long as all three samples (2 to 4 hours, 4 to 12 hours, and 12 to 24 hours post-dose) were obtained for each participant from week-4, week-12, week-24 samples.

Week	Sample Times Relative to Dose
4	1 pre-dose[a] sample AND 1 sample 2 to 4 hr post dose[b]
12	1 pre-dose sample[a] AND 1 sample 4 to 12 hr post dose[b]
24	1 pre-dose sample[a] AND 1 sample 12 to 24 hr post dose [b]

a. Pre-dose samples will be collected immediately before the dose (i.e. within 15 minutes) which will be taken under observation at the clinic. Pre-dose samples should be collected 20-28 hours post previous dose.

b. All sample timepoints must be obtained from each participant. These samples may be drawn at any time during the specified interval.

Note: Participants are to complete a dosing diary card for 3 days prior to PK sampling visit. The PK visit should be re-scheduled if the participant took their morning dose prior to coming into the clinic on the PK sampling day.

Bioanalysis: Plasma sample analysis were conducted at (b) (4) . Plasma concentrations were determined using validated LC-MS/MS methods P1170 for DTG and P1165 3TC (Bioanalytical Report DTG, 3TC). The assay methods were the same as those used in support of Study 204862 (Tango). A total of 11 and 7 method validation reports were submitted for DTG and 3TC, respectively. Assay for DTG was validated over a concentration range of 20.0 – 20000 ng/mL in human K_2EDTA plasma. Assay for 3TC was validated over a concentration range of 2.50 – 2500 ng/mL in human K_2EDTA plasma. The bioanalytical portion of the study appear acceptable.

PK analyses: Intensive PK concentrations were analyzed by NCA methods using Phoenix WinNonlin version 8.0. The PK results are presented in **Table 8**. Overall, the PK parameters for DTG and 3TC following DOVATO one tablet orally administered once daily in treatment-naïve adolescents are considered comparable (similar or no clinically meaningful differences) to those observed in adults and pediatric patients at the approved doses of individual products.

6.4. Pharmacometrics Assessment

The pharmacokinetics (PK) of of DOVATO have been previously characterized through population PK (popPK) modelings in adults. The established popPK models for the single entities, DTG and 3TC, were used to support the current dosing (Applicant's previous popPK can be found at: EDR link). In this submission, sparse PK data from adolescent subjects are available from the ongoing DANCE study for refitting the popPK models. The Applicant's objectives of the popPK modeling are as follows: 1) to evaluate the predictive performance of the established popPK models for 3TC and DTG in adolescent subjects receiving DOVATO (i.e., external evaluation), 2) to update popPK model parameters (i.e., model refitting), and 3) to compare the Bayesian posterior-predicted exposures of the DANCE study subjects to those of adults. Of note, DTG has been approved for pediatric subjects down to 4 weeks of age, weighing at least 3 kg; 3TC alone has been approved for pediatric subjects down to 3 months. The respective labels for DTG and 3TC can be found here and here.

A total of 32 adolescent subjects, contributing 402 and 400 plasma concentrations for DTG and 3TC, respectively, were pooled with 361 TANGO study subjects. The number of subjects and plasma PK observations included in the final NONMEM dataset are summarized by study in **Table 11**. No subjects or plasma concentrations were excluded from DANCE study based on conditional-weighted residuals. For summary of baseline characteristics of the pooled population, refer to Tables 5, 6, and 7 in the Applicant's popPK report (pages 31-36).

Table 9. Plasma Concentrations in PopPK Dataset

Analyte	Study	Total Number of Subjects	Number (%) of Observations Available for PK Analysis	Number (%) of Intensive Sampling Observations	Number (%) of Sparse Sampling Observations	Number (%) of Predose BLQs	Number (%) of Postdose BLQs	Total Number of Observations
Dolutegravir (DTG)	TANGO	361	2,599 (100)	298 (11.47)	2,301 (88.53)	0 (0)	0 (0)	2,599
Dolutegravir (DTG)	DANCE	32	402 (100)	120 (29.85)	282 (70.15)	0 (0)	0 (0)	402
Lamivudine (3TC)	TANGO	361	2,582 (100)	298 (11.54)	2,284 (88.46)	0 (0)	0 (0)	2,582
Lamivudine (3TC)	DANCE	32	400 (100)	119 (29.75)	281 (70.25)	0 (0)	0 (0)	400

Source: Applicant's popPK report, Table 4, page 30

DTG PK

The external evaluation step undertaken by the Appliacnt demonstrated that the popPK model did not truly capture the pooled PK data. To correct the model misspecification shown via diagnostic plots after pooling adolescents data, Asian or Black/African American effect on apparent clearance (CL/F) was added to the existing model (i.e., base model). For the refined final model parameters, there was a 29.9% difference on the weight effect on apparent central volume of distribution (Vc/F); all other parameters had less than 5.2% change from the existing popPK model (i.e., adult only model). The model generally is acceptable in describing the adolescent DTG PK with relative standard errors (RSE) <20.9% (and in line with the model fit for TANGO PK data). The shirnkages are acceptable at 28.1% or below. Refer to the Applicant's popPK report for detailed discussion and model diagnostics. The final model is a linear 1-compartment model with first-order absorption and elimination. Inter-individual variaiblty (IIV) was included on CL/F and proportional error term. Overall, the final popPK model for DTG is acceptable in deriving the posterior predictions and exposure metrics of the DANCE population. Exposure metrics derived from Bayesian posterior predictions are summarized in **Table 12**.

3TC PK

Similar steps for modeling analysis were undertaken for 3TC. Given the misspecification in describing the pooled adolescent and adult PK data, a model refinement was performed. The final base model removed Black/African American race on CL/F without affecting model predictive performance. This is reasonable based on rule of parsimony. The Applicant's refitted base model had parameter differences of <2.56% when compared to those of the previously developed model (and removal of race effect on clearance); parameters were estimated with reasonable precision (generally <26.8% RSE except between-subject covariance RSE at 40.6%). The final popPK model demonstrated numerical precision for the parameters (RSE <28.4%) and the 95% confidence interval (from the sampling importance resampling procedure). The model is generally acceptable in describing the adolescent 3TC PK. The shirnkages are low (<9.22%). Refer to the Applicant's popPK report for detailed discussion and model diagnostics. The final model is a

linear 2-compartment model with first-order elimination and absorption (from depot compartment). IIV was included on CL/F, Vc/F, and proportional error term. Overall, the final popPK model for 3TC is acceptable in deriving the posterior predictions and exposure metrics of the DANCE population. Exposure metrics derived from Bayesian posterior predictions are summarized in **Table 13**.

Overall, the PK of DTG and 3TC following repeat oral administration are similar between adolescent and adult subjects. No dosing adjustment is required from the currently recommended dosing regimen.

Table 10. Summary of Steady-state DTG Exposure Metrics Following Once Daily Dosing of DTG/3TC FDC Tablet

	Adults (TANGO)			Adolescents (DANCE)		
	$AUC_{0-\tau,ss}$ (mg*h/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{0-\tau,ss}$ (mg*h/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
N	361	361	361	32	32	32
Geomean (95% CI)	56.9 (55.1, 58.8)	5.24 (5.09, 5.38)	1.07 (0.998, 1.15)	78.2 (70.3, 86.9)	6.71 (6.27, 7.19)	1.46 (1.18, 1.80)
%CV	94.6	84.2	170	91.6	69.5	154
Median (min – max)	56.2 (24.9 – 141)	5.21 (2.76 – 10.6)	1.17 (0.0259 – 4.68)	78.5 (36.6 - 129)	6.62 (4.03 - 12.3)	1.56 (0.331 – 3.54)
Percentiles						
5%	33.7	3.44	0.369	45.2	5.3	0.436
25%	46.1	4.35	0.752	68.3	6.04	1.21
50%	56.2	5.21	1.17	78.5	6.62	1.56
75%	71	6.22	1.65	98.7	7.16	2.03
95%	94.8	8.34	2.62	116	9.15	3.01

%CV=percentage of the coefficient of variation; 3TC=lamivudine; AUC0-τ,ss=area under the plasma drug concentration-time curve from predose to the end of the dosing interval at steady state; CI=confidence interval; Cmax,ss= maximum plasma concentration at steady state ; Cmin,ss=minimum plasma concentration at steady state; DTG=dolutegravir; FDC=fixed-dose combination; geomean=geometric mean; max=maximum; min=minimum; N= number of subjects with available information; PK=pharmacokinetic; ss=steady state
Source: Applicant's popPK report, Table 11, page 53

Table 11. Summary of Steady-state 3TC Exposure Metrics Following Once Daily Dosing of DTG/3TC FDC Tablet

	Adults (TANGO)			Adolescents (DANCE)		
	$AUC_{0-\tau,ss}$ (mg*h/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{0-\tau,ss}$ (mg*h/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
N	361	361	361	32	32	32
Geomean (95% CI)	12.7 (12.2, 13.2)	2.53 (2.45, 2.61)	0.0863 (0.0799, 0.0933)	14.7 (12.8, 16.9)	2.95 (2.7, 3.23)	0.106 (0.0699, 0.159)
%CV	103	91.2	187	112	82.8	312
Median (min – max)	11.8 (4.41 - 66.4)	2.49 (1.12 - 12.2)	0.0727 (0.0203 - 1.42)	13.4 (7.73 - 43.9)	2.93 (1.94 - 4.81)	0.079 (0.0258 - 1.26)
Percentiles						
5%	8.33	1.59	0.0367	9.19	2.16	0.0279
25%	10.1	2.04	0.0523	11.7	2.32	0.0426
50%	11.8	2.49	0.0727	13.4	2.93	0.079
75%	14.5	3.06	0.116	16.6	3.48	0.239
95%	26.5	4.03	0.453	33.6	4.63	1.09

%CV=percentage of the coefficient of variation; 3TC=lamivudine; AUC0-τ,ss=area under the plasma drug concentration-time curve from predose to the end of the dosing interval at steady state; CI=confidence interval; Cmax,ss= maximum plasma concentration at steady state ; Cmin,ss=minimum plasma concentration at steady state; DTG=dolutegravir; FDC=fixed-dose combination; geomean=geometric mean; max=maximum; min=minimum; N= number of subjects with available information; PK=pharmacokinetic; ss=steady state
Source: Applicant's popPK report, Table 21, page 78

7. Clinical Virology

Virologic Failure and Resistance

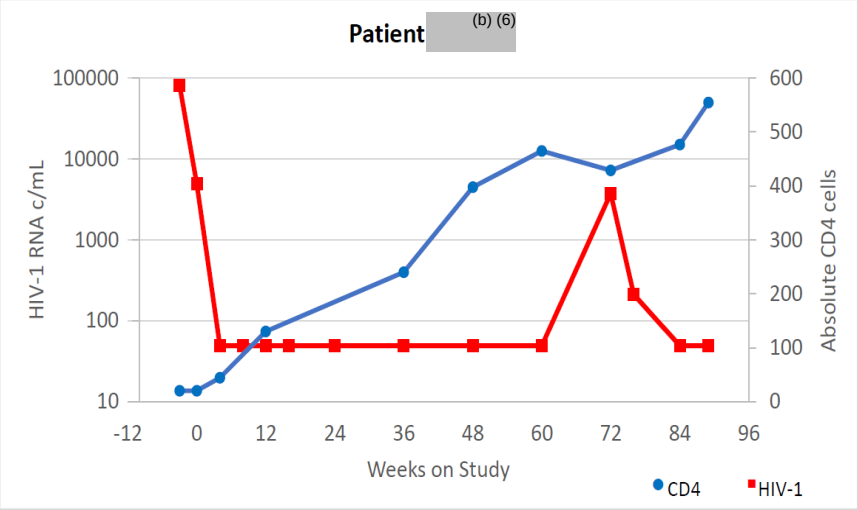
All available data submitted including primary endpoint (Week 48) through Week 96 were used to assess virologic failure and development of resistance.

One subject (PID [redacted] (b) (6)) with HIV-1 subtype AE met confirmed virologic withdrawal criteria (HIV-1 RNA >200 copies/mL) at Week 72. The subject entered the study with HIV-1 RNA at 4936 copies/mL and was suppressed through Week 60 with HIV-1 RNA of <40 copies/mL. At Week 72, their HIV-1 RNA increased to 3752 copies/mL and was confirmed 4 weeks later upon subsequent testing with an HIV-1 RNA of 210 copies/mL. The subject resuppressed and at Weeks 84 and 96, on study and on study drug had an HIV-1 RNA of <40 copies/mL. The Baseline genotypic and phenotypic testing showed no evidence of pre-existing NRTI or INSTI resistance (no resistance to 3TC or DTG). Samples drawn at suspected virologic failure failed to amplify and no genotypic or phenotypic data are available for this timepoint.

We requested the applicant attempt again to obtain INSTI and NRTI genotypic and phenotypic resistance data for the Week 72 sample (viral load = 3752 copies/mL) for this subject.

The Week 72 sample was tested multiple times and the applicant does not believe that further testing would result in any additional data. The Day 1 sample (after 3 attempts) did produce both genotypic and phenotypic results for PR, RT and IN. Unfortunately, the Week 72 timepoint only produced genotypic and phenotypic results for PR and RT. All 3 attempts of producing IN genotypic and phenotypic results failed. Results from Week 72 testing showed no emergent lamivudine-associated resistance and with no results from IN testing, there were no available results to assess emergent dolutegravir-associated resistance.

The subject's virus was able to fully resuppress after confirmed virologic withdrawal and remain suppressed through to the withdrawal visit (three months later) and an additional increase of 126 $CD4^+$ cells observed from the suspected virologic withdrawal through to withdrawal.



Summary
One subject met confirmed virologic withdrawal criteria through Week 96. This subject had no detectable treatment emergent NRTI resistance (INSTI result unavailable) through Week 96.

No new information was added to Section 12.4 of the DOVATO package insert.

8 Safety

Overview

The data for the safety review are the Week 48 results from the DANCE study using the ITT-E population n=32. Using the Applicant's SDTM and AdaM datasets, the primary clinical reviewer verified the key safety analyses presented in this section using JMP 16.1.0 and JMP clinical 8.0. The Applicant used MedDRA version 23.0 for coding. The Division of AIDS (DAIDS) Table for grading the Severity of Adult and Pediatric Adverse Events (AEs), version 2.1 (March 2017) was used to determine severity of AEs. In this section AEs refer to events regardless of causality and Adverse Drug Reactions (ADR) refer to events that are at least possibly related to study drug. Overall, the safety findings are consistent with those of the applicant, and no new significant safety issues were identified that are not currently included in labeling.

Table 14 provides a summary of reported treatment emergent adverse events, SAE's (serious adverse events), and Deaths through week 48.

Table 12. Overview of reported adverse events through week 48

Treatment emergent events	DTG/3TC FDC N=32 (%)
Any AE	28(88)
Grade 1 to 2 AEs	27(84)
Grade 3 AEs	1(3)
Grade 4 AEs	0(0)
Drug-related AEs (*Grade 3)*	1(3)
AEs leading to study withdrawal	1(3)
Serious Adverse Events (SAEs)	2(6)
Deaths	0(0)

Source: Clinical Reviewer's Analysis of ADLS, ADLB, and ADVS datasets (DANCE); JMP 16.1.0

Deaths

There were no deaths reported in the DANCE study.

Serious Adverse Events (SAEs)

Two SAEs were reported (anal abscess and vulvovaginal warts) and both were considered not related to study drug.

Dropouts or Discontinuations Due to Adverse Events

One Grade 3 event of glomerular filtration rate decrease was reported and led to study drug withdrawal (see description in section below for details).

Treatment emergent adverse events

Table 15 contains summarizes the most common adverse events reported in ≥ 2 participants through week 48. As displayed in Table 14 most adverse events reported were grade 1 or 2 (84%) and included nasopharyngitis, folliculitis, upper respiratory tract infection, allergic cough, anal abcsess, decreased apettite, genital herpes, headache, pharyngitis, allergic rhinitis, and vulvogaginal candidiasis. None of these events were considered to be study drug related, which is reasonable.

Table 13 Most common adverse events (reported in ≥ 2 participants)

Preferred Term	DTG/3TC FDC N=32 (%)
Any adverse event	28(88)
Nasopharyngitis	6(19)
Folliculitis	3(9)
Upper respiratory tract infection	3(9)
Allergic cough	2(6)
Anal abscess	2(6)
Decreased appetite	2(6)
Genital herpes	2(6)
Headache	2(6)
Pharyngitis	2(6)
Rhinitis allergic	2(6)
Vulvovaginal candidiasis	2(6)

Source: Clinical Reviewer's Analysis of ADLS, ADLB, and ADVS datasets (DANCE); JMP 16.1.0

Only one event was considered drug related. One Grade 3 event of glomerular filtration rate decrease was reported and led to study drug withdrawal. The Applicant was queried on this event (IR dated November 9, 2023) and details of the event are as follows based on the Applicant's response to IR:

Case details as reported by Applicant:

- Grade 3 non-serious adverse event (AE) of Glomerular filtration rate decreased was reported in an asymptomatic 17-year-old male participant (PID (b) (6)) on study days 114 and 160. Although this led to withdrawal from the study at study day 164, Creatinine was normal throughout.
- At baseline, the participant had no underlying renal or other medical conditions, normal Creatinine, Grade 2 creatinine based eGFR, normal Cystatin C and a BMI of 18.95 kg/m^2 (based on a height of 165 cm and a weight of 51.6 kg)
- There were no concomitant medications at this or later timepoints during the study. Before the eGFR decreased events, the participant experienced four Grade 1 non-serious AEs, including ocular discomfort (day 6), oropharyngeal discomfort (day 27), hordeolum (day 81), and productive cough (day 113). All the events resolved within a maximum of 10 days and did not require any change in treatment.

- The Grade 2 creatinine based eGFR persisted from Baseline up to Week 12 (range from 60 to 64 ml/min/1.73m^2). Two days after Week 16 (day 114), a Grade 3 creatinine based eGFR (58 ml/min/1.73m^2 with normal Creatinine) was assessed by the Site PI as related to study medication, resulting in study drug being held. Grade 3 eGFR persisted with re-testing on study days 122 and 128 (although normal Creatinine),but improved to Grade 2 on the final re-test day 135 (68ml/min/1.73m^2). Study drug was restarted on study day 133.
- Additionally, urinalysis at Week 16 and follow-up visits were negative for protein and blood, and urinary albumin-to-creatinine ratio and urinary protein-to-creatinine ratio were normal at Baseline, Week 12, and follow-up visits. Creatinine was also normal from Baseline throughout the study. Cystatin C and Cystatin C based eGFR were normal at Baseline, although they were not further tested during the study. No treatment was required due to the AE of Glomerular filtration rate decreased, and there were no renal AEs reported for this participant.
- Eight days prior to the Week 24 timepoint (day 160), another Grade 3 eGFR (59 ml/min/1.73m^2 with normal Creatinine) considered related by the investigator was observed and resulted in permanent study drug discontiuation (day 164). Follow-up results (up to day 192) showed improvement to a Grade 2 eGFR with return to Baseline values (range from 61 to 66 ml/min/1.73m^2). No further data were reported for this participant.

<u>The Applicant's position on grade 3 event:</u>

- Withdrawal from the study treatment due to the Grade 3 decrease eGFR reflected a conservative interpretation of protocol (Protocol Amendment 2) toxicity management guidance effective at the time of the event, and because of this event, the protocol was amended to allow for more flexibility in the management of decline in renal function.
- The eGFR decrease reflects a limitation of the formula being used for the participant per protocol guidance for pediatric patients (Bedside Schwartz). As this participant was at the cutoff for using adult formulas, it has been noted that use of CKD-EPI Creatinine Age, Sex Equation (2021) would have resulted in normal eGFR values for a 17-year-old male.

<u>Clinical Reviewer Assessment on Grade 3 event:</u>

DTG is known to have an inhibitory effect on the renal organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine, this pharmacodynamic effect has been shown to have no impact on renal function as reflected in current labeling. This finding is consistent with the patient maintaining normal renal function and creatinine levels throughout the study. It is difficult to ascertain whether this event occurred as a result of the study drug and/or the use of the pediatric versus adult eGFR calculation formulas. This case did not warrant labeling updates.

There were no Grade 4 AEs reported.

There was one pregnancy reported at Week 60. The participant discontinued study medication on Week 60 and initiated treatment with Tenofovir, Lamivudine Dolutegravir, FDC (300mg/300 mg/50 mg). This FDC is available in Kenya where this participant resides.

The applicant provided additional details on the pregnancy as follows:

The 18-year-old participant reported that she attended antenatal clinics and received folic acid and ferrous sulphate. At 40 weeks of gestation, the participant gave birth to a male neonate via spontaneous vaginal delivery, with no apparent congenital anomaly. Birth weight was 2690 grams (5 pounds15 ounces). APGAR scores were 9 and 10, indicating the neonate was born in good health. The neonate was discharged on nevirapine and zidovudine and the mother continued with Tenofovir, Lamivudine Dolutegravir, FDC (300mg/300 mg/50 mg).

This single case report with a positive pregnancy outcome, as reported by the Applicant, does not warrant a labeling update at this time.

Adverse events of special interest

The safety issues discussed below were selected for further discussion based on known effects of one or more of the individual components of DOVATO (dolutegravir and lamivudine), known class effects; and the clinical review of the original NDA 211994 application which included the submission-specific safety issues of immune reconstitution inflammatory syndrome events, drug hypersensitivity and rash, hepatobiliary disorders, psychiatric disorders including suicidality/suicidal ideation and behaviors/suicidality events, other psychiatric adverse events, depression events, gastrointestinal disorders, musculoskeletal disorder, renal disorders.

Immune reconstitution inflammatory syndrome (IRIS) events

There were no IRIS events through week 48.

Drug hypersensitivity and rash

Three participants (9%) reported a skin reaction and included Grade 1 dermatitis allergic reaction, Grade 1 contact dermatitis, and Grade 2 pruritic rash. A hypersensitivity reaction was also reported in one participant; however, this was determined to be an allergy to amoxicillin/clavulanic acid. The onset of the three skin reaction events with respect to treatment duration were reported as follows:

- Grade 1 dermatitis allergic reaction occurred at study day 132 and resolved on study day 135 without interruption of study intervention

- Grade 1 contact dermatitis occurred at study day 126 and resolved on study day 128 without interruption of study intervention
- Grade 2 pruritic rash occurred at study day 169 and resolved on study day 253 without interruption of study intervention

None of these events were considered study drug related. The causality assessments are reasonable considering both grade 1 events spontaneously resolved within 2 to 3 days of onset and occurred about 31 weeks after initiation of treatment with DOVATO. The grade 2 pruritic rash occurred 42 weeks after initiating DOVATO and resolved without study drug interruption. This lack of temporal relationship between the events and treatment initiation suggests the skin reactions are unlikely to be related to the use of DOVATO as drug sensitivity/allergic events typically occur within hours to days after starting treatment.

There were no reports of Grade 3 or higher rashes and no reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme.

Hepatobiliary disorders

No reports of hepatobiliary disorders

Psychiatric disorders including suicidality/suicidal ideation and behaviors/suicidality events

Three participants reported psychiatric disorder AEs including a grade 1 conversion disorder, grade 2 depression/ suicidal, and grade 2 suicidal ideation. None of the AEs were considered to be drug-related by the Investigator.

The two participants who experienced depression/suicidal and suicidal ideation events both had a history of psychiatric conditions. These events are currently labeled in section 6, Adverse Reactions, of the DOVATO USPI.

The grade 1 event of conversion disorder was reported as ‘hysteria’ in a 17-year-old female participant from Kenya. The participant experienced hysteria for one day; she initiated study treatment on (b) (6) followed by onset of hysteria episode on (b) (6) The participant had no reported psychiatric medical history. The causality assessment is difficult to ascertain because of timing of the event in relation to initiating DOVATO, the lack of severity, and the rapid resolution of the event, despite continued treatment with DOVATO. The hysteria event occurred 2 days after initiating treatment with DOVATO and was considered non-serious grade 1 and resolved within 24 hours. At this time, this one case does not warrant label updates.

Gastrointestinal disorders

Five participants (16%) experienced grade 1 gastrointestinal disorder events inclusive of abdominal pain upper, aphthous ulcer, food poisoning, hemorrhoids,

hyperchlorhydria, and nausea. These events were reported as not related to study drug.

The labeling of the DOVATO USPI currently lists gastrointestinal disorders in section 6, Adverse Reactions, specifically abdominal pain. Labeling updates are not warranted at this time.

Musculoskeletal disorders

Musculoskeletal and connective tissue disorders were reported in 3 participants (9%) and included a grade 1 arthralgia, grade 1 myalgia, and grade 2 back pain. These events were reported as not related to study drug. Both arthralgia and myalgia are listed in subsection 6.2, post marketing adverse reactions of the DOVATO USPI, it is reasonable these events could have been attributed to study drug. Additional labeling updates based on these events are not warranted at this time.

Renal disorders

The grade 3 glomerular filtration rate decrease was discussed above in detail. No labeling updates are warranted at this time.

Laboratory Findings

Clinical laboratory measurements were collected at different time points throughout the study, in general there were no new additional safety findings in the adolescent population. The sections below discuss the week 48 (post baseline) reported laboratory graded abnormalities.

General Chemistries

Table 17 below outlines the chemistry graded laboratory abnormalities. The majority of the laboratory abnormalities were grade 1 or 2. Grade 3 or 4 abnormalities are discussed further below. Updates to the labeling based on these abnormalities are not warranted at this time.

Table 14.Chemistry Graded Laboratory Abnormalities through week 48

Parameter	**DTG/3TC FDC N=32(%)**
Alanine Aminotransferase	
Grade 1	1(3)
Alkaline Phosphatase	
Grade 1	1(3)
Grade 2	2(6)
Aspartate Aminotransferase	
Grade 1	1(3)
Bilirubin	

Grade 1	1(3)
Calcium	
Grade 2	1(3)
Grade 4	1(3)
Carbon Dioxide	
Grade 1	12(38)
Grade 2	5(16)
Grade 4	2(6)
Creatinine Kinase	
Grade 1	1(3)
Creatinine	
Grade 1	2(6)
GFR from Creatinine Adjusted for BSA (mL/min/1.73m^2)	
Grade 2	13(41)
Grade 3	6(19)
Glucose	
Grade 1	5(16)
Grade 2	1(3)
Potassium	
Grade 1	1(3)
Sodium	
Grade 1	5(16)
Grade 2	1(3)

Source: Clinical Reviewer's Analysis of ADLB datasets; JMP 16.1.0

Grade 4 increase in calcium (3.42 mmol/L; reference range: 2.2-2.55) was reported in 1 participant at Week 16; calcium was within the reference range at all other timepoints before and after Week 16.

Two Grade 4 low carbon dioxide/low bicarbonate abnormalities were reported by the applicant as follows:

- One participant had a Grade 1 decrease in carbon dioxide at baseline through Week 12. At Week 24 a Grade 4 abnormality (2 mmol/L) was observed. At Week 36 and 48 the abnormality was Grade 1 but increased to Grade 2 at Week 72. The participant did not have any signs of renal impairment or metabolic acidosis or relevant AEs at the same time as the Grade 4 abnormality nor at the other scheduled laboratory assessments.

- Another participant also had a Grade 1 decrease carbon dioxide at baseline and at week 48. Decreased carbon dioxide observations fluctuated between Grade 2 and 4 through Week 60; Grade 4 (2mmol/L) at Week 8, Grade 2 (2 mmol/L) at Week 12 and Grade 4 (6 mmol/L) at Week 60. There were no signs of renal impairment or relevant AEs at these timepoints.

Given the 19 cases of graded carbon dioxide abnormalities the Applicant assessed the changes from baseline over time as shown in Table 16 below. A small, but stable decrease is observed at Week 4 to 36 and at Week 48.

The Applicant assessment appears reasonable in that the decreases in carbon dioxide were not clinically significant and no consistent pattern for the decreases was apparent. There were no cases of metabolic acidosis or renal toxicity reported in these participants, indicating the labs were not of clinical significance. Of note 4 of the 5 Grade 2 and both Grade 4 abnormalities occurred at the same site and maybe related to a laboratory sample handling issue.

Table 15. Carbon Dioxide measurement changes from baseline

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Population: Safety Data as of: 04FEB2022

Table 3.20
Summary of Chemistry Changes from Baseline by Visit at or prior to Week 48

Test (units)	N	Actual Relative Time	n	Mean	SD	Median	Q1	Q3	Min.	Max.
Carbon Dioxide (mmol/L)	32	Baseline	32	21.78	2.574	22.00	21.0	23.0	13.0	26.0
		Week 4	28	-1.42	2.207	-1.00	-2.0	-0.5	-8.0	3.0
		Week 8	30	-0.97	3.469	-1.00	-2.0	1.0	-16.0	5.0
		Week 12	31	-0.90	2.625	-1.00	-3.0	1.0	-5.0	7.0
		Week 16	29	-1.11	2.432	-1.00	-2.1	1.0	-7.0	4.0
		Week 24	28	-0.75	4.858	-0.50	-2.0	0.5	-19.0	10.0
		Week 36	29	-0.86	2.850	-1.00	-2.0	0.0	-7.0	7.0
		Week 48	28	0.18	2.056	0.00	-1.0	1.0	-4.0	7.0

Source: Table 3.20 DANCE CSR and clinical reviewer's analysis of ADLB datasets using JMP clinical 16.1.0

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Liver Findings

There were no Hy's Law cases that occurred in the DANCE study. ALT, AST, Bilirubin abnormalities were all grade 1 or 2.

Renal Findings

Creatinine

A mean change from Baseline of 14.63 µmol/L (range: −2.7 to 52.2 µmol/L) was observed after 48 weeks of treatment. These findings are aligned with the current labeling in the DOVATO USPI.

Estimated Glomerular Filtration Rate

Grade 3 post-baseline treatment-emergent eGFR decreases from creatinine adjusted for BSA was reported in

- Three (9%) participants through Week 24
- Six (19%) participants through Week 48

- The case narratives reported that one of these participants had an intercurrent infection diagnosed at the timepoint of, and after the Grade 3 result. There were no associated AEs in the renal and urinary disorders and signs of renal impairment (assessed using cystatin or urinalysis) for the remaining 5 participants. Of these, 4 participants (including 1 participant who had a Grade 3 eGFR at Week 4, consistent with the timing of known DTG effect on creatinine due to the effect on the OCT2 transporter) had an improvement in renal function with continued treatment with study intervention. The other pariticpant discontinued treatment and was discussed above.

Grade 2 eGFR decreases from creatinine adjusted for BSA was reported in

- Thirteen (41%) participants up to Week 48

All participants experienced increases in creatinine. DTG is known to inhibit OCT2, mild serum creatinine elevations are expected and consistent with what has been seen in the adult studies.

One participant experienced a Grade 3 GFR decreased which is discussed above in more detail.

No additional renal or urinary AEs were reported in the DANCE study.

Urinary albumin-to-creatinine (uACR)/protein-to creatinine ratios (uPCR)

As outlined in Table 17 below, median uACR and uPCR changes from baseline remained stable at Week 12, Week 24, and Week 48.

Table 17: Changes from Baseline by visit for Urine Albumin/Creatinine ratio and Urine Protein/Creatinine Ratio

Changes from Baseline by visit for Urine Albumin/Creatinine Ratio (g/mol)				
	Baseline	Week 12	Week 24	Week 48
Mean	1.31	-0.26	-0.61	5.31
Median	0.65	0.05	0.15	-0.05
Changes from Baseline by visit for Urine Protein/Creatinine Ratio (g/mol)				
	Baseline	Week 12	Week 24	Week 48
Mean	12.74	-0.68	-0.22	0.02
Median	9.00	-0.30	0.35	-0.30

Source: Clinical Reviewer's Analysis of ADLB datasets

Through week 48, five participants had elevated uACRs above the upper limit of normal (ULN), of which one participant had an uACR value of 81 g/mol accompanied by an elevated creatinine level and grade 3 eGFR. This participant was diagnosed with an intercurrent infection at the abnormal timepoint measurements. The

information provided on this participant is suggestive of other factors affecting these laboratory abnormalities.

Through week 48, seven participants had elevated uPCRs above the ULN, one of which had elevated creatinine levels and was described in the preceding paragraph. All other participants with elevated uPCR values did not have abnormal creatinine levels.

Labeling updates are not warranted at this time.

Lipid Parameters and Hematology Parameters

Lipid and hematology parameters were reviewed and the observed trends were consistent with previously observed trends for INSTI+NRTI regimens.

Lipid parameters

Cholesterol and triglycerides toxicities were all grade 1 or 2. Mean (and median change) from baseline in fasting lipids at week 48 were as follows:

- Direct LDL: −0.04mmol/L (−0.03 mmol/L)
- Direct HDL: +0.19 mmol/L (0.20 mmol/L)
- Triglycerides: +0.10 mmol/L (0.07 mmol/L)
- Total Cholesterol: +0.25mmol/L (0.40 mmol/L)

Hematology Parameters

Hematology toxicities were all grade 1 or 2. Mean (and median change) from baseline in hematology parameters at week 48 were as follows:

- Hemoglobin: 4.87 g/L (3 g/L)
- Neutrophils: 0.59×10^9 L (0.69×10^9 L)
- Leukocytes was 0.99×10^9L (1.00×10^9 L).

These events were not clinically significant and do not warrant a labeling update at this time

Tanner Staging

At Screening the participants had Tanner staging score II to V (sexual maturity rating). As expected in the growing adolescent population, tanner scores increased from baseline through Week 48.

Electrocardiograms

A 12-lead ECG was performed at baseline. No additional ECGs were required per protocol and as such no treatment emergent findings to report.

Vital Sign Measurements

Expected changes were observed in height and weight in this growing adolescent population. One participant experienced a grade 1 worsening obesity AE which was not considered study drug related. The causality assessment is reasonable but also plausible that DOVATO might have played a role in the worsening of this participant's weight given the current labeling for DOVATO in the post-marketing subsection of weight increase.

Blood pressure and heart rate were recorded at the screening visit to provide a baseline assessment. No additional assessments were conducted per protocol and as such there are no treatment emergent findings to report.

Safety Analyses by Demographic Subgroups

Sex

In the DANCE study most participants were male, roughly 66 % (21/32) as seen in Table 4 above. As outlined in Table 21, 59% of males experienced an adverse event as compared to 28% of females. Interpretation of the clinical significance with respect to sex differences for adverse events is difficult due to the small sample size of females enrolled. The most commonly reported events in both males and females were common cold and upper respiratory tract infection.

Table 16. Any Treatment Emergent AEs by Sex

	DTG/3TC FDC N=32 (%)
Males	19 (59)
Females	9 (28)

Source: Clinical Reviewer's Analysis of ADAE datasets; JMP 16.1.0

Table 17.Study Drug Related AEs by Sex

	DTG/3TC FDC N=32 (%)
Males	1(3)
Females	0

Source: Clinical Reviewer's Analysis of ADAE datasets; JMP 16.1.0

Table 18. Most Commonly reported AEs, All Grades, Irrespective of Causality, by Sex

Preferred Term	Males N=19 (%)	Females N=9 (%)
Common Cold	4 (21)	2 (22)

Upper Respiratory tract Infection	1(11)	2(22)

Source: Clinical Reviewer's Analysis of ADAE datasets; JMP 16.1.0

Race

The DANCE study was conducted in Asian and African countries and as such 59% of participants were Asian and 41% were Black. In this trial, no differences in safety were observed between the racial groups and do not warrant any label changes.

Age

The DANCE study only enrolled adolescents therefore analysis by age was not warranted.

Safety Update Report

This safety update provided additional available safety data for DOVATO from the DANCE study through May 16, 2023 (original sNDA provided data through Feb 4, 2022) including summaries of deaths, SAEs, AEs leading to withdrawal, pregnancies, and laboratory toxicities, as well as the post-marketing data as outlined below:

- Deaths: no new deaths occurred
- SAEs: Two additional SAEs reported in two participants of contact lens related corneal ulcer in both eyes and major depression, neither of which were considered related to the use of DOVATO and treatment was not interrupted
- No AEs leading to withdrawal
- No pregnancies reported
- Laboratory toxicities: one grade 2 eGFR decrease with normal creatinine levels (considered study drug related), one grade 1 proteinuria, and one grade 2 LDL abnormality
- Post-marketing data: no new safety signals identified from post-marketing reports

Overall, this report did not identify any new safety signals or safety concerns that warranted label updates.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The use of DOVATO in adolescent patients 12 years of age and older and weighing at least 25 kg is supported by the following:

- Open-label study (DANCE) in adolescent participants
- DOVATO population PK models
- Pivotal phase 3 trials in adults, GEMINI-1 and GEMINI-2, and TANGO

DANCE is a study conducted to fulfil the required pediatric assessments under PREA (21 U.S.C. 355c), PMR 3590-3 The required pediatric assessments were issued in the initial approval letters for DOVATO dated April 8, 2019 (DOVATO Approval letter) and the subsequent PMR release and reissue letter dated March 7, 2022(PMR release and reissue letter).

11.Other Relevant Regulatory Issues

None.

12. Recommendations/Risk Benefit Assessment

- Regulatory Action

We recommend approval of this sNDA for DOVATO to expand the treatment population to include adolescents aged ≥12 years and weighing ≥25 kg.

Our recommendation is based on review of the PK, safety, and efficacy (antiviral activity) data from the DANCE study; in addition, our recommendation also considered the available adult PK, safety, and efficacy data from the adult studies, GEMINI-1, 2, and TANGO. Approval of this sNDA will expand the FDC treatment options for adolescents with HIV-1 infection.

- Benefit Risk Assessment

Because the course of HIV infection and the effects of ARV drug products are considered sufficiently similar in pediatric and adult patients, pediatric efficacy of ARV drug products is generally extrapolated from adult trials based on matching the PK between adults and pediatrics. In addition to PK, safety and HIV-RNA data to assess antiviral activity are collected during the pediatric studies. The design of the DANCE trial was consistent with the Guidance for Industry: Pediatric HIV Infection: Drug Product Development for Treatment. (https://www.fda.gov/media/113319/download)

The PK in adolescents was similar to treatment-naïve and virologically suppressed adults based on data reviewed from the DANCE study and additional evidence derived from previously reviewed adequate and well-controlled studies in adults GEMINI-1, GEMINI-2 (treatment-naïve adults) and TANGO (virologically suppressed adults). The totality of these data provide support for the expansion of the use of DOVATO in the adolescent population.

The DANCE safety data through Week 48 suggests that DOVATO is generally safe and well-tolerated in adolescent participants. There were no deaths or drug related SAEs. There was one Grade 3 clinical event of decreased glomerular filtration rate that lead to discontinuation,and was considered related to the use of DOVATO.

No new or unique safety findings in adolescents compared to adults were observed in the review of the DANCE safety database.

Overall, the safety and efficacy data in adolescent participants from the DANCE trial were comparable to those observed in adults. DOVATO's favorable benefit-risk profile support its use in the adolescent population aged ≥12 years and older and weighing ≥ 25 kg.

13.Labeling

This section was updated to reflect the changes made to the label as described below. The blue font indicates additions and the blue font with strikethrough indicates the deletions.

Prescribing Information and Patient Information

The USPI (United States Prescribing Information) and PPI (Patient Package Insert) have been agreed to and are summarized below.

The labeling has been updated to reflect changes in the indication, extending the use of DOVATO in adolescents 12 years of age and older and weighing at least 25 kg. Changes were also made to subsection 8.2, Lactation, to align updated treatment guidelines.

Corresponding changes from the full prescribing information was made to Patient Information.

Please note that the numbering in this section is that of the label only and is different than the numbering in the rest of this review.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DOVATO is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older and weighing at least 25 kg with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies ~~per~~ /mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of DOVATO.

2.2 Recommended Dosage

DOVATO is a fixed-dose combination product containing 50 mg of dolutegravir and 300 mg of lamivudine. The recommended dosage regimen of DOVATO in adults and adolescents 12 years of age and older and weighing at least 25 kg is one tablet taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]*.

Rationale: The DANCE study enrolled 32 adolescent participants aged 12 to less than 18 years of age weighing at least 25 kg.The PK in adolescents was similar to treatment-naïve and virologically suppressed adults based on data reviewed from the this study and additional evidence derived from previously reviewed adequate and well-controlled studies in adults GEMINI-1, GEMINI-2 (treatment-naïve adults) and TANGO (virologically suppressed adults). The totality of these data provide support for the expansion of the use of DOVATO in the adolescent population.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Clinical Trial Experience in Adolescents

The safety of DOVATO was evaluated in HIV-1 infected treatment-naïve subjects between the ages of 12 to less than 18 years and weighing at least 25 kg (N = 32) through Week 48, in an open label clinical trial, DANCE (Trial 205861). Overall, the observed safety profile in adolescent subjects was similar to those seen in adults *[see Use in Specific Populations (8.4), and Clinical Studies (14.4)].*

Rationale: The DANCE safety data through Week 48 suggests that DOVATO is generally safe and well-tolerated in adolescent participants. No new or unique safety findings in adolescents compared to adults were observed in the review of the DANCE safety database.

8.2 Lactation

Risk Summary

~~The Centers for Disease Control and Prevention recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.~~

Dolutegravir and lamivudine are present in human milk. There is no information on the effects of DOVATO or the components of DOVATO on the breastfed infant or the effects of the drugs on milk production.

~~Because~~Potential risks of ~~the potential for~~breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults~~,~~ instruct mothers not to breastfeed if they are receiving DOVATO.

Rationale: Language was updated based on revised CDC and DHHS perinatal HIV Treatment Guidellines

8.4 Pediatric Use

The safety and efficacy of DOVATO for the treatment of HIV-1 infection have been established in adolescents 12 years of age and older and weighing at least 25 kg. Use of DOVATO for this indication is supported by DANCE trial in treatment-naïve adolescents and evidence from adequate and well-controlled trials in adults, GEMINI-1, GEMINI-2 (treatment-naïve adults) and TANGO (virologically suppressed adults) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies(14)]*. Overall, the safety and efficacy data in adolescent subjects from the DANCE trial were comparable to those observed in adults, and there was no clinically significant difference in exposure for the components of DOVATO *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]*.

The safety and efficacy of DOVATO have not been established in pediatric patients less than 12 years of age or weighing less than 25 kg.

Rationale: Updated to include supportive trial information for use in the pediatric population with information from DANCE trial and previously reviewed GEMIN-1, 2 and TANGO studies.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Pediatric Subjects: In adolescents receiving DOVATO, dolutegravir and lamivudine exposures were higher as compared to adults; however the differences in exposure were not considered clinically significant. Lamivudine and dolutegravir exposures were within the observed ranges at the recommended doses in adults and pediatrics receiving the individual components of DOVATO (Table 8).

Table 8. Pharmacokinetic Parameters Following Dovato in Adolescent Subjects Aged 12 to Less than 18 Years Weighing at Least 25 kg (n = 32)

		Pharmacokinetic Parameter Estimates Geometric Mean (CV%)		
Age/weight	Dose	$AUC_{(0-24)}$ mcg·h/mL	C_{max} mcg/mL	C_{24} mcg/mL
12 to <18 years and ≥25 kg	Dolutegravir 50 mg once daily	78.2 (91.6)	6.71 (69.5)	1.46 (154)
12 to <18 years and ≥25 kg	Lamivudine 300 mg once daily	14.7 (112)	2.95 (82.8)	0.106 (312)

Rationale: Updated to include PK data from DANCE trial that supported the expansion of the indication down to the adolescent age group.

Drug Interaction Studies

Change: Drug interaction information for Daclatasvir was removed.
Rationale: Information was removed as the product is no longer available as a US marketed product.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

14.4 Clinical Trial Results in Adolescent Subjects

The 48 week efficacy of DOVATO was evaluated in an open-label multicenter trial (DANCE) in 30 evaluable treatment-naïve HIV-1–infected adolescents aged 12 to less than 18 years and weighing at least 25 kg. 87% (26/30) of subjects achieved HIV-1 RNA <50 copies/mL at Week 48, and the mean increase from baseline in CD4+ cell count was 234 cells/mm^3 at Week 48 *[see Adverse Reactions (6.1), Use in Specific Population (8.4) and Clinical Pharmacology (12.3)].*

Rationale: Updated with information efficacy findings from the DANCE trial as described in the efficacy section above.

16 HOW SUPPLIED/STORAGE AND HANDLING

Blister pack of 30 tablets with child-resistant closure NDC 49702-246-33.

Rationale: Updated with blister pack availability and supported by previous CMC only supplement, S20. This update was missed during the S20 approval.

17 PATIENT COUNSELING INFORMATION

Lactation

~~Instruct mothers~~Inform individuals with HIV-1 infection ~~not to breastfeed because~~that the potential risks of breastfeeding include: (1) HIV-1 ~~can be passed to the baby~~ transmission (in ~~the breast milk~~HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults *[see Use in Specific Populations (8.2)]*.

Rationale: Updated to align with updated CDC and DHHS perinatal guidelines.

14. Recommended Comments to the Applicant

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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