Clinical Review, Cross-Discipline Team Leader (CDTL) Review, and Division Director Summary Review

Date	January 4, 2022
From	Stephanie Troy, MD (Clinical Reviewer) Sarah Connelly, MD (CDTL) Yodit Belew, MD (Associate Director for Therapeutic Review)
Subject	Combined Clinical Review, CDTL Review, and Division Director Summary Memo
NDA/BLA #, Supplement#	NDA 210806 S-07 NDA 210807 S-08
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	July 27, 2021
PDUFA Goal Date	January 27, 2022
Proprietary Name / Established (USAN) names	PIFELTRO (doravirine, or DOR) and DELSTRIGO (DOR/3TC/TDF)
Dosage forms / Strength	100 mg tablet (DOR) and 100 mg/300 mg/ 300 mg fixed dose combination tablet (DOR/3TC/TDF) for oral use.
Indication	Treatment of HIV-1 infection in adult and pediatric patients weighing at least 35 kg
Dosing Regimen	100 mg once daily by mouth (DOR) or 100 mg/300 mg/300 mg once daily by mouth (DOR/3TC/TDF)
Recommended:	Approval

1. Introduction

This review summarizes the data package submitted by Merck to support labeling changes for PIFELTRO and DELSTRIGO to expand treatment to pediatric patients weighing at least 35 kg. The data package includes the final study report and associated data sets for Protocol Number 027, IMPAACT 2014: "*Phase I/II study of the Pharmacokinetics, Safety and Tolerability of Doravirine (MK-1439) and Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (MK-1439A) in HIV-1 infected Children and Adolescents*." The data package also includes a population pharmacokinetics (PK) analysis to estimate the PK exposure of DOR for 1000 virtual subjects weighing at least 35 kg regardless of age based on the NHANES database. P066, an ongoing study of DOR and DOR/3TC/TDF in subjects 4 weeks to <12 years of age, and an additional planned study in neonates, are not included in this supplement.

The current application partially fulfills the PREA PMR requirements for DOR and DOR/3TC/TDF by fulfilling the following two PMRs:

- NDA 210806 PMR 3415-1:
  - Conduct a study to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of DOR in HIV-1 infected pediatric subjects less than 18 years of age and weighing at least 35 kg. The safety and antiviral activity of DOR in pediatric subjects must be evaluated for a minimum of 24 weeks.

- NDA 210807 PMR 3416-1:
    - Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of DOR/3TC/TDF fixed dose combination (FDC) product in HIV-1 infected pediatric subjects less than 18 years of age and weighing at least 35 kg. Subjects must be followed for a minimum of 24 weeks to assess the safety and antiviral activity of doravirine/lamivudine /tenofovir disoproxil fumarate FDC product. A clinical trial in pediatric subjects weighing at least 35 kg may not be required if dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products.

2. Background

HIV is a significant public health concern, both globally and domestically. At the end of 2020, there were an estimated 38 million people living with HIV globally, and 680,000 deaths related to HIV in 2020 (https://www.who.int/news-room/fact-sheets/detail/hiv-aids). In the United States in 2019, 36,801 people received a new diagnosis of HIV, of whom 1667 were 19 years or younger, and over one million adults and adolescents were living with HIV (https://www.cdc.gov/hiv/statistics/overview/index.html). Without effective treatment, HIV leads to progressive destruction of the immune system and premature death in almost all cases. However, effective treatment can suppress HIV replication, preserve and restore the immune system, reduce HIV-associated morbidity, and ultimately improve long term survival to approximate a normal lifespan.

Standard of care HIV treatment is lifelong and generally involves the administration of two to three drugs from different mechanistic classes targeting different events in the HIV life cycle. Approved drugs belong to eight mechanistic classes: nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (InSTIs), CCR5 antagonists, fusion/entry inhibitors, attachment inhibitors, and CD4-directed post-attachment HIV-1 inhibitors. Six of these eight classes include drugs that have been approved for treatment of HIV-1 in patients <18 years of age (https://www.fda.gov/drugs/hiv-treatment/hiv-treatment-information-children).

Doravirine (DOR) is an NNRTI indicated for the treatment of HIV-1 infection in adults in combination with other antiretroviral (ARV) agents. DOR/3TC/TDF is a fixed-dose combination tablet of DOR plus the previously approved nucleos(t)ide reverse transcriptase inhibitors (NRTIs) lamivudine (3TC) and tenofovir disoproxil fumarate (TDF). DOR/3TC/TDF is indicated as a complete regimen for the treatment of HIV-1 infection in adults. Both DOR and DOR/3TC/TDF were approved for use in treatment-naïve adult patients on August 30, 2018. On September 19, 2019, the indication was expanded to a switch indication for use in patients who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to DOR or DOR/3TC/TDF. This supplement was submitted to expand the indications for DOR and DOR/3TC/TDF treatment to include pediatric patients weighing at least 35 kg.

3. CMC/Device

The drug product used in the clinical trials submitted in these sNDA submissions is identical to the approved tablet formulations of DOR and DOR/3TC/TDF. These sNDA submissions contain no new CMC information.

4. Nonclinical Pharmacology/Toxicology

Extensive nonclinical studies with DOR, 3TC, and TDF have previously been conducted and deemed acceptable. Additional nonclinical data were not needed for this sNDA approval. Please refer to the original NDA for DOR and DOR/3TC/TDF for further details.

5. Clinical Pharmacology/Biopharmaceutics

A summary of the review and conclusions of the clinical pharmacology reviewer, Xiaoxioa Yang, with some additional safety considerations, is described below; please see Dr. Yang's full review for more details. The PK analysis supports the use of the DOR 100 mg daily dose in pediatric patients weighing at least 35 kg.

The PK data in this submission included both the PK analysis from P027, which only enrolled pediatric subjects ≥45 kg into the multiple dose cohort, as well as a population PK analysis to estimate the PK exposure of DOR for 1000 virtual subjects weighing at least 35 kg regardless of age. From the PK analysis from P027, DOR exposures for pediatric patients ≥45 kg are generally comparable with adults. From the population PK analysis conducted by Dr. Eliford Kitabi, DOR exposures for pediatric patients 35 to <45 kg are generally higher compared with Phase 3 adult data.

Use of the 100 mg daily DOR dose in pediatric subjects weighing at least 35 kg is not anticipated to decrease efficacy based on the PK analysis. Statistically significant exposure-response relationships were identified between DOR PK (C_{24} and AUC_{0-24}) and nearly all evaluated efficacy endpoints over the exposures achieved at the 100 mg qd dose in the adult Phase 3 studies (P018 and P021) submitted with the original NDA. A trend of lower efficacy response and higher virologic failure rates were observed for exposures below the 10^{th} percentile (C_{24}=560 nM and AUC_{24}=27.5 µM*hr) in the adult Phase 3 studies. However, pediatric subjects weighing 35 to <45 kg are predicted to have comparable DOR C_{24} and higher DOR AUC_{0-24}, and pediatric subjects ≥45 kg have similar DOR exposure (C_{24} and AUC_{0-24}), compared to adults when taking DOR 100 mg daily.

Use of the 100 mg daily DOR dose in pediatric subjects weighing at least 35 kg is not anticipated to decrease safety based on PK analysis. In the adult Phase 2 and Phase 3 studies, an acceptable safety profile was observed across the range of DOR exposures. The observed incidence of neuropsychiatric adverse events (studies P007 and P021) and the change in lipid profiles from baseline (studies P007, P018, and P021) were similar across different DOR

exposure quartiles (C_{max} and AUC_{0-24}). Pediatric subjects ≥45 kg have similar DOR exposure (C_{max} and AUC_{0-24}) compared to adults when taking DOR 100 mg daily. The projected population means for C_{max} and AUC_{0-24} for pediatric patients 35 to <45 kg are higher compared to adult Phase 3 data with the DOR 100 mg daily dose; however, only 1.9% and 1.3% of simulated virtual pediatric patients are expected to have steady state C_{max} and AUC_{0-24} values exceeding the upper bounds of exposure for safety (C_{max} of 5215 nM and AUC_{0-24} of 98.6 µM*hr) as established in adults.

Of note, labeling for Epivir (3TC) recommends the adult dose (300 mg daily) as a component of HIV-1 treatment for pediatric patients weighing at least 25 kg, and labeling for Viread (TDF) recommends the adult dose (300 mg daily) as a component of HIV-1 treatment for pediatric patients weighing at least 35 kg.

6. Clinical Microbiology

The one subject in P017 who met criteria for protocol-defined virologic failure had no emergence of genotypic or phenotypic resistance to DOR, 3TC, or TDF. Please see Dr. Naeger's review for more details.

7. Clinical/Statistical- Efficacy

7.1 Overview of the Trial Design

P027, or IMPAACT 2014, is an ongoing Phase 1/2 multicenter, open-label, non-comparative study in children and adolescents with HIV-1 infection (age 12 to <18 years, who weigh ≥35 kg). Two cohorts were sequentially enrolled, with enrollment in Cohort 2 dependent on supportive PK and safety results from Cohort 1:

- Cohort 1: Up to 20 subjects who were virologically-suppressed on a combination of an InSTI (dolutegravir or raltegravir) plus two NRTIs were given a single dose of DOR 100 mg on top of their current ARV regimen.
    - The primary objectives were to evaluate PK and 2-week safety and tolerability
    - Cohort 1 remained open with Amendment 2 of the protocol to try to enroll a minimum of 4 evaluable subjects between 35 to ≤45 kg.
- Cohort 2: Up to 45 subjects who were either previously treatment-naïve or virologically-suppressed on an ARV regimen were given once daily DOR/3TC/TDF (100/300/300 mg) as their ARV regimen for a planned duration of 96 weeks
    - The primary objective was to evaluate the 24-week safety and tolerability of DOR/3TC/TDF in HIV-1-infected children and adolescents.
    - PK, virologic efficacy, and immunologic response were secondary objectives
    - Subjects in Cohort 1 were eligible for later enrollment in Cohort 2 as virologically-suppressed subjects.
    - Per Amendment 2, enrollment in Cohort 2 only opened to subjects >45 kg as an insufficient number of subjects between 35 to ≤45 kg had been enrolled into Cohort 1.

- Cohort 2 is ongoing with treatment planned through 96 weeks.

This submission contains complete data for Cohort 1 through Week 2 and for Cohort 2 through Week 24. There were no protocol deviations for Cohort 1 and 7 subjects with protocol deviations in Cohort 2 (all laboratory assessment deviations, 4 for Week 16 sample collections that were not done due to the COVID-19 pandemic). None of the protocol deviations met DAIDS critical events criteria.

7.2 Disposition and Baseline Demographics

In P027 Cohort 1, 11 subjects were screened, 10 subjects were enrolled, and 9 were treated with a single oral DOR 100 mg tablet (the 10th enrolled subject was lost to follow-up after enrollment but prior to dosing). In Cohort 2, 52 subjects were screened, 45 subjects were enrolled and treated, 44 subjects completed treatment through Week 24, and one subject discontinued due to pregnancy after 8 weeks of treatment.

Subject baseline demographics and disease characteristics are summarized in Table 1 below. Notably, only one subject (who was in Cohort 1) weighed <45 kg, and only two subjects in Cohort 2 were treatment-naïve. No subjects in either cohort were co-infected with hepatitis B or C. The most common prior ARV regimens among the 43 virologically-suppressed subjects in Cohort 2 were efavirenz, emtricitabine, and tenofovir disoproxil fumarate (18/43 or 42%), followed by 3TC, nevirapine, and zidovudine (6/43 or 14%) and 3TC, abacavir, and lopinavir/ritonavir (6/43 or 14%).

Table 1: Baseline Demographics and Disease Characteristics in P027

Demographics and Disease Characteristics	**Cohort 1 N=9 n (%)**	**Cohort 2 N=45 n (%)**
Age at Baseline (Years)		
Median	15	15
Min, Max	12, 16	12, 17
Sex		
Male	7 (78%)	19 (42%)
Female	2 (22%)	26 (58%)
Race		
Black or African American	7 (78%)	10 (22%)
White	2 (22%)	0
Asian	0	35 (78%)
Ethnicity		
Hispanic or Latino	0	1 (2%)
Not Hispanic or Latino	9 (100%)	44 (98%)
Country		
South Africa	0	9 (20%)
Thailand	0	35 (78%)
United States	9 (100%)	1 (2%)
Weight at baseline (kg)		

Median	49	52
Min, Max	40, 91	45, 80
Baseline plasma HIV-1 RNA (copies/ml)		
0 - <40	9 (100%)	43 (96%)
500,000 - < 1,000,000	0	2 (4%)
CD4 Cell Count (cells/mm3)		
Median	760	713
Min, Max	449, 1137	84, 1397
ARV Treatment Status		
Virologically-suppressed on ARV	9 (100%)	43 (96%)
ARV treatment-naïve	0	2 (4%)
Among virologically-suppressed subjects only:	*(n=9)*	*(n=43)*
Class of Prior ARVs		
NRTI	9 (100%)	43 (100%)
NNRTI	0	32 (74%)
InSTI	9 (100%)	1 (2%)
PI	0	10 (23%)
Duration of Prior ARVs (days)		
Median	613	1018
Min, Max	97, 1805	98, 5423

Source: Adapted from clinical study report for P027, Tables 10-5, 10-6, and 14.1-3.

7.3 Intervention Compliance and Extent of Exposure

In Cohort 1, the nine subjects included in the as-treated population took the single dose of DOR 100 mg.

In Cohort 2, per an adherence questionnaire, 100% of subjects had ≥90% compliance and 73% (33/45) of subjects had 100% compliance with the study intervention regimen. Duration of treatment was >8 and ≤16 weeks for one subject, >24 and ≤36 weeks for 12 subjects, >36 and ≤48 weeks for 21 subjects, and >48 weeks for 11 subjects by the data cutoff time period for this study report.

7.4 Summary of PK Results

In Cohort 1, all subjects had intensive PK sampling from Day 0 continuing up to 72 hours post-dose (pre-dose and 1-, 2-, 4-, 8-, 12-, 24-, 48-, and 72-hours post-dose). The DOR exposures met the target exposures for Cohort 1; the DOR geometric mean single-dose AUC_{0-inf} was <64.8 µM/h, and the DOR geometric mean predicted $C_{24,ss}$ was >560 nM. The Applicant wrote that the PK from Cohort 1 supported proceeding with the 100 mg DOR dose "for participants weighing ≥45 kg in Cohort 2." Please see the Applicant's table (Table 2) below.

Table 2

Descriptive Statistics for DOR Pharmacokinetic Parameter Values Following Oral Administration of DOR 100 mg Single Dose
All Treated Population, Cohort 1

Descriptive Statistics	Age (yr)	Weight (kg)	AUC0-inf (h.µM)	C24,ss,pred (nM)	C24,SD,obs (nM)	C24 Accum. Ratio	Cmax,ss,pred (µM)	Cmax,SD,obs (µM)	Cmax Accum. Ratio	Tmax (h)	Apparent Terminal t1/2 (h)	CL/F (L/h)	Vz/F (L)
N	9	9	9	9	9	9	9	9	9	9	9	9	9
Geometric Mean	14.3	54.2	34.8	690	514	1.34	2.76	2.14	1.29	-	11.8	6.75	115
Geometric CV (%)	11.2	25.8	43.2	65.8	56.5	11.7	28.2	25.9	10.5	-	25.0	43.2	32.6
Minimum	12.0	40.3	20.0	335	282	1.15	2.08	1.51	1.16	1.00	7.82	3.19	65.7
Median	15.0	48.7	31.3	630	446	1.36	2.70	2.08	1.28	3.78	12.2	7.49	111
Maximum	16.0	90.8	73.6	1720	1240	1.61	5.11	3.73	1.56	7.75	16.0	11.7	198
Mean	14.3	55.9	37.7	812	584	1.35	2.87	2.21	1.30	-	12.1	7.24	120
SD	1.58	15.8	17.1	502	332	0.16	0.928	0.642	0.14	-	2.88	2.71	38.5
CV (%)	11.0	28.3	45.2	61.8	56.8	11.8	32.4	29.1	10.7	-	23.8	37.5	32.2

All doses were adult tablets.

Source: Taken from the clinical study report for P027, Tables 11-1.

In Cohort 2, the first 10 subjects enrolled had intensive PK evaluations on Day 8 (pre-dose and 1-, 2-, 4-, 8-, 12-, and 24-hours post-dose). DOR plasma concentrations were lower than expected from Cohort 1 for Cohort 2 at Week 1, which was felt to be due to CYP3A induction as 8 of the 10 subjects in the intensive PK cohort had switched from efavirenz, a moderate CYP3A inducer; steady state conditions for DOR were not attained at Week 1 for subjects who switched from efavirenz. Day 8 DOR PK parameters are shown in the Applicant's table (Table 3) below.

Table 3:

Descriptive Statistics for Steady State DOR Pharmacokinetic Parameter Values Following Oral Administration of DOR/3TC/TDF Once Daily for Participants with Semi-intensive Sampling
All Treated Population, Cohort 2

Descriptive Statistics	Age (yr)	Weight (kg)	AUC0-24,ss (h.µM)	C0,ss (nM)	C24,ss (nM)	Cmax,ss (µM)	Tmax (h)	CL/F (L/h)
N	10	10	10	10	10	10	10	10
Geometric Mean	15.5	55.1	22.9	266	282	2.13	-	10.3
Geometric CV (%)	9.3	20.0	47.0	61.2	73.8	42.7	-	47.0
Minimum	14.0	45.2	8.03	91.4	76.0	0.80	1.92	6.14
Median	16.0	56.1	24.3	330	347	2.13	1.95	9.67
Maximum	17.0	79.8	38.3	486	596	3.56	3.95	29.3
Mean	15.6	56.1	24.7	301	331	2.27	-	11.4
SD	1.43	11.7	8.82	137	166	0.776	-	6.72
CV (%)	9.2	20.9	35.8	45.3	50.0	34.2	-	58.8

All doses were adult tablets.

Source: Taken from the clinical study report for P027, Tables 11-2.

All subjects in Cohort 2 had sparse PK sampling pre-dose on Day 0 and Week 4; random sampling at Week 8 and Week 12; and pre-dose and 0.5 to 2 hours post-dose at Week 24 and Week 48. At Week 4 through Week 24, the geometric means of the pre-dose (trough) DOR concentrations were >560 nM (the target concentration). One subject, who experienced a protocol-defined virologic failure at Week 24, had DOR, 3TC, and TFV concentrations below

the limit of quantification at Week 8, suggesting missed doses. The DOR PK parameters from the sparse sampling are shown in the Applicant's table (Table 4) below.

Table 4

Descriptive Statistics for DOR Plasma Concentrations (nM) by Nominal Time Following Oral Administration of DOR/3TC/TDF Once Daily for All Participants
All Treated Population, Cohort 2

Study Visit	Time Point	N	Geometric Mean	Geometric CV%	Min	Median	Max	Arithmetic Mean	SD	CV%	Interquartile Range
Baseline	PREDOSE	45	.	.	0.00	0.00	0.00	0.00	0.00	.	(0.00, 0.00)
Week 4	PREDOSE	45	747	108.7	47.2	835	3930	1020	771	75.9	(507, 1340)
Week 8	RANDOM	44	1320	239.1	0.00	1870	3770	1840	937	50.8	(968, 2560)
Week 12	RANDOM	44	2020	49.3	625	2120	6970	2250	1130	50.1	(1590, 2730)
Week 24	PREDOSE	43	1090	63.0	353	1180	3600	1270	700	55.1	(633, 1810)
Week 24	0.5-2 HOURS	43	1870	52.0	533	1820	4150	2080	918	44.1	(1580, 2750)

Interquartile Range = (25th percentile, 75th percentile).
Values below the Lower Limit of Quantification (<1.000 ng/mL) are set to 0.

Source: Taken from the clinical study report for P027, Tables 11-5.

Reviewer Comment: The Applicant's PK data from P027 support dosing in pediatric patients weighing at least 45 kg. Notably, the reduced DOR exposures following cessation of EFV are already included in labeling. To support dosing in pediatric subjects weighing 35 to <45 kg, the Applicant submitted a population PK analysis estimating the PK exposure of DOR for 1000 virtual subjects weighing at least 35 kg regardless of age based on the NHANES database. We agree with the Sponsor that the population PK analysis supports the 100 mg daily DOR dose in pediatric subjects weighing 35 to <45 kg. Please see Section 5 above for a summary of the clinical pharmacology reviewer's assessment of that analysis. A subsection on pediatric patients, including a table on the steady state pharmacokinetics for doravirine in HIV-1-infected pediatric patients aged 12 to less than 18 years and weighing at least 35 kg based on population PK analysis, will be included in section 12.3 (Pharmacokinetics) of the DOR and DOR/3TC/TDF labels

7.5 Summary of Efficacy

Virologic efficacy was measured by HIV-1 RNA levels below defined viral load cutoffs (<40, <50, and <200 copies/mL). The 43 virologically-suppressed subjects in Cohort 2 maintained HIV-1 RNA levels below each viral load cutoff at Week 24, except for two of the 43 subjects who had missing HIV-1 RNA data at Week 24 (one who dropped out of the study due to pregnancy after Week 8 with HIV-1 RNA <40 copies/mL at discontinuation, and one who had missing data for <40 and <50 copies/mL at that timepoint due to low specimen volume but had HIV-1 RNA <200 copies/mL). At each of the prior timepoints (Weeks 0, 2, 4, 8, 12, and 16), between 81 and 100% (35 to 43 out of 43) of subjects had HIV-RNA <40 copies/mL, and 88 to 100% (38 to 43 out of 43) of subjects had HIV-RNA <200 copies/mL. Of the two treatment-naïve subjects, one achieved HIV-1 RNA levels below <200 copies/mL by Week 12 and <50 and <40 copies/mL by Week 16 and then maintained HIV-1 RNA levels below each cutoff through Week 24. The other treatment-naïve subject achieved HIV-1 RNA levels below <200 copies/mL at Week 16 but did not maintain this at Week 24 and was the study's single protocol-defined virologic failure (see next paragraph for more details). Mean CD4 count

increased over 24 weeks by 79 cells/mm^3 in the 43 virologically-suppressed subjects and by 204 cells/mm^3 in the 2 treatment-naïve subjects. See the Applicant's table (Table 5) below for a summary of the efficacy results.

Table 5

Efficacy Analysis at Week 24
All Treated Population, Cohort 2

	Treatment-Naive (N=2)		Virologically-Suppressed (N=43)		Total (N=45)	
	n/N	% [95% CI]	n/N	% [95% CI]	n/N	% [95% CI]
Observed Failure Approach						
Proportion of participants with HIV-1 RNA <40 copies/mL	1/2	50.0 (1.3, 98.7)	41/41	100.0 (91.4, 100.0)	42/43	97.7 (87.7, 99.9)
Proportion of participants with HIV-1 RNA <50 copies/mL	1/2	50.0 (1.3, 98.7)	41/41	100.0 (91.4, 100.0)	42/43	97.7 (87.7, 99.9)
Proportion of participants with HIV-1 RNA <200 copies/mL	1/2	50.0 (1.3, 98.7)	42/42	100.0 (91.6, 100.0)	43/44	97.7 (88.0, 99.9)
FDA Snapshot Approach						
Proportion of participants with HIV-1 RNA <40 copies/mL	1/2	50.0 (1.3, 98.7)	41/43	95.3 (84.2, 99.4)	42/45	93.3 (81.7, 98.6)
Proportion of participants with HIV-1 RNA <50 copies/mL	1/2	50.0 (1.3, 98.7)	41/43	95.3 (84.2, 99.4)	42/45	93.3 (81.7, 98.6)
Proportion of participants with HIV-1 RNA <200 copies/mL	1/2	50.0 (1.3, 98.7)	42/43	97.7 (87.7, 99.9)	43/45	95.6 (84.9, 99.5)
	Mean [n]	(95% CI)	Mean [n]	(95% CI)	Mean [n]	(95% CI)
Change from baseline in CD4 cell count (cells/mm3)	203.5 [2]	(-99.0, 578.3)	79.0 [41]	(12.7, 145.3)	84.8 [43]	(21.1, 148.4)
Change from baseline in CD4 percent	7.3 [2]	(-7.6, 23.1)	-1.9 [41]	(-3.2, -0.7)	-1.5 [43]	(-2.8, -0.2)

Due to low specimen volume, some participants' plasma samples were diluted by a factor of 5 before being tested. This dilution increased the assay's limit of quantification (LoQ) from 40 to 200 copies/mL. In the analysis of proportion of patients with HIV-1 RNA <40 and <50 copies/mL, such records were treated as missing values. Samples for one participant at Week 24 were diluted.
For binary endpoints: n/N with % (95% CI) was reported for each group, where 95% CI is the exact 95% confidence interval.
For continuous endpoints: mean changes with the 95% confidence intervals were reported. The 95% CIs were calculated based on t-distribution.
N = Number of participants in each group; n = Number of participants in each subcategory.

Source: Taken from the clinical study report for P027, Tables 11-8.

As noted above, one treatment-naïve subject in Cohort 2 had protocol-defined virologic failure, defined as 2 consecutive plasma HIV-1 RNA test results ≥200 copies/mL (at or after Week 24 for treatment-naïve subjects). This subject was a 14-year-old Asian female with past medical history of HIV (subtype C), gonococcal infection, latent syphilis, eosinophilia, eosinophilic pustular folliculitis, lice infestation, and intellectual disability who had HIV-1 RNA of 507,507 copies/mL and CD4 count of 84 cells/mm^3 at baseline. After starting on DOR/3TC/TDF daily, her HIV-1 RNA dropped to 6248 copies/mL on Day 14 and a nadir of 183 copies/mL on Day 105 but then increased to 60,050 and 491,843 copies/mL on Day 168 and 203, respectively. Her CD4 count increased to 302 cells/mm3 on Day 28 and 342 cells/mm3 on Day 84 but also decreased on Day 158 to 258 cells/mm^3. Her PK samples on Day 56 were <1.00 µg/L for DOR, 3TC, and tenofovir, suggesting noncompliance with dosing that week, but DOR concentrations were measurable at all other timepoints, and her overall percent compliance was reported as 96.7%. The investigator considered her virologic failure to be possibly due to noncompliance with study medication, and the subject was counseled regarding adherence and allowed to continue with the study medication; the HIV-1 RNA subsequently decreased to 1521 copies/mL on Day 266. The subject had no evidence of baseline HIV-1 resistance substitutions and had no emergence of phenotypic or genotypic resistance to DOR, 3TC, or TDF.

Analysis of efficacy endpoints by demographic factors was generally not informative given the small sample size in this trial. We noted that the CD4 counts in virologically-suppressed

subjects in Cohort 2 decreased from baseline at Week 24 in the 8 black or African American subjects (mean change -165.1 cells/mm^3, 95% CI: -299.1, -31.1) but increased from baseline at Week 24 in the 33 Asian subjects (mean change 138.2 cells/mm^3, 95% CI: 75.7, 200.6); however, the baseline mean CD4 count was substantially higher in the black or African American versus the Asian subjects (892.8 versus 702.1 cells/mm^3), which could help explain this difference. Of note, in the original NDA review for DOR and DOR/3TC/TDF, treatment-naïve black or African American subjects who were taking DOR/3TC/TDF versus EFV/FTC/TDF in study PN021 (DRIVE-AHEAD) had a higher mean CD4 count change from baseline at Week 48 (197 versus 136 cells/mm^3, respectively), with a treatment difference of 60.6 cells/mm^3 (95% CI 2.8, 118.4 cells/mm^3) favoring DOR/3TC/TDF. In addition, the mean change from baseline of CD4+ T cells at Week 48 in PN021 was similar in the 63 black or African American DOR/3TC/TDF recipients compared to all DOR/3TC/TDF recipients (197 versus 198 cells/mm^3, respectively). Therefore, there is not a pattern of decreased CD4 count increases on DOR/3TC/TDF in black or African American subjects across trials.

Patient Experience Data:
All 9 subjects in Cohort 1 reported no problems taking the DOR tablet and thought it tasted average (6/9 subjects) or good (3/9 subjects). In terms of the DOR tablet size and shape, 4/9 subjects thought it was average, and 5/9 thought it was a little large but manageable. All subjects in Cohort 2 were offered the choice of the oral tablet or an oral granule formulation of DOR/3TC/TDF, and all subjects opted to take the tablet. All 45 subjects in Cohort 2 reported no problems taking the DOR/3TC/TDF tablet, and 43/45 (96%) thought it tasted average, good, or very good (2/45 thought it tasted bad). In terms of the DOR/3TC/TDF tablet size and shape, 24/45 (53%) subjects thought it was average, and 21/45 (47%) thought it was a little large but manageable. All 45 subjects thought the daily dosing frequency was "average or not too often".

Reviewer Comment: We agree with the Applicant's proposed description of P027 clinical trial results in Section 14.3 of the label, although for completeness we recommend adding in the median baseline weight of study subjects to clarify that Cohort 2 only went down to 45 kg.

8. Safety

8.1 Overview and Methods

The source of data for the safety review is the Week 24 results from the Phase 1/2 study P027 (IMPAACT 2014). Using the Applicant's SDTM and ADaM datasets, the primary clinical reviewer verified the key safety analyses presented in this section using JMP 15.0, unless otherwise specified. The Applicant used MedDRA version 23.0 for coding.

Table 6 summarizes the major safety results from the 24-week data of P027.

Table 6: Cumulative Safety Overview of P027 through Week 24

	Cohort 1	Cohort 2

	N=9 n (%)	Treatment-Naïve N=2 n (%)	Virologically-suppressed N=43 n (%)	Total N=45 n (%)
Any AE	**4 (44%)**	**2 (100%)**	**43 (100%)**	**45 (100%)**
Maximum Toxicity Grade				
Grade 1 (mild)	3 (33%)	1 (50%)	10 (23%)	11 (24%)
Grade 2 (moderate)	1 (11%)	1 (50%)	24 (56%)	25 (56%)
Grade 3 (severe)	0	0	9 (21%)	9 (20%)
Grade 4 (potentially life-threatening)	0	0	0	0
Fatal SAEs	0	0	0	0
Any SAE	0	0	1 (2%)	1 (2%)
Drug-related SAEs	0	0	0	0
AEs Leading to discontinuation	0	0	0	0
Drug-related AEs	0	1 (50%)	0	1 (2%)
Drug-related Grade 3 or 4 AEs	0	0	0	0

Data Source: Adapted from clinical study report for P027, Table 12-1, 12-2, 14.3-33, 14.3-34 and confirmed with the P027 ADAE dataset.

A safety update was submitted on October 21, 2021 with safety data through the database lock of July 7, 2021, which covered safety data through at least Week 48 for all subjects in Cohort 2. The safety data in the update were similar to the safety data submitted in the original sNDA and did not raise new safety concerns. Between Week 24 and the data cut off for the safety update, one additional subject had an SAE (grade 3 scrotal abscess, not related), and the one subject with SAEs reported in the sNDA had two additional SAEs (mild COVID-19, and Grade 4 ALT increased in the setting of new-since-enrollment hepatitis C virus infection). Three additional subjects discontinued study treatment (in addition to the one subject who discontinued due to pregnancy described in Section 9.4 below): a second subject due to pregnancy (which resulted in a live birth at 40 weeks gestation with no reported congenital abnormalities), the subject with the SAE of life-threatening ALT increased and a new diagnosis of hepatitis C virus infection, and a treatment-naïve subject due to noncompliance.

The data submitted in this sNDA are adequate to characterize the safety profile of DOR and DOR/3TC/TDF once daily in adolescent subjects. There were no unique safety concerns in the adolescent population relative to safety findings seen in adult subjects in the Phase 3 trials. We agree with the Applicant's updates to Section 6.1 of the label summarizing the safety findings in this trial.

8.2 Deaths

There were no deaths during the study.

8.3 Serious Adverse Events (SAEs)

There was one subject who reported an SAE in the first 24 weeks of the study (who also had a second SAE at ~Week 38); neither of his SAEs were considered related to study drug or resulted in study drug interruption of discontinuation. The subject was 15 years old at enrollment, Asian, male, virologically-suppressed, and in Cohort 2. On Day 75 after DOR/3TC/TDF initiation he developed an SAE of grade 3 gastroenteritis associated with mild abdominal pain, severe diarrhea, mild dyspepsia, moderate lethargy, and mild nausea and vomiting. He was treated with fluids and antibiotics (ciprofloxacin), and the gastroenteritis was considered resolved on Day 78 when the subject was discharged with no discharge medications. On Day 266 after DOR/3TC/TDF initiation (after 24 weeks), he also developed an SAE of grade 2 lip injury for which he received no treatment and which was considered resolved on Day 270. This subject remains in the study and has been virologically-suppressed (HIV-1 RNA <40 copies/mL) throughout.

8.4 Dropouts and/or Discontinuations Due to Adverse Events (AEs)

There were no dropouts or discontinuations due to AEs through Week 24. One subject in Cohort 2 discontinued from the study after the Week 8 visit due to pregnancy (and later decided to electively terminate the pregnancy); all other dosed subjects completed the study (Cohort 1) or were continuing in the study at Week 24 (Cohort 2).

8.5 Treatment Emergent Adverse Events and Adverse Drug Reactions

In this section, the term adverse event (AE) indicates the event occurred irrespective of causality. The term adverse drug reaction (ADR) indicates the AE was deemed at least possibly related to study drug by the investigator. All AEs and ADRs discussed in this section were treatment emergent, meaning the AE or ADR occurred while receiving study drug or within 14 days of discontinuation. Adverse events were graded for toxicity using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.

In Cohort 1 through Day 14 after DOR administration, seven AEs were reported in four of the nine subjects, none of which were considered serious or drug-related. With the exception of mild diarrhea, all were related to mild or moderate laboratory abnormalities, only one of which was seen in more than one subject (mild increased AST).

In Cohort 2 through Week 24, all 45 subjects reported AEs. The most common AEs, seen in 96% of subjects, were transient laboratory abnormalities in the Investigations System Organ Class, including GFR decreased (42% of subjects), ALT increased (40% of subjects), blood creatinine increased (27% of subjects), AST increased (27% of subjects), and carbon dioxide decreased (20% of subjects). Laboratory values over time in Cohort 2 are discussed in more detail in Section 9.6 below, and grade 3 AEs related to laboratory abnormalities are discussed in more detail in the next paragraph. AEs, excluding incidental laboratory abnormalities, that were seen in at least 5% of subjects in Cohort 2 are shown in Table 7.

Table 7: Adverse Events Through Week 24 (All Grades) Reported in ≥5% of Total Cohort 2 Subjects, Excluding Laboratory Findings

Dictionary-Derived Terms	Treatment-Naïve N=2 n (%)	Virologically-suppressed N=43 n (%)	Total N=45 n (%)
Any non-Laboratory AE	**1 (50%)**	**28 (65%)**	**45 (100%)**
Cough or productive cough	0	12 (28%)	12 (27%)
Blood pressure increased or Hypertension	0	8 (19%)	8 (18%)
Headache	0	6 (14%)	6 (13%)
Nasal congestion	0	6 (14%)	6 (13%)
Rhinorrhea	0	5 (12%)	5 (11%)
Nasopharyngitis	0	4(9%)	4 (9%)
Oropharyngeal pain	0	3 (7%)	3 (7%)
Acne	1 (50%)	2 (5%)	3 (7%)

Data Source: Adapted from the P027 ADAE dataset and the clinical study report for P027, Table 12-3.

There were 9 subjects with Grade 3 AEs during the trial, all virologically-suppressed subjects in Cohort 2. None of these Grade 3 AEs were considered related to study drug administration, and none resulted in discontinuation or interruption of DOR/3TC/TDF. No subjects had Grade 4 or higher AEs. Grade 3 AEs included the following:

- Glomerular filtration rate (GFR) decreased or blood creatinine increased (n=3)
  - One subject had Grade 3 increased blood creatinine and GFR decreased on Day 34 which resolved to normal levels on Day 37.
  - One subject had Grade 3 GFR decreased on Day 50 and 137 and Grade 3 increased blood creatinine on Day 155. These events were defined by the change from the baseline creatinine level of 0.46 mg/dL, but the subject never had a creatinine level above the normal range (the highest level was 0.72 on Day 155). On Day 180, the creatinine was down to 0.59 mg/dL.
  - One subject had GFR decreased on Day 17 that was considered recovering/resolving (narrative not provided). This subject also never had a creatinine level above the normal range (the highest level was 0.65), but the AE was based on a change from the baseline creatinine level of 0.45 mg/dL.
- Hypertension or blood pressure increased (n=4)
  - The events occurred on Days 31, 57, 113, and 169 and were not resolved. Narratives were not provided.
  - The four subjects with these AEs had maximum systolic blood pressures recorded of 147,143, 140, and 146, and maximum diastolic blood pressures recorded of 99, 83, 84, and 85.
    - *Overall in Cohort 2, there were no clinically significant changes in blood pressure from baseline over 24 weeks.*
- ALT increased (n=1)
  - This subject had Grade 2 ALT (139 IU/L) at baseline that increased to Grade 3 (160 IU/L) on Day 9. The ALT remained Grade 3 on Day 12 but resolved to Grade 1 by Day 32 and to normal levels by Day 178. The increased ALT was

associated with increased AST values but normal bilirubin, and no treatment was given for the events.

- Diarrhea and gastroenteritis (n=1): the gastroenteritis was considered serious and is described further in Section 9.3 above.

There was only one ADR in the trial, a Grade 1 dizziness in a 17-year-old Asian, male, treatment-naïve subject in Cohort 2 that occurred on the same day as initial dosing. The ADR resolved three days later despite continued treatment with DOR/3TC/TDF.

8.6 Laboratory Findings and Associated Safety Analyses

Graded laboratory events through Week 24 were not uncommon in Cohort 2 but were generally grade 1 or 2. The most common graded laboratory abnormalities were elevated alanine aminotransferase (16/45 or 36% of subjects, 1/45 Grade 3), elevated creatinine (12/45 or 27%, 2/45 Grade 3), elevated aspartate aminotransferase (9/45 or 20% of subjects, none Grade 3), elevated lipase (6/45 or 13%, none Grade 3), and elevated alkaline phosphatase (5/45 or 11%, none Grade 3). Changes in liver parameters were generally mild, transient, asymptomatic, and not associated with bilirubin increases. No subjects met Hy's Law Criteria for drug-induced liver injury.

There were no clinically significant changes over time for laboratory parameters, vital sign measurements, or physical examination assessments in either Cohort 1 or 2, even for laboratory parameters and vital sign measurements which were frequently reported as AEs. For example, in Cohort 2, the mean and median changes in systolic blood pressure from baseline at Week 24 were -2.5 and 0 mm Hg, and the mean and median changes in ALT from baseline at Week 24 were 1 and 2 IU/L. Height (mean change from baseline at Week 24 of 1.1 cm, 95% CI 0.6, 1.6 cm) and weight (mean change from baseline at Week 24 of 3.5 kg, 95% CI 2.4, 4.6 kg) both increased over the 24 weeks of the study in Cohort 2, as would be expected in this age group.

8.7 Adverse Events of Interest

The adverse events of special interest for 3TC and TDF have already been well-characterized, and these drugs have been licensed for use in adolescents for years. The adverse events of interest for further safety evaluation for DOR, based on the original DOR and DOR/3TC/TDF NDA reviews or NNRTI class-related concerns, include neuropsychiatric events, hepatotoxicity, biliary AEs, serum ALT and AST elevations, rash and hypersensitivity reactions, and alopecia. Through Week 24 in Cohort 2:

- Neuropsychiatric events: A total of seven subjects had 8 AEs in the nervous system disorders class. These AEs included mild dizziness (n=1, the only ADR in the study), mild headache (n=6), and moderate lethargy associated with severe gastroenteritis (the one subject with an SAE). These AEs were transient and lasted 1 to 3 days.
- Hepatotoxicity and biliary AEs:
    - A total of two subjects had 6 AEs in the hepatobiliary disorders SOC, all hyperbilirubinemia. The AE was mild and resolved after 35 days in one subject. The second subject had bilirubin of 1.3 at baseline which increased

to 1.68 (mild) at Day 29 and ranged up and down from 1.41 to 1.97 (moderate) though Day 260 (the last recorded measurement). This subject had no other graded liver laboratory abnormalities and no other reported AEs except transient mild hypokalemia.

- Serum ALT and AST elevations: A total of 21 subjects had 75 AEs reported for elevated ALT or AST. One subject (described in Section 9.5) had a maximum toxicity grade of severe, and six subjects had a maximum toxicity grade of moderate. The elevations were predominantly transient without a clear temporal pattern and resolved on continued DOR/3TC/TDF.

- Rash and hypersensitivity reactions: A total of 5 subjects had 12 AEs in the skin and subcutaneous disorders SOC. These included three AEs of acne (one moderate), two AEs of papules (one moderate), three AEs of other rashes (two moderate), two AEs of mild pruritus (starting on Day 39 and 21 and lasting 7 and 11 days, respectively), and one AE of moderate urticaria (starting on Day 23 and lasting one day). None of these AEs were considered serious or related to study drug.
- Alopecia: There were no AEs of alopecia in this study.

DOR and DOR/3TC/TDF labeling already includes neuropsychiatric events, rash, serum ALT and AST elevations, and bilirubin elevations. No labeling changes are warranted based on the safety findings in this submission.

8.8 Special Populations

As previously discussed, one subject discontinued from the study due to pregnancy after 8 weeks of treatment and subsequently elected to terminate the pregnancy. No subjects in P027 reported an overdose. The total number of subjects was too small to ascertain any safety trends based on intrinsic factors.

9. Advisory Committee Meeting

Not applicable (there was no Advisory Committee Meeting held for this application).

10. Other Relevant Regulatory Issues

None.

11. Labeling

The DOR and DOR/3TC/TDF labeling have been updated to extend the population to include HIV-1 infected pediatric patients weighing at least 35 kg. Negotiations with the Applicant on the exact language in the labels are currently ongoing.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

We recommend approval of this supplemental NDA to expand the population to include pediatric patients weighing at least 35 kg. Our recommendation is based on review of the totality of information available, including safety and efficacy data in pediatric subjects 12 to 17 years of age, PK data with once daily DOR/3TC/TDF administered to pediatric subjects 12 to 17 years of age weighing at least 45 kg in P027, and the population PK analysis to estimate the DOR exposures in pediatric patients weighing 35 to <45 kg.

- Risk Benefit Assessment

The risk benefit assessment for use of DOR and DOR/3TC/TDF in pediatric patients weighing at least 35 kg is favorable. Approval of this supplement will expand the treatment armamentarium for adolescents infected with HIV-1, including addition of a new once daily fixed-dose combination tablet which could improve treatment adherence. The efficacy and safety profiles of once daily DOR and DOR/3TC/TDF through Week 96 were established in the adult Phase 3 trials P018 and P021. An analysis of the data from P027, in which 45 pediatric patients between 12 and 17 years of age and weighing ≥45 kg received once daily DOR/3TC/TDF for 24 weeks, did not raise any efficacy or safety concerns. In addition, the population PK analysis, combined with efficacy and safety data from the adult trials, did not raise any efficacy or safety concerns with use of the 100 mg daily DOR dose in pediatric patients weighing ≥35 kg.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

- Recommended Comments to Applicant

None.

Appendix 1

Clinical Investigator Financial Disclosure
Review

Application Number: 210806/S-07 and 210807/S-08

Submission Date(s): July 27, 2021

Applicant: Merck Sharp & Dohme Corp.

Product: Doravirine (DOR) and DOR/3TC/TDF

Reviewer: Stephanie Troy, MD

Date of Review: January 4, 2022

Covered Clinical Study (Name and/or Number): P027, or IMPAACT 2014

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **65 investigators total (8 principal investigators, 57 sub-investigators)**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **none**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **none (certified for 61 investigators, the remaining 4 sub-investigators did not return the requested information despite multiple due diligence attempts)**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): **Not applicable** Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **4**		

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The applicant adequately disclosed financial interests/arrangements with clinic investigators as recommended in the guidance for industry, *Financial Disclosure by Clinical Investigators*, and by 21 CFR 54.4. None of the 65 investigators are employed by the applicant. Four sub-investigators did not return the requested information about financial disclosures, and the remaining 61 investigators (94%) have no financial interests or arrangements with the applicant, as defined in 21 CFR 54.2.

The investigator financial disclosures do not raise questions about the integrity of the data. The pharmacokinetic and virologic efficacy endpoints are objective laboratory measurements that are assessed centrally and not vulnerable to investigator bias. In addition, none of the investigators reported financial interests or arrangements with the applicant.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

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/

STEPHANIE B TROY
01/05/2022 11:33:16 AM

SARAH M CONNELLY
01/05/2022 11:39:23 AM

YODIT BELEW
01/05/2022 11:42:52 AM