24 February 2022
EMA/CHMP/PRAC/104864/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Procedure No. EMEA/H/C/WS2065

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Delstrigo	doravirine / lamivudine / tenofovir disoproxil	EMEA/H/C/004746/WS2065/0026
Pifeltro	doravirine	EMEA/H/C/004747/WS2065/0019

Worksharing applicant (WSA) Merck Sharp & Dohme B.V.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
3TC	lamivudine
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AIP	Analysis Implementation Plan
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC0-24	area under the plasma concentration-time curve from time zero to 24 hours postdose
BLQ	Below limit of quantitation
C24	plasma drug concentration, 24 hours post dose
cART	combination antiretroviral therapy
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum concentration
CSR	clinical study report
DAIDS	Division of AIDS
DOR	doravirine (MK-1439)
DOR/3TC/TDF	doravirine/lamivudine/tenofovir disoproxil fumarate (MK-1439A)
DTG	dolutegravir
EFV	efavirenz
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
HIV-1	human immunodeficiency virus type 1
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
InSTI	integrase strand-transfer inhibitor
NHANES	National Health and Nutrition Examination Survey
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleos(t)ide reverse transcriptase inhibitor
OF	observed failure (approach to missing data)
PDVF	protocol-defined virologic failure
PENTA	Paediatric European Network for Treatment of AIDS
PI	protease inhibitor
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PMR	Postmarketing Requirement
PPSR	Proposed Pediatric Study Request
PREA	Pediatric Research Equity Act
PSP	Pediatric Study Plan
PWR	Pediatric Written Request
QD	once daily
RAL	raltegravir
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SmPC	Summary of Product Characteristics
TDF	tenofovir disoproxil fumarate
TFV	Tenofovir
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 28 July 2021 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the new indication to the paediatric population weighing at least 35 kgs for PIFELTRO and DELSTRIGO. Sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP for each product have also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial corrections and to update the list of local representatives in the Package Leaflet.

The worksharing procedure requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) for Pifeltro (doravirine), P/0177/2021, on the agreement of a paediatric investigation plan (PIP) covering children from birth to less than 18 years of age. At the time of submission of the application, the PIP P/0177/2021 was not yet completed as some measures were deferred.

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) for Delstrigo (doravirine, tenofovir disoproxil, lamivudine), P/0176/2021, on the agreement of a paediatric investigation plan (PIP) covering children from birth to less than 18 years of age. At the time of submission of the application, the PIP P/0176/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	28 July 2021
Start of procedure:	14 August 2021
CHMP Rapporteur Assessment Report	8 October 2021
PRAC Rapporteur Assessment Report	13 October 2021
PRAC members comments	20 October 2021
Updated PRAC Rapporteur Assessment Report	20 October 2021
PRAC Outcome	28 October 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	4 November 2021
Request for supplementary information (RSI)	11 November 2021
PRAC Rapporteur Assessment Report	31 January 2022
CHMP Rapporteur Assessment Report	9 February 2022
PRAC Outcome	10 February 2022
CHMP members comments	14 February 2022
Updated CHMP Rapporteur Assessment Report	16 February 2022
Opinion	24 February 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Combination antiviral therapy with human immunodeficiency virus type-1 (HIV-1) protease and reverse transcriptase inhibitors has significantly reduced acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality. However, emerging multi-class drug-resistant human immunodeficiency virus (HIV) strains as well as potential long-term toxicities warrant development of new antiretroviral therapies without or with limited cross-resistance to available drugs.

Disease or condition

Treatment of human immunodeficiency virus (HIV)-1 infection.

State the claimed the therapeutic indication

Delstrigo is indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir (see sections 4.4 and 5.1).

Delstrigo is also indicated for the treatment of adolescents aged 12 years and older weighing at least 35 kgs who are infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil (see sections 4.4 and 5.1).

Pifeltro is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults, adolescents and children weighing at least 35 kgs infected with HIV-1 without past or present evidence of resistance to the NNRTI class (see sections 4.4 and 5.1).

Epidemiology

HIV-1 infection remains a major public health concern. In a 2020 report, the World Health Organization (WHO) estimated that in 2019 there were 1.7 million [1.2 million-2.2 million] new HIV-1 infections worldwide. Of the 1.7 million estimated new infections, 1.5 million [1.1 million-2.0 million] were adults and 150,000 [94,000-240,000] were in children less than 15 years of age. Approximately 84% of child infections occurred in sub-Saharan Africa. Overall, the global incidence of new HIV-1 infections among children less than 15 years of age has decreased over the past decade due to improved access to mother-to-child prevention services.

Biologic features

HIV-infected children may have more rapid disease progression and accelerated damage of the developing immune system compared to adults, with higher viral loads and less effective immunological responses to HIV-1 infection than their adult counterparts. Of all global deaths in 2019, 95,000 [61,000–150,000] were in children less than 15 years of age.

Clinical presentation, diagnosis

The clinical presentation and diagnosis of HIV is well-known and not further discussed in this assessment report.

Management

Treatment of HIV requires use of combination antiretroviral therapy. The choice of the combination regimen depends on the status of the patient, particularly in terms of plasma HIV viral load, CD4 cell counts, any previous treatment(s), prior treatment failure, and intolerance to treatment. The most commonly used guidelines are those developed by the World Health Organization (WHO) [World Health Organization, 2019], the European AIDS Clinical Society (EACS) [EACS, 2019], the Department of Health and Human Services (DHHS) in the USA [Department of Health and Human Services, 2019] and the PENTA (for use in children and adolescents) [PENTA2019].

Treatment options in children are more limited compared to adults.

2.1.2. About the product

Pifeltro (doravirine) and Delstrigo (doravirine/tenofovir disoproxil/lamivudine) are approved in the EU for the treatment of HIV-infection in adult patients. Doravirine is the most recently approved NNRTI, tenofovir and lamivudine are well known nucleoside analogues. The present indications read: Pifeltro is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class (see sections 4.4 and 5.1). Delstrigo is indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir (see sections 4.4 and 5.1).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Draft CHMP guidelines (CPMP/EWP/633/2002 Rev. 3) on the "Clinical development of medicinal products for treatment of HIV infection" are available.

The WSA did not seek Scientific advice at the CHMP.

2.1.4. General comments on compliance with GLP, GCP

The study is stated to comply with the principles of Good Clinical Practice.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The present application intends to extend the approved indication for doravirine (DOR) containing medicinal products (single active substance in Pifeltro and part of fixed dose combination (FDC) in Delstrigo which also contains lamivudine and tenofovir) to the paediatric population. A non-clinical overview has been provided to supports the supplemental marketing application for expanding the current use of DOR and the FDC tablet in adult patients with HIV-1 infection to include use in paediatric patients weighing $\geqslant$35 kg with HIV-1.

2.2.1. Toxicology

A brief summary of the toxicological dossiers is provided below. No combination toxicity studies have been conducted for the FDC.

2.2.1.1. Doravirine

The DOR non-clinical safety program submitted in the original application for the adult indication is also used for this procedure. The DOR toxicology program included safety pharmacology studies, in-vitro and in-vivo genetic toxicity assays, repeat-dose oral toxicity studies in mice up to 3 months duration, in rats up to 6 months duration and in dogs up to 9 months duration, carcinogenicity studies in rats and rasH2 transgenic mice, a male and female fertility study in rats, embryofoetal developmental studies in rats and rabbits, a pre-and post-natal developmental study in rats, and a study in juvenile rats. In the repeat-dose toxicity studies, the age of rats and dogs at the start of exposure (7-8w of age in rats in 3–6-month studies and 25w to 29w of age in dogs in 9-month study) corresponded roughly to human children or adolescent age, respectively. No adverse findings were observed at maximal feasible doses. In the rat juvenile toxicity study, exposure started from PND14. The genotoxicity assessment did not identify any genetic toxicity for DOR (in-vitro or in-vivo). The carcinogenicity studies (2-years in rats, 6 months in transgenic rasH2 mice) found no evidence of carcinogenic potential.

2.2.1.1.1. Developmental toxicity

There were no adverse effects detected in the DART program including the prenatal and postnatal development study (PPND). In the rat juvenile toxicity study (exposure between PND14 and PND55, using doses up to 300mg/kg), there was no toxicity based on the endpoints of mortality, clinical signs, body weights, food consumption, developmental landmarks, open field motor activity, haematology and serum biochemistry parameters, gross observations, organ weight changes, or histomorphology changes.

2.2.1.1.2. Toxicokinetic data and exposure margins

The clinical pharmacokinetic profile of DOR was similar in adults and paediatric patients weighing at least 35 kg and there were no meaningful changes in exposure in paediatric patients weighing at least 35 kg, when compared to adults that would impact exposure margins. A 100 mg QD DOR clinical dose corresponds to a systemic geometric mean exposure of $AUC_{0\text{-}24h}$ of 37.8µM x hr and a Cmax of 2.26µM. In the repeat-dose toxicity studies, the DOR systemic $AUC_{0\text{-}24h}$ exposures achieved in animals were at least 5x above clinical $AUC_{0\text{-}24h}$ exposures at 100mg QD. For the rasH2 carcinogenicity study, the exposure margin to humans was ~6x while the 2-year rat study had an exposure margin of ≥7.5x. The $AUC_{0\text{-}24h}$ exposure margins for the rat juvenile toxicity study was ~9x.

2.2.1.2. Lamivudine

The toxicological profile of lamivudine (3TC, oral exposure) has been evaluated in a standard toxicology program including repeat-dose toxicity studies up to 12 months duration in rats and dogs, a full genotoxicity program, rat and mouse ~2-year carcinogenicity studies and a full DART program. Toxicity findings in the general toxicity studies were reductions in red cell counts, occasionally associated with reductions in total lymphocyte counts (but without effects on bone marrow cytology) at supratherapeutic exposures. A modified PPND study involving exposure of pregnant and lactating rats plus the direct oral administration to their juvenile offspring did not identify any clinically relevant concerns for the paediatric patient population.

2.2.1.3. Tenofovir

Tenofovir (TDF) has been toxicologically characterized for oral exposure in repeat-dose toxicity studies using rats (up to 42w exposure), dogs (up to 42w exposure) and non-human primates (up to 24 months exposure), a full genotoxicity program, rat and mouse ~2-year carcinogenicity studies and a full DART program. Of interest to paediatric indications, renal and bone toxicity and a decrease in serum phosphate concentration was observed in the general toxicity studies. Renal toxicity was noted in all animal species tested. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. The bone toxicity was classified as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The clinical relevance of the renal and bone findings presently unknown.

2.2.1.3.1. Toxicokinetic data and exposure margins

The bone toxicity in young adult rats and dogs occurred at exposures ≥5x the exposure in paediatric or adult patients; bone toxicity occurred in juvenile monkeys ≥40-fold the exposure in patients. Renal toxicity was noted at AUC exposure margins of 2-20x.

2.2.2. Ecotoxicity/environmental risk assessment

The MAH has submitted a justification for not providing an updated ERA for the active substances. Based on PEC/PNEC ratios, the original ERA concluded that DOR is unlikely to pose a risk to the environment. DOR is also not considered a bioaccumulative or PBT substance/candidate. The MAH presented arguments that the assumptions in the previously approved ERA regarding patient population (present application for adult, applied for indication also for children and adolescents that weigh >35kg BW), dose, and market penetration remain relevant today (see discussion).

2.2.3. Discussion on non-clinical aspects

The toxicological programs for Doravirine (DOR) and lamivudine (3TC) have not identified any toxicity that can be easily identified as being relevant for the paediatric population. For tenofovir (TDF), renal and bone toxicity has been observed across several animal species at exposure margins to humans that in some cases are <10x. The clinical relevance of these findings remains unclear. Overall, the provided non-clinical overview is acceptable for the present application.

Regarding the ERA(s), the applicant had not provided any updated ERA or an estimate how much the extension of the indication to children will increase the total exposure and simply claims that there will be no change in total exposure. This was resolved after submission of an updated ERA (solved in Annex 2).

2.2.4. Conclusion on the non-clinical aspects

In conclusion, this application of extension of indication to the paediatric population 12 years and older weighing at least 35 kgs for Delstrigo (doravirine, lamivudine, tenofovir disoproxil) and Pifeltro (doravirine) in the treatment of HIV-1 does not lead to a significant increase in environmental exposure. Therefore, Delstrigo and Pifeltro are not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number, Countries, Status	Study Design	Study Population	Primary Endpoints	Secondary and Other Endpoints
Study Number: P027V01MK1439 Countries: Thailand, South Africa, and US Status: Ongoing	Study Design: Phase 1/2 multicenter, open-label study of the PK, safety, and tolerability of DOR and DOR/3TC/TDF in children and adolescents with HIV-1 infection (age 12 to <18 years, who weigh at least 35 kg) Study Intervention: Cohort 1: A single dose of DOR (100 mg) added to their current regimen of DTG or RAL plus 2 NRTIs. All participants received the tablet. Cohort 2: DOR/3TC/TDF (100 mg/300 mg/300 mg) QD. Oral granule formulation was offered in Cohort 2 but was not chosen by any participant. All participants received the tablet. Treatment and Follow-up: Cohort 1: Single dose of DOR + 2 weeks of safety follow-up postdose Cohort 2: 96 weeks of DOR/3TC/TDF QD + 2 weeks (up to 4 weeks)	Cohort 1 (N=9) • Virologically suppressed participants • Male: 7 • Female: 2 • Median Age (Range): 15.0 yrs (12.0 to 16.0 yrs) • Median Weight (Range): 48.7 Kg (40.3 to 90.8 Kg) Cohort 2 (N=45) • Virologically suppressed (N=43) and antiretroviral treatment-naïve (N=2) participants • Male: 19 • Female: 26 • Median Age (Range): 15.0 yrs (12.0 to 17.0 yrs) • Median Weight (Range): 51.6 Kg (45.1 to 79.8 Kg)	Cohort 1 *Pharmacokinetics* Single dose AUC0-inf, Cmax, and C24hr of DOR *Safety and Tolerability through Week 2* • Safety Outcome: All adverse events, regardless of severity grade • Toxicity Endpoints Related to Study Drug: ≥ Grade 3, serious, discontinuation of study drug • Death (Grade 5 AE), regardless of relationship to study drug Cohort 2 *Safety and Tolerability through Week 24* • Safety Outcome: All adverse events, regardless of severity grade • Toxicity Endpoints Related to Study Drug: ≥ Grade 3, serious, discontinuation of study drug • Death (Grade 5 AE), regardless of relationship to study drug	Secondary Endpoints (Cohort 2) *Pharmacokinetics through Week 1* • AUC0-24hr, Cmax, and C24hr of DOR, 3TC, and tenofovir *Virologic Efficacy at Weeks 24, 48, and 96* • Plasma HIV-1 RNA<200 copies/mL • Plasma HIV-1 RNA<50 copies/mL • Plasma HIV-1 RNA<40 copies/mL • Log10 drop from baseline in plasma HIV-1 RNA (ART-naïve participants) *Immunologic Response at Weeks 24, 48, and 96* • Change in CD4 count and percent from baseline *Safety and Tolerability through Weeks 48 and 96* • Safety Outcome: All adverse events, regardless of severity grade • Toxicity Endpoints Related to Study Drug: ≥ Grade 3, serious, discontinuation of study drug • Death (Grade 5 AE) regardless of relationship to study drug Other Endpoints (Cohort 2) • Pharmacokinetics of DOR, 3TC, and tenofovir through Week 48 • Genotypic and phenotypic measures of resistance at baseline and at virologic failure • Self-reported measures of acceptability, palatability, and adherence

Study Number, Countries, Status	Study Design	Study Population	Primary Endpoints	Secondary and Other Endpoints
	of safety follow-up postdose			

2.3.2. Pharmacokinetics

Based on data from P027 and population PK analysis, the PK of DOR 100 mg in the paediatric population weighing at least 35 kg administered alone or as DOR/3TC/TDF has been characterized. DOR steady-state PK in adolescents weighing at least 35 kg following administration of 100-mg QD DOR is similar to that in adults at the same dose.

P027 study - PK

A single Phase 1/2, PK, safety and tolerability trial (P027; also known as MK-1439 P027; or IMPAACT 2014, DAIDS Study No. #34150) was conducted to support the approval of DOR and DOR/3TC/TDF in HIV-1 infected paediatric patients weighing at least 35 kg. The marketed formulations of DOR and DOR/3TC/TDF were used in this study and therefore no new biopharmaceutic studies were conducted beyond what was described in the 2.7.1 for the initial marketing applications submitted for the adult program.

Cohort 1 will assess the PK of doravirine only (single dose).

Cohort 2 will assess the steady-state sparse pharmacokinetics of DOR, 3TC, and tenofovir once daily in 40 evaluable participants weighing ≥35 kg (or the weight determined in Cohort 1), using intensive PK sampling at Week 1 and sparse PK sampling through 48 weeks. In addition, Cohort 2 will evaluate the steady-state intensive pharmacokinetics of TFV and 3TC given as the FDC to the first 10 participants enrolled into Cohort 2. The study included 2 Cohorts with Intensive/sparse PK (see Table 1 below).

Table 1:

Cohort		N	DOR 100 mg Formulation	Dose Regimen	PK Sampling	Timepoints
1		9	Adult DOR tablet	Single Dose	Intensive	Predose, and 1, 2, 4, 8, 12, 24, 48, 72 hr post-dose
2		10	Adult DOR/3TC/TDF tablet	Once Daily	Semi-intensive	Week 1 (at SS): predose, and 2, 4, 12, 24 hr post-dose
2		35			Sparse	Study entry: predose; Week 4: predose; Week 8, 12: random; Week 24: predose, 0.5 – 2 hr post-dose; Week 48: predose, 0.5 – 2 hr post-dose

The analysis population was predominately Asian (65%) and black (32%), and the remainder white (4%), and equally distributed between male (48%) and female (52%). The overall median (range) for age and weight were 15 (12 to 17) years and 52 (40 to 91) kg, respectively.

2.3.3. PK modelling

popPK model DOR

Dataset

A total of 395 PK samples were collected from 54 participants through Week 24. A total of 55 BLQ samples were excluded from the analysis, of which 53 were collected at Week 0 before the first administered DOR dose.

Table 2: Summary of P027 PK Samples

Cohort	Week	Nominal TALD (h)	All	Excluded BLQ TAFD≤ 0	Excluded BLQ TAFD>0	Excluded Other	Final popPK
1	0	Predose	9	8	0	1	0
		1	9	0	1	0	8
		2	9	0	0	0	9
		4	9	0	0	0	9
		8	9	0	0	0	9
		12	9	0	0	0	9
		24	9	0	0	0	9
		48	9	0	0	0	9
		72	9	0	0	0	9
	All	All	81	8	1	1	71
2	0	Predose	45	45	0	0	0
	1	Predose	10	0	0	0	10
		2	10	0	0	0	10
		4	10	0	0	0	10
		12	10	0	0	0	10
		24	10	0	0	0	10
	4	Predose	45	0	0	1	44
	8	Random	44	0	1	1	42
	12	Random	44	0	0	0	44
	24	Predose	43	0	0	0	43
		0.5 - 2	43	0	0	0	43
	All	All	314	45	1	2	266
All	All	All	395	53	2	3	337
TALD = time after last dose; TAFD = time after first dose							

Source: p027nmpk04-outliers-mdv.csv

Methods

Population PK modeling was performed with the software package NONMEM, version 7.3.0. The pediatric population PK model utilized the same structure as the final adult model. As a result, these parameters, along with residual error were estimated directly from the pediatric data. As the semi-intensive and sparse sampling schemes may limit the ability to precisely characterize DOR absorption for Cohort 2 participants, ka was specified with an informative prior from the adult model. Similarly, interindividual variability on CL/F and V/F were also specified with informative priors from the adult model, due to the limited number of participants compared to the adult model. To capture anticipated weight-related changes in DOR disposition in the pediatric population, fixed-exponent allometry for CL/F and V/F were included. The estimates for parameters with Bayesian informative priors (absorption kA, covariate CLAGE, and IIV on CL/F and V/F) did not change significantly from the adult model.

Final adolescent model

Table 3: Parameter estimates of the final DOR adolescent popPK model

Parameter	Unit	Prior	Estimate	%RSE	%CV	CI95Low	CI95 High	%Shrinkage
CL/F	L/h	--	5.95	5.40	--	5.32	6.57	--
V/F	L	--	133	9.16	--	109	156	--
KA	1/h	1.42	1.39	0.851	--	1.37	1.42	--
Age on CL	%/yr	-0.540	-0.538	0.305	--	-0.541	-0.535	--
EFV on CL	%	--	73.1	20.7	--	43.4	103	--
IIV CL/F	--	0.104	0.101	1.59	32.6	0.0977	0.104	25.1
IIV V/F	--	0.098	0.0977	1.09	32.0	0.0956	0.0997	49.4
RV	--	--	0.520	10.6	55.7	0.412	0.628	8.54

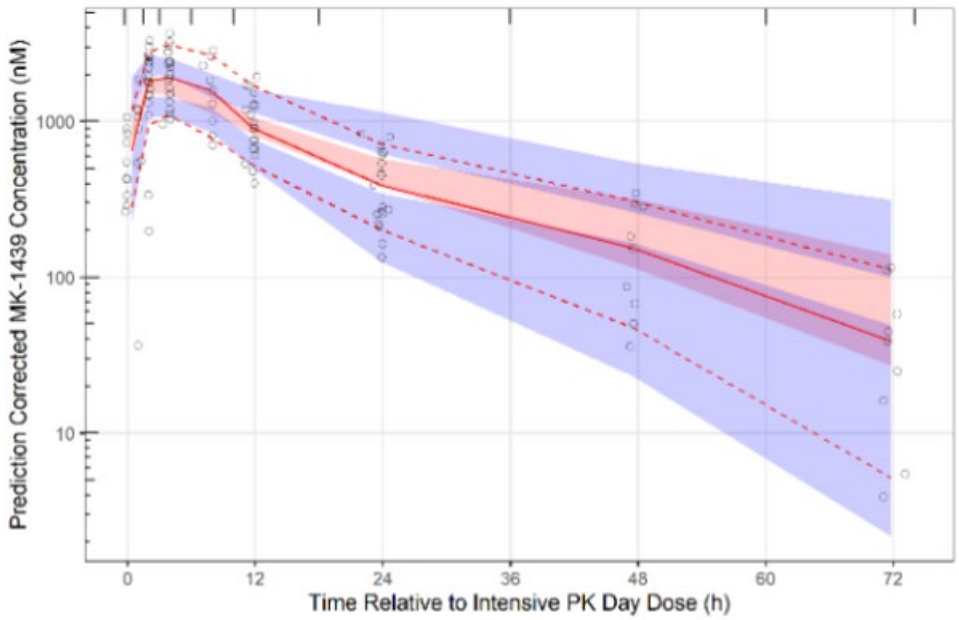
CL/F = apparent clearance; V/F = apparent volume; KA = absorption rate;
IIV = inter-individual variability (log-normal variance);
RV = residual variability (log-normal standard deviation);
CL/F_i = apparent clearance for i^{th} individual adjusted for individual covariates = $CL/F * CLAGE_i * CLEFV_i * (WT_i / 52)^{0.75}$;
$CLAGE_i = 1 + AgeOnCL * (AGE_i - 15)$;
$CLEFV_i = 1 + EFVonCL * EFV_i$ (switch from EFV, Cohort 2, Week 1);
V/F_i = apparent volume adjusted for individual covariates = $V/F * (WT_i / 52)$;
%RSE = % relative standard error = 100 * SE / Estimate;
%CV = % coefficient of variation = $100 * \sqrt{(e^{Variance}-1)}$;
CI95% = 95% confidence interval = Estimate ± 1.96*SE;

Source: mk1439-027-poppk-run2.xml

Model evaluation using visual predictive checks and goodness of fit plots showed that the paediatric model adequately described DOR plasma concentrations from P027. Estimates of individual SS PK parameters for each participant in P027 that were obtained from the final population PK model were compared against DOR PK from adults in the Phase 3 trials. Individual PK parameters were also used to investigate potential trends between DOR PK and intrinsic and extrinsic factors. Simulations of DOR steady-state PK for the 100-mg QD dose for a typical paediatric population (N=1000) weighing at least 35 kg, regardless of age, were also conducted based on age and weight covariates sampled from the NHANES database. The simulated population also included individuals in the 35 to <45 kg weight range.

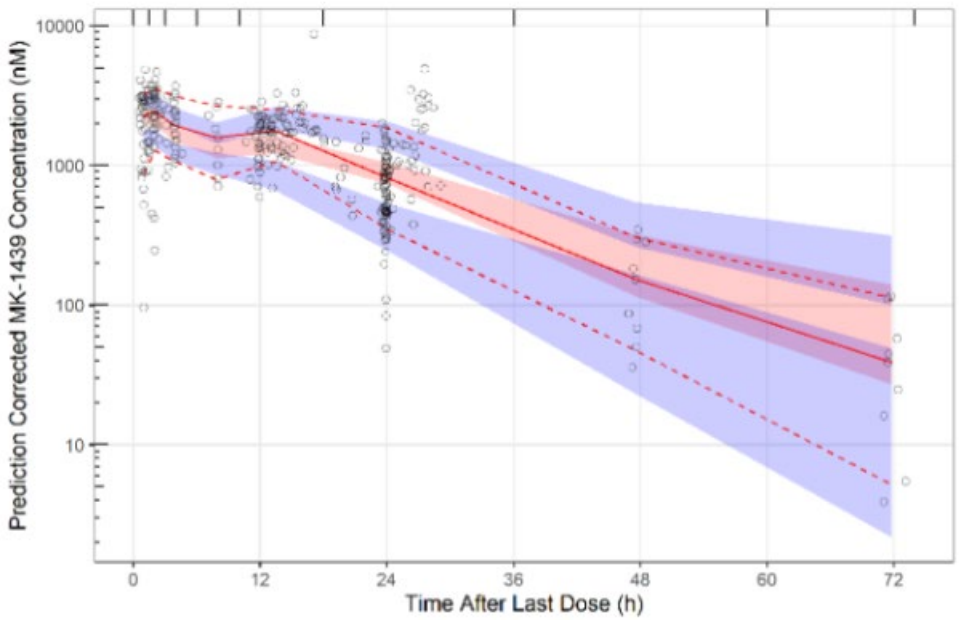
Prediction-corrected (pc) visual predictive checks (pcVPCs) of DOR PK were generated according to Bergstrand et al. (2011) and demonstrate that the paediatric population PK model adequately characterizes DOR PK in adolescents. [Figure 1] shows the pcVPC for intensive PK from Cohorts 1 (single dose of 100 mg DOR) and 2 (at Week 1, with once daily dosing of DOR/3TC/TDF for all participants including those switching from EFV); [Figure 2] shows the pcVPC for all P027 PK data from Cohort 1 and Cohort 2 (intensive and sparse).

Figure 1: pcVPC for Intensively Sampled PK data in MK-1439 P027 Cohort 1 (single dose 100 mg DOR) and Cohort 2 (once daily 100 mg DOR at Week1)



Time is relative to the intensive PK day dose. Open black circles represent the individual pc observations, the solid red line represents the smoothed median (pc) observation, while the lower and upper dotted red lines represent the smoothed 10th and 90th percentiles of the pc observations, respectively. The red shaded region represents the smoothed 90% confidence interval of the median pc simulations, while the lower and upper shaded blue regions represent the smoothed 90% confidence intervals of the 10th and 90th percentiles of the pc simulations, respectively.

Figure 2: pcVPC for All Intensively and Sparsely Sampled PK data in MK-1439 P027 Cohort 1 (single dose 100 mg DOR) and Cohort 2 (once daily 100 mg DOR)



Time is actual time since last dose. Open black circles represent the individual pc observations, the solid red line represents the smoothed median (pc) observation, while the lower and upper dotted red lines represent the smoothed 10th and 90th percentiles of the pc observations, respectively. The red shaded region represents the smoothed 90% confidence interval of the median pc simulations, while the upper and lower shaded blue regions represent the smoothed 90% confidence intervals of the 10th and 90th percentiles of the pc simulations.

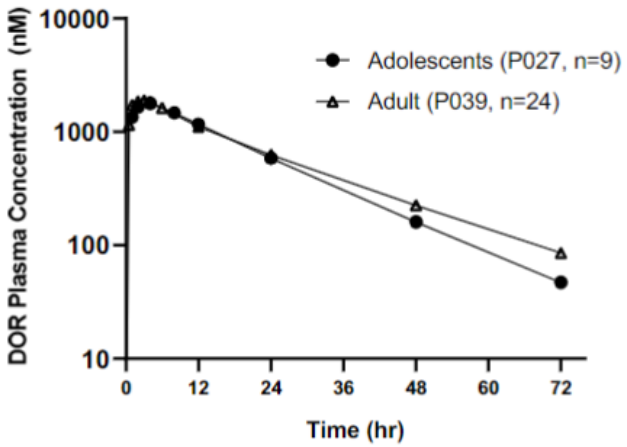
2.3.4. PK in target population (adolescents weighing 35+ kg)

DOR exposure adolescents vs adults

The DOR concentration-time profile in adolescent participants in Cohort 1 of P027 was similar to that observed in adults.

Figure 3

Arithmetic mean DOR Plasma Concentration-time Profile Following Administration of 100-mg Single Dose DOR to HIV-1 Infected Adolescents (P027, Cohort 1) and Healthy Adults (MK-1439-039)

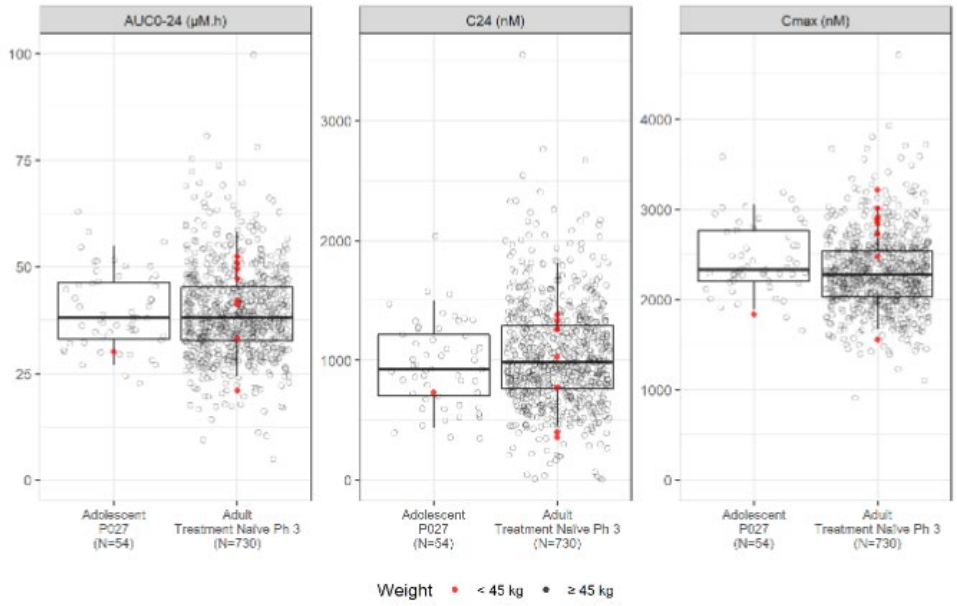


Source: [Ref. 5.3.5.2: P027V01MK1439: Figure 11-1], (P039MK1439: Figure 11-1 part of the original marketing application for adult indications)

Estimates of steady-state DOR PK parameter values were obtained for each of the 54 participants in P027 using the pediatric population PK model (below)

Figure 4

DOR Steady-State PK Following Administration of DOR 100 mg QD in Adolescent (P027) and Adult Treatment Naïve HIV-1 Infected Participants

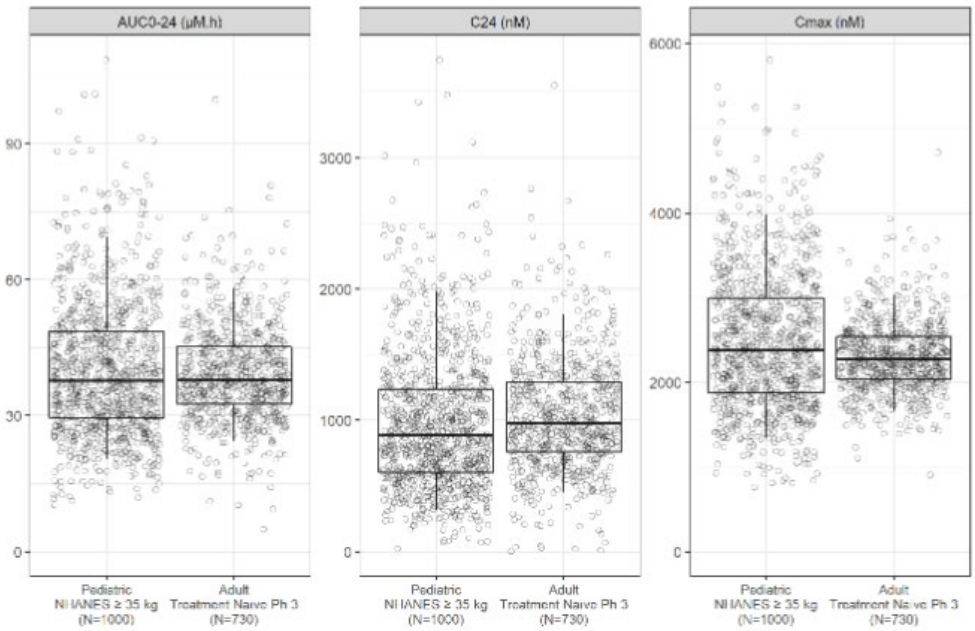


Center lines are medians, boxes are 25th and 75th quartiles, and whiskers are 5th and 95th percentiles. The single P027 participant and 8 adults with weight < 45 kg are shown as a solid red dots.
Source: [Ref. 5.3.5.3: 05KXBX]

Because only one P027 participant was in the 35 to <45 kg weight range and all participants were ≥12 years of age, steady-state DOR exposures following administration of 100 mg QD in the paediatric population weighing ≥35 kg, regardless of age, were projected based on covariates obtained from the NHANES database. The simulated NHANES paediatric population comprised 1,000 individuals with a median (range) age 13.2 (6.2, 17.9) years and median (range) weight of 53.6 (35.0, 159) kg.

Figure 5

DOR Steady-State PK Following Administration of DOR 100 mg QD in an NHANES Pediatric Population Weighing at Least 35 kg and Adult Treatment Naïve HIV-1 Infected Participants



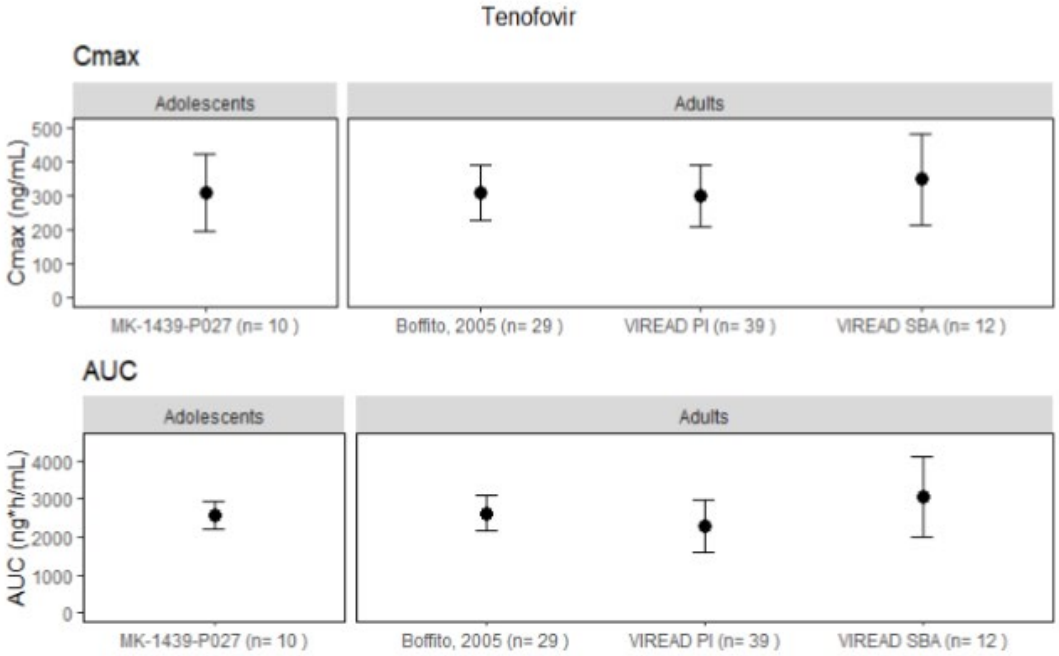
Center lines are medians, boxes are 25th and 75th quartiles, and whiskers are 5th and 95th percentiles.
Source: [Ref. 5.3.5.3: 05KXBX]

Exposure tenofovir adolescents vs adults

Steady state tenofovir AUC0-24 and Cmax in adolescents from P027 are presented along with published single dose or steady-state PK for 300 mg TDF in adults (figure below). The PK of tenofovir in adolescents from P027 were consistent with that achieved in adults and adolescents receiving the 300-mg dose of tenofovir disoproxil containing product. Consequently, the recommended 300-mg QD dose of TDF in the paediatric population ≥35 kg is also anticipated to result in similar PK when administered as part of DOR/3TC/TDF.

Figure 6

Comparison of Arithmetic Mean (SD) Cmax and AUC for Tenofovir Following Oral Administration of DOR/3TC/TDF 100 mg/300 mg/300 mg to Adolescents and Single or Multiple Dose Tenofovir Disoproxil Fumarate 300 mg to Healthy and HIV-1 Infected Adults

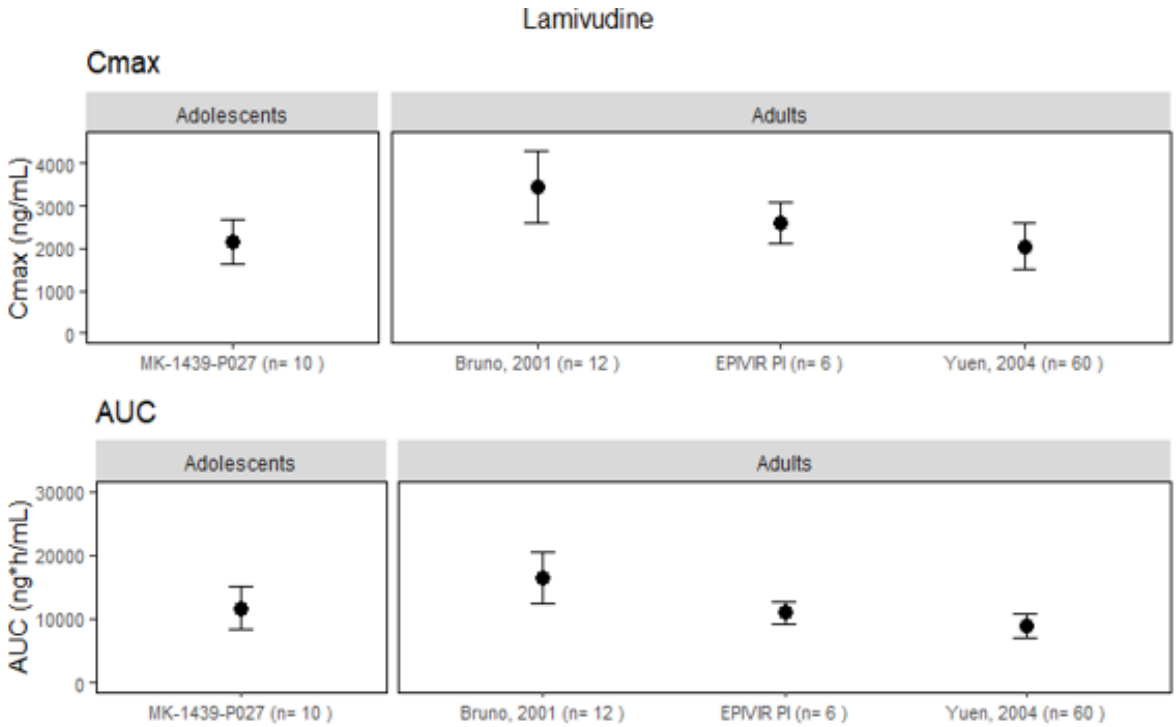


AUC presented as AUC0-inf for single dose and AUC0-24 for multiple dose; PI = Prescribing Information
Sources: [Ref. 5.4: 04P95P]; SBA = FDA summary basis of approval [Ref. 5.4: 04668S]; Boffito, 2005 [Ref. 5.4: 045VD3]

Exposure 3TC adolescents vs adults

The recommended dose of lamivudine containing product in the paediatric population ≥35 kg is 300 mg QD. In P027, adolescents received 300-mg 3TC as part of the DOR/3TC/TDF tablet, consistent with the recommended dose of lamivudine containing product in this population. Steady-state 3TC AUC0-24 and Cmax in adolescents from P027 are presented below along with published single dose or stead-state PK for 300-mg 3TC in adults.

Figure 7

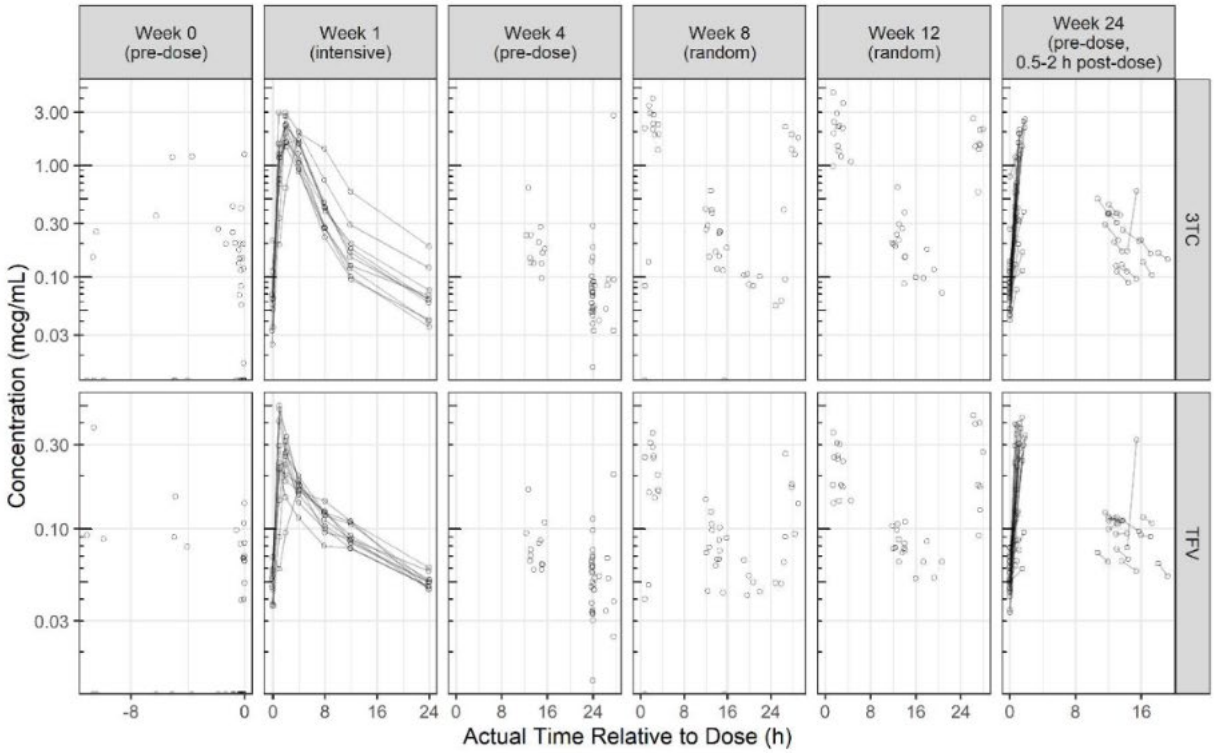


AUC presented as AUC0-inf for single dose and AUC0-24 for multiple dose; PI=prescribing iInformation
Sources: [Ref. 5.4: 04P95N]; Yuen 2004 [Ref. 5.4: 045V6Q]; Bruno 2001 [Ref. 5.4: 045V6S]

Observed lamivudine and tenofovir PK data

All lamivudine and tenofovir plasma concentrations obtained through Week 24 are plotted by actual time relative to dose for each study week in [Figure 8].

Figure 8 : Lamivudine (3TC) and tenofovir (TFV) plasma concentration by actual time relative to dose across study weeks following administration of DOR/3TC/TDF (Week 1 intensive: N=10, sparse sampling: N+35))



2.3.5. Discussion on clinical pharmacology

The extrapolation approach (efficacy) is suitable for antiviral agents because the PD target is expected to respond similarly to similar exposure in both adult and paediatric patients. PK for Doravirine, lamivudine and tenofovir in adolescents weighing at least 35 kg is expected to be similar to adults. The applicant uses tenofovir disoproxil containing product and lamivudine containing product as references for Tenofovir and Lamivudine.

A single Phase 1/2, PK, safety and tolerability trial (P027) was conducted to support the approval of DOR and DOR/3TC/TDF in HIV-1 infected paediatric patients weighing at least 35 kg.

In study P027 (adolescents over 35 kg), the applicant studied same doses for lamivudine and TDF as approved as single agent and other fixed dose combinations. The plan regarding PK was to use all PK data for doravirine, lamivudine and tenofovir. However, for lamivudine and tenofovir, the applicant has only used semi-intensive PK data from cohort 2 and discarded the sparse PK-data from 35 subjects. This approach was questioned in round 1. The applicant has now provided a figure with all the observed data for lamivudine and tenofovir. The exposure from sparse sampling is overlapping with the exposure from the rich sampling. This provides support that the exposure metrics derived from the observed PK data for the intensive sampling are adequate.

The paediatric population PK model for doravirine utilized the same structure as the final adult model. Allometric scaling with fixed exponents was included, this is supported. Age was included as a covariate; it is not understood why age was included on top of body weight based allometric scaling. However, since the age impact on clearance is very small for 12-17 years in the model, this issue is not further pursued.

The company has provided new pcVPCs. Cmax is somewhat underpredicted but overall, the Doravirine popPK models' predictive performance is deemed adequate.

The observed data as well as the model predicted exposure in P027 and the simulated exposure using NHANES population support that the Doravirine exposure in paediatric patients is similar to adults. While only one adolescent weighed under 45 kg in the P027 study, some adults weighed under 45 kg and the model predictions (using allometric scaling) are considered sufficient.

Tenofovir and lamivudine PK in adolescents weighing at least 35 kg is expected to be similar to adults. The provided observed data support this. The observed data is however only from semi-intensive PK part of study P027. It appears that sparse PK data for tenofovir and lamivudine from 35 adolescents have been discarded. This is not considered good practice. Further, no popPK model was used for tenofovir or lamivudine. PopPK models would allow for incorporation of sparse PK data in the PK analysis.

The main concern here is with regards to lack of long-term tenofovir safety data; with a limited paediatric program, the PK should be well characterized. There is large discrepancy in quality of PK data regarding what has been presented for Doravirine and what is presented for tenofovir and lamivudine.

2.3.6. Conclusions on clinical pharmacology

The extrapolation approach (efficacy) is suitable for antiviral agents. Whenever safety concerns are not specific for adolescents and children, safety is also extrapolated from adults.

With regards to tenofovir, long-term safety cannot be fully extrapolated from adults as tenofovir may have a different safety profile in subjects who are still growing.

Doravirine exposure has generally been adequately characterized. The popPK model is considered adequate. The exposure in adolescents over 35 kg is similar to adults based on provided figures and the provided effects table.

Without data, it is very probable that using same TDF and 3TC dose as in adolescents weighing ≥ 35 kg for tenofovir disoproxil containing product and lamivudine containing product would be adequate also for Delstrigo. The company has now provided an adequate presentation of the observed tenofovir and lamivudine PK data and the dose is supported.

All OCs regarding clinical pharmacology are resolved.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

There are no dose-response studies in this application.

2.4.2. Main study

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

MK-1439-027 (also known as International Maternal Paediatric Adolescent AIDS Clinical Trials Network [IMPAACT] 2014 and as Division of AIDS [DAIDS] Study No. #34150) is a Phase I/II multi-site, open-label study of the pharmacokinetics (PK), safety, and tolerability of doravirine (DOR) and doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) in children and adolescents with HIV-1 infection, 12 years to <18 years of age, and who weigh at least 35 kg.

The study is ongoing and efficacy data at 24 weeks and 48 weeks have been analysed.

Methods

Study participants

MK-1439-027 enrolled 2 cohorts in staggered fashion. Cohort 1 assessed the PK and safety of a single, oral dose of DOR 100 mg, with intensive PK evaluation completed on Day 1. All participants had safety follow-up through 2 weeks post-dose. Following the enrolment of 9 evaluable participants in Cohort 1, of whom 8 weighed at least 45 kg, enrolment was paused while the PK and safety data were reviewed by the protocol team and the Study Monitoring Committee, with options of resuming enrolment into Cohort 1, opening Cohort 2 enrolment, or assessing next steps for the study. Following this review, Cohort 2 was opened only to participants weighing at least 45 kg (because only 1 PK evaluable participant in Cohort 1 weighed between 35 kg and ≤45 kg), while Cohort 1 enrolment of participants 35 kg to ≤45 kg remained open aiming to complete the target number of 4 participants. When the total enrolment target was achieved in Cohort 2, enrolment for the study was considered completed. No additional participants were enrolled in Cohort 1.

Inclusion Criteria

All the following criteria had to be met in order for individuals to be enrolled in this study:

1. Age 12 years to <18 years at entry
2. Weight greater than or equal 35 kg at entry
3. Confirmed HIV-1-infection based on documented testing of two samples collected at different timepoints
4. ART exposure, virologic suppression, and resistance requirements

Exclusion Criteria

Participants were excluded from the study if, at any time during the screening period, any of the following were identified:

1. Evidence of decompensated liver disease manifested by the presence of or a history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs or symptoms of advanced liver diseases
2. For Cohort 2 only, detectable hepatitis C virus (HCV) by RNA PCR or current or planned treatment with direct antiviral agent for HCV
3. Presence of any active AIDS-defining opportunistic infection
4. Used, or anticipates using, chronic systemic immunosuppressive agents or systemic interferon (eg. for treatment of HCV infection) within 30 days prior to study entry
5. Diagnosed with current active tuberculosis and/or is currently being treated with a rifampicin-containing regimen

Treatments

A single dose of DOR 100 mg was administered to participants in Cohort 1.

The adult DOR/3TC/TDF tablet (100/300/300 mg) was administered once daily (QD) in Cohort 2. The doses of lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) in DOR/3TC/TDF administered to adolescents were the recommended doses for this age and weight range based on the United States (US) and European Union prescribing information for TDF containing product and 3TC containing product.

The FDC oral granule formulation was made available to participants in Cohort 2 but was not used in this study. The contents of 3 capsules were equivalent to the adult dose of DOR 100 mg/3TC 300 mg/ TDF 300 mg.

Objectives

Secondary Objectives for Cohort 2	Secondary Endpoints for Cohort 2
- Evaluate the pharmacokinetics of DOR, 3TC, and tenofovir in children and adolescents with HIV-1 infection receiving DOR/3TC/TDF, using intensive (tenofovir and 3TC) and semi-intensive (DOR) PK sampling at Week 1.	- AUC0-24,ss, Cmax,ss, and C24,ss of DOR, 3TC, and TFV
- Evaluate the 24-, 48-, and 96-week virologic efficacy of DOR/3TC/TDF in children and adolescents with HIV-1 infection.	- Plasma HIV-1 RNA<200 copies/mL - Plasma HIV-1 RNA<50 copies/mL - Plasma HIV-1 RNA<40 copies/mL - Log10 drop from baseline in plasma HIV-1 RNA (treatment-naïve participants)
- Evaluate the 24-, 48-, and 96-week immunologic response (CD4 cell count and percentage change from baseline) of children and adolescents with HIV-1 infection.	- Change in CD4 count and percent from baseline

- Evaluate the 48- and 96-week safety and tolerability of DOR/3TC/TDF administered in children and adolescents with HIV-1 infection.	- Safety outcome: all AEs, regardless of severity grade
	- Toxicity endpoints:
	  - Grade 3 or higher AEs assessed as related to study drug
	  - SAEs assessed as related to study drug
	  - Permanent discontinuation of study drug due to AEs assessed as related to study drug
	  - Grade 5 AEs (death) regardless of relationship to study drug

Note: Adverse events (AEs) were assessed for relationship to study drug by the investigator.	

Cohort 2 is a single-armed overall assessment of tolerability, with a limited number of participants and outcomes would be regarded as descriptive. Efficacy and safety are still bridged to that obtained in adults (provided similar drug exposures). However, TDF (renal/) bone toxicity is a specific issue, that have been considered of particular importance for growing youngsters in prior regulatory procedures. Having the single-arm design and lack of DEXA-scanning in mind, this study will not shed any further light on the safety concern of TDF.

Outcomes/endpoints

Safety Assessment

Safety and tolerability of DOR and DOR/3TC/TDF were evaluated by cohort based on assessment of adverse events (AEs), vital signs, and clinical laboratory values of all participants exposed to study intervention (the All Treated Population). Primary safety analyses were conducted with data through

Week 2 for Cohort 1, and through week 24 for Cohort 2. Cumulative safety data including Week 48 are also available for Cohort 2 (safety update report-SUR).

Efficacy Assessment

Efficacy was a secondary endpoint evaluated in Cohort 2 only, evaluating plasma HIV-1 RNA at 24-, 48-, and 96-weeks. All efficacy analyses were conducted using the All Treated Population comprising participants who took at least 1 dose of study intervention. Missing values were addressed using the FDA Snapshot approach and the OF approach for virologic efficacy endpoints and OF approach for immunologic efficacy endpoints. Virologic efficacy by subgroup was analysed using both the OF and FDA Snapshot approaches; immunologic efficacy by subgroup was analysed by the OF approach.

Both efficacy and safety endpoints are well-established in the field of HIV clinical trials. According to the 2013 EMA draft guidelines on the clinical development of medicinal products for the treatment of HIV infection, a specific demonstration of antiviral efficacy in paediatric patients is not required. As it is assumed that the PK/PD relation for a direct acting antiviral is roughly similar regardless of the age of the patient, the efficacy of a dose that yields sufficiently similar exposure in children, compared to adults, would be inferred.

Sample size

Cohort 1: Up to 20 participants to achieve at least 12 evaluable participants

Cohort 2: Up to 45 participants to achieve at least 40 evaluable participants

The study is not powered to allow a precise estimation efficacy or to generate a comprehensive safety database in children. Rather, efficacy and safety will primarily be bridged through PK/PD.

Randomisation and Blinding (masking)

The study was not randomized or blinded. All participants were treated with the study drug.

Statistical methods

Analysis methods of efficacy

The Primary Outcome Measures in study were safety. Virologic suppression and Immunologic response were included as a Secondary Outcome Measures in cohort 2. No hypothesis testing was to be performed.

Virologic responses for Cohort 2 participants, based on plasma HIV-1 RNA (copies/mL), will be assessed at Week 24. Virologic outcomes at additional time points might also be evaluated. Virologic failure was defined as HIV-1 RNA

- >200 copies/mL,
- >50 copies/mL, and
- >40 copies/mL, and were presented in three separate analyses.

The proportion of participants with plasma HIV-1 RNA
Immunologic response (change from baseline in CD4+ T-cell count and percent) were also to be presented.

PK Analyses:

The mean concentrations at nominal times were used to plot the linear and semi-log concentration-time profiles for intensive or semi-intensive sampling for DOR, 3TC, or TFV.

The PK parameters for DOR, 3TC, and TFV for intensive or semi-intensive sampling were calculated using non-compartmental analysis methods. In Cohort 1, the steady state PK parameters for DOR were predicted from single dose PK using non-parametric super positioning. The PK parameters were summarized using descriptive statistics.

The DOR PK targets for Cohort 1 to support multiple doses of DOR/3TC/TDF in Cohort 2 were steady state plasma drug concentration, 24 hours post-dose (observed) (C24,ss) >560 nM, the lower bound for efficacy based on Phase 3 adult studies in treatment-naïve participants with HIV-1 infection, and area under the plasma concentration-time curve from time zero to infinity (AUC0-inf)< 64.8 μM·h, the exposure associated with 200 mg QD in adults.

In Cohort 2, individual plasma DOR, 3TC, and TFV concentrations for sparse samples were summarized at each time point using descriptive statistics.

All DOR PK data from both Cohorts 1 and 2 were included in a population PK analysis and reported separately.

Analysis sets

- **All Treated Population:** Participants who have taken at least one dose of study drug
- **PK/Efficacy/Immunologic Response Analysis Population(s)** The primary PK/efficacy/immunologic response analyses for both cohorts were based on the All Treated Population, which included participants who took at least 1 dose of study intervention (Cohort 1, N=9; Cohort 2, N=45). No participants were excluded from the primary PK/efficacy/immunologic response analyses.
- **Safety Analysis Population** Safety analyses were based on the All Treated Population.

Missing data

MISSING HIV-1 RNA DATA: The Observed Failure Approach was to be used. Based on this approach, missing values are considered as failures for participants missing data due to discontinuation of study drug as a result of virologic failure or for non-treatment related reasons with last available RNA >200/50/40 copies/mL; otherwise participants with missing values are excluded. In the context of a single arm study this approach is conservative.

For regulatory submission purposes, the primary definition of virologic outcome was to be calculated according to a Missing, Switch or Discontinuation = Failure (MSDF) algorithm – as codified by the FDA's snapshot algorithm. Participants were to be classified as non-responders if they have missing HIV-1 RNA data throughout the analysis window surrounding the time point of interest. If participants discontinue the study drug prior to the time point of interest, virological failure will be determined by the HIV-1 RNA measurement at the time of discontinuation, if discontinuation occurred for reasons other than AE or death. For participants who have data collected within the analysis window of interest, virologic success or failure will be determined by the last available HIV-1 RNA measurement within that analysis window.

Sensitivity analyses

Since the missing HIV-1 RNA and CD4 values for Cohort 2 participants were to be imputed, sensitivity analyses were to be performed to assess the effects of these data imputations on the final results.

Subgroup analyses

The log drop from baseline in plasma HIV-1 RNA will be calculated and summarized for ART naïve participants. Data for virologically suppressed patients were also presented separately.

Multiplicity

No multiple testing procedure was specified, as testing was not planned for this study. Virologic efficacy was a secondary endpoint and was presented for both missing data approaches, and for all three cut-points.

Interim analyses

Dose was valuated after Cohort 1. An independent IMPAACT Study Monitoring Committee (SMC) reviewed this study regularly. No interim analysis for efficacy was planned or performed.

As efficacy will primarily be bridged through PK/PD, efficacy evaluation was not the focus in this study. In this context the statistical methodology used is considered adequate. This was a single arm study, which limits the efficacy analyses.

Virologic efficacy was a secondary endpoint, and no multiple testing procedure was specified, since testing was not planned for the study. This is acceptable, in the context that efficacy evaluation is not considered critical for the support of an extended indication. It may however limit the possibility to make claims in the SmPC.

Missing data was coded using an Observed Failure Approach, and using a Missing, Switch or Discontinuation = Failure (MSDF) algorithm – as codified by the FDA's snapshot algorithm. This is considered acceptable.

Study conduct

Part of this study was conducted during the COVID-19 pandemic. Clinical investigator study sites were located in the following 3 countries: Thailand, South Africa, and the US.

The first participant first visit was 02-JUL-2018 and the data cut-off date for the 24-week analysis was 30-SEP-2020. 48-week data was provided with the request for supplemental information (15-DEC-2021). The date of the last participant visit in week 48 was 20-JAN-2021. The study is ongoing.

The original protocol has been amended 3 times.

Amendment #1 (07-MAY-2018):

- To include language that informs participants that other US, local, and international regulatory entities may also review study records.
- To update the target steady-state C24hr for Cohort 1 to be consistent with the steady-state C24hr obtained in adults at the proposed dose.
- To update blood volume to assay 3TC and TDF for Cohort 2 intensive PK to 2.0 mL.
- To include testing of CD4 cell count at Weeks 64, 80, and 96.
- To correct Section 4.1.5.3 related to requirements for virologic suppression.
- To indicate that treatment-naïve participants should be recalled for confirmatory HIV-1 RNA testing if they have an HIV-1 RNA level ≥200 copies/mL after about 6 months on study.
- To remove inadvertent procedures included for selection and confirmation of formulation at the Cohort 1 Entry Visit."

Amendment #2 (26-APR-2019):

- To allow enrollment into Cohort 2 for children in the >45kg weight group, while attempting, but not requiring, to enroll at least 4 participants with weight between 35 kg and ≤45 kg into Cohort 1. In February 2019, the IMPAACT SMC conducted a safety and PK review of data for 9 evaluable Cohort 1 participants. Based on review of all available data, the SMC agreed that the 100 mg QD dose of DOR met protocol-specified safety and PK guidelines. The SMC also agreed that currently available data are sufficient to support opening Cohort 2 to accrual of participants weighing more

than 45 kg. The requirement to enroll a minimum of 5 participants in the 35 to ≤45 kg weight group into Cohort 2 was also revised to attempt to enroll this number but not require a minimum number of participants.
- To update, via protocol Clarification Memorandum (CM) #1, that the protocol criteria to allow enrollment of virologically suppressed participants was met.

Amendment #3 (10-JUN-2020): This amendment was implemented to manage study conduct as a result of the COVID-19 pandemic.
- To clarify and correct certain procedural specifications in the protocol, and incorporate the contents of protocol CM #2, which was issued on 31-MAR-2020 to safeguard the health and wellbeing of study participants in the context of circulating SARS-CoV-2 and the associated COVID-19 pandemic.

The protocol was amended three times. The study was single arm and open label, so it is reasonable to assume that results were known to the sponsor at the time of amendments. However, the nature of the amendments is not causing any concern.

Results

Participant flow

In Cohort 1, 10 were allocated and 9 received study intervention. One participant enrolled was not treated because of being lost to follow-up (ie, did not return to the study site).

In Cohort 2, 45 enrolled and all received study intervention.

Table 4 - Disposition of Enrolled Participants (Cohort 1)

	Total (N=10) n (%)
Treated	9 (90.0)
Not Treated	1 (10.0)
Completed Study	9 (90.0)
Discontinued Study	1 (10.0)
Lost to follow-up	1 (10.0)

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory.

Table 5 - Disposition of Enrolled Participants (Cohort 2) Weeks 0 to 24

	Treatment-Naive (N=2) n (%)	Virologically-Suppressed (N=43) n (%)	Total (N=45) n (%)
Treated	2 (100.0)	43 (100.0)	45 (100.0)
Not Treated	0 (0)	0 (0)	0 (0)
Participants Completed Week 24	2 (100.0)	42 (97.7)	44 (97.8)
Discontinued Study Treatment	0 (0)	1 (2.3)	1 (2.2)
Pregnancy	0 (0)	1 (2.3)	1 (2.2)
Discontinued Study	0 (0)	1 (2.3)	1 (2.2)
Pregnancy	0 (0)	1 (2.3)	1 (2.2)

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory.

Table 6 – Disposition of Enrolled Participants (Cohort 2)

	Treatment-Naive (N=2) n (%)	Virologically-Suppressed (N=43) n (%)	Total (N=45) n (%)
Treated	2 (100.0)	43 (100.0)	45 (100.0)
Not Treated	0 (0)	0 (0)	0 (0)
Participants Completed Week 24	2 (100.0)	42 (97.7)	44 (97.8)
Participants Completed Week 48	2 (100.0)	42 (97.7)	44 (97.8)
Completed Study Treatment (Week 96)	0 (0)	0 (0)	0 (0)
Discontinued Study Treatment	1 (50.0)	3 (7.0)	4 (8.9)
Adverse event	0 (0)	1 (2.3)	1 (2.2)
Non-compliance with study drug	1 (50.0)	0 (0)	1 (2.2)
Pregnancy	0 (0)	2 (4.7)	2 (4.4)
Completed Study (Week 96)	0 (0)	0 (0)	0 (0)
Discontinued Study	1 (50.0)	2 (4.7)	3 (6.7)
Non-compliance with study drug	1 (50.0)	0 (0)	1 (2.2)
Pregnancy	0 (0)	2 (4.7)	2 (4.4)

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory.

Recruitment

This study is ongoing; the current report contains complete data for Cohort 1 through Week 2, and for Cohort 2 through Week 48.

In Cohort 1, 11 participants were screened across 4 sites in the US. In Cohort 2, 52 participants were screened across 5 sites in the US, Thailand, and South Africa.

Conduct of the study

Baseline data

Table 7 – Participants Baseline Characteristics by Cohort All Treated Population

	Cohort 1	Cohort 2			Total
	(N=9) n (%)	Treatment-Naive (N=2) n (%)	Virologically-Suppressed (N=43) n (%)	All Cohort 2 (N=45) n (%)	(N=54) n (%)
Sex					
Male	7 (77.8)	1 (50.0)	18 (41.9)	19 (42.2)	26 (48.1)
Female	2 (22.2)	1 (50.0)	25 (58.1)	26 (57.8)	28 (51.9)
Race					
Black or African American	7 (77.8)	0 (0)	10 (23.3)	10 (22.2)	17 (31.5)
White	2 (22.2)	0 (0)	0 (0)	0 (0)	2 (3.7)
Asian	0 (0)	2 (100.0)	33 (76.7)	35 (77.8)	35 (64.8)
Ethnicity					
Hispanic or Latino	0 (0)	0 (0)	1 (2.3)	1 (2.2)	1 (1.9)
Not Hispanic or Latino	9 (100.0)	2 (100.0)	42 (97.7)	44 (97.8)	53 (98.1)
Weight at Baseline (kg)					
35 - <45	1 (11.1)	0 (0)	0 (0)	0 (0)	1 (1.9)
≥ 45	8 (88.9)	2 (100.0)	43 (100.0)	45 (100.0)	53 (98.1)
Region					
Africa	0 (0)	0 (0)	9 (20.9)	9 (20.0)	9 (16.7)
Asia/Pacific	0 (0)	2 (100.0)	33 (76.7)	35 (77.8)	35 (64.8)
North America	9 (100.0)	0 (0)	1 (2.3)	1 (2.2)	10 (18.5)
WHO Stage					
Stage 1	0 (0)	1 (50.0)	42 (97.7)	43 (95.6)	43 (79.6)
Stage 2	0 (0)	1 (50.0)	1 (2.3)	2 (4.4)	2 (3.7)
Not applicable	9 (100.0)	0 (0)	0 (0)	0 (0)	9 (16.7)
Class of Prior ARTs					
NRTI	9 (100.0)	0 (0)	43 (100.0)	43 (95.6)	52 (96.3)
NNRTI	0 (0)	0 (0)	32 (74.4)	32 (71.1)	32 (59.3)
INSTI	9 (100.0)	0 (0)	1 (2.3)	1 (2.2)	10 (18.5)
PI	0 (0)	0 (0)	10 (23.3)	10 (22.2)	10 (18.5)
Not applicable	0 (0)	2 (100.0)	0 (0)	2 (4.4)	2 (3.7)
Baseline Plasma HIV-1 RNA[a] (copies/mL)					
0 - <40	9 (100.0)	0 (0)	43 (100.0)	43 (95.6)	52 (96.3)
500,000 - <1,000,000	0 (0)	2 (100.0)	0 (0)	2 (4.4)	2 (3.7)
Baseline Hepatitis Status[b]					
Hepatitis B and/or C Positive	N/A	0 (0)	0 (0)	0 (0)	0 (0)
Hepatitis B Positive Only	N/A	0 (0)	0 (0)	0 (0)	0 (0)
Hepatitis C Positive Only	N/A	0 (0)	0 (0)	0 (0)	0 (0)
Hepatitis B and C Negative	N/A	2 (100.0)	43 (100.0)	45 (100.0)	45 (83.3)

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory; N/A = Not applicable.
[a]All participants with HIV-1 RNA <40 copies/mL are Virologically-Suppressed. The two participants with HIV-1 RNA >100,000 copies/mL are Treatment-Naive with baseline values of 507,507 copies/mL and 832,974 copies/mL.
[b]Evidence of hepatitis B surface antigen or evidence of hepatitis C antibody.

Table 8 – Summary of Other Important Baseline Characteristics by Cohort All Treated Population

		Cohort 1	Cohort 2			Total
		(N=9)	Treatment-Naive (N=2)	Virologically-Suppressed (N=43)	All Cohort 2 (N=45)	(N=54)
Age (year)	n	9	2	43	45	54
	mean	14.3	15.5	15.0	15.0	14.9
	std dev	1.6	2.1	1.6	1.6	1.6
	median	15.0	15.5	15.0	15.0	15.0
	minimum	12.0	14.0	12.0	12.0	12.0
	maximum	16.0	17.0	17.0	17.0	17.0
Weight at Baseline (kg)	n	9	2	43	45	54
	mean	55.9	59.3	53.5	53.8	54.1
	std dev	15.8	8.4	7.9	8.0	9.5
	median	48.7	59.3	51.5	51.6	51.5
	minimum	40.3	53.3	45.1	45.1	40.3
	maximum	90.8	65.2	79.8	79.8	90.8
Duration of Prior ARTs (day)	n	9	0	43	43	52
	mean	614.2		1882.3	1882.3	1662.8
	std dev	511.3		1649.6	1649.6	1586.4
	median	613.0		1018.0	1018.0	938.0
	minimum	97.0		98.0	98.0	97.0
	maximum	1805.0		5423.0	5423.0	5423.0
CD4 Cell Count (cells/mm3)	n	9	2	42	44	53
	mean	788.2	99.0	747.2	717.8	729.7
	std dev	203.9	21.2	254.0	283.1	270.9
	median	760.0	99.0	715.0	713.0	716.0
	minimum	449.0	84.0	315.0	84.0	84.0
	maximum	1137.0	114.0	1397.0	1397.0	1397.0
CD4 Percent (%)	n	9	2	42	44	53
	mean	36.2	7.6	34.3	33.1	33.6
	std dev	5.4	2.7	7.3	9.1	8.6
	median	36.0	7.6	34.4	34.2	34.5
	minimum	28.0	5.7	18.9	5.7	5.7
	maximum	43.0	9.5	50.0	50.0	50.0
HIV-1 RNA Baseline[a] (log10 copies/mL)	n	9	2	43	45	54
	mean	1.6	5.8	1.6	1.8	1.7
	std dev	0.0	0.2	0.0	0.9	0.8
	median	1.6	5.8	1.6	1.6	1.6
	minimum	1.6	5.7	1.6	1.6	1.6
	maximum	1.6	5.9	1.6	5.9	5.9

N = Number of participants in each group; n = Number of participants with non-missing data.
[a]Since the assay's lower limit of quantification is 40 copies/mL, all participants with HIV-1 RNA value of <40 copies/mL are imputed as having 39 copies/mL.

All but 1 participant in the study weighed ≥45 kg at baseline, with the 1 participant being in the 35 to <45 kg weight group of Cohort 1.

Except for the two treatment-naïve participants all in Cohort 2 were virologically suppressed and the mean CD4 counts at baseline were >700 cells/mm^3, there seem to be a missing value for one participant at baseline.

The 2 treatment-naïve participants both had baseline HIV-1 RNA levels >500,000 copies/mL and CD4 counts <120 cells/mm3.

Table 9 – Concomitant Antiretroviral Therapies All Treated Population, Cohort 1

Concomitant Antiretroviral Therapies	Total (N=9) n (%)
Participants with one or more concomitant antiretroviral therapies	9 (100.0)
INSTI +/- NRTI	0 (0)
3TC, ABC, DTG	4 (44.4)
ABC, RAL, ZDV	1 (11.1)
DTG, FTC, TAF	4 (44.4)

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory.

Numbers analysed

Numbers of participants (planned and analysed):

In Cohort 1, up to 20 participants, 12 to <18 years old, with HIV-1 infection were planned to be enrolled to achieve 8 evaluable participants weighing at least 45 kg (with an attempt to enrol approximately 4 evaluable participants weighing between 35 to ≤45 kg). As of the data cut-off or database lock date for this report, 10 participants were allocated to treatment in Cohort 1 of which 9 were evaluable.

In Cohort 2, up to 45 participants, 12 to <18 years old with HIV-1 infection were to be enrolled to achieve 40 evaluable participants in the weight group approved for Cohort 1 (with an attempt to enrol approximately 5 participants in the 35 to ≤45 kg weight group, if this weight group enrolled and was approved in Cohort 1). As of the 24-week data cut-off or database lock date for this report, 45 participants weighing ≥45 kg were allocated to treatment in Cohort 2 of which all were evaluable. Forty-four participants completed study treatment through Week 48.

Outcomes and estimation

Table 10 – Compliance Summary All Treated Population, Cohort 2 Weeks 0 to 24

Percent Compliance	Treatment-Naive (N=2) n (%)	Virologically-Suppressed (N=43) n (%)	Total (N=45) n (%)
100%	1 (50.0)	32 (74.4)	33 (73.3)
99 to 90%	1 (50.0)	11 (25.6)	12 (26.7)

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory.
Percent compliance is defined as (30 days - days of missing treatment)/30*100.
Compliance values represent an average of all available adherence data up to and including Week 24.

Table 11 – Participants on Study Drug by Dose and Duration of Treatment All Treated Population

Dose (DOR/3TC/TDF)	>8 - ≤16 wks	>16 - ≤24 wks	>24 - ≤36 wks	>36 - ≤48 wks	>48 wks	Total	Median, Range of Days on Study Drug	Mean (SD) of Days on Study Drug
100mg/300mg/300mg	1	0	12	21	11	45	310 (57, 373)	296.4 (58.5)

Cohort 2 - All available data as of SUR database Lock

Dose (DOR/3TC/TDF)	>8 - ≤24 wks	>24 - ≤36 wks	>36 - ≤48 wks	>48 - ≤64 wks	>64 - ≤80 wks	>80 wks	Total	Median, Range of Days on Study Drug	Mean (SD) of Days on Study Drug
100mg/300mg/300mg	1	0	0	2	14	28	45	590 (57, 651)	559.7 (98.4)

Table 12 – 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.

Table 13 – Efficacy Analysis at Week 48 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)	40/42	95.2 (83.8, 99.4)	41/44	93.2 (81.3, 98.6)
Proportion of participants with HIV-1 RNA <50 copies/mL	1/2	50.0 (1.3, 98.7)	40/42	95.2 (83.8, 99.4)	41/44	93.2 (81.3, 98.6)
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)	40/43	93.0 (80.9, 98.5)	41/45	91.1 (78.8, 97.5)
Proportion of participants with HIV-1 RNA <50 copies/mL	1/2	50.0 (1.3, 98.7)	40/43	93.0 (80.9, 98.5)	41/45	91.1 (78.8, 97.5)
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)	175.0 [2]	(-99.0, 937.4)	75.5 [41]	(6.7, 144.3)	80.1 [43]	(14.2, 146.0)
Change from baseline in CD4 percent	9.1 [2]	(-7.6, 29.4)	-0.9 [41]	(-2.1, 0.3)	-0.4 [43]	(-1.7, 0.9)

Due to low specimen volume, some participants' plasma samples were diluted by a factor of 1.5 or 5 before being tested. This dilution increased the assay's limit of quantification (LoQ) from 40 to 60 or 200 copies/mL respectively. 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 two participants at Week 48 were diluted (by a factor of 1.5 each).
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.

Table 14 – Proportion of Participants With HIV-1 RNA < 40 Copies/mL Over Time FDA Snapshot Approach All Treated Population, Cohort 2 Weeks 0 to 48

	Treatment-Naive		Virologically-Suppressed		Total	
Week	n/N	% [95% CI]	n/N	% [95% CI]	n/N	% [95% CI]
Week 0	0/2	0.0 (0.0, 84.2)	43/43	100.0 (91.8, 100.0)	43/45	95.6 (84.9, 99.5)
Week 2	0/2	0.0 (0.0, 84.2)	39/43	90.7 (77.9, 97.4)	39/45	86.7 (73.2, 94.9)
Week 4	0/2	0.0 (0.0, 84.2)	42/43	97.7 (87.7, 99.9)	42/45	93.3 (81.7, 98.6)
Week 8	0/2	0.0 (0.0, 84.2)	39/43	90.7 (77.9, 97.4)	39/45	86.7 (73.2, 94.9)
Week 12	0/2	0.0 (0.0, 84.2)	40/43	93.0 (80.9, 98.5)	40/45	88.9 (75.9, 96.3)
Week 16	1/2	50.0 (1.3, 98.7)	35/43	81.4 (66.6, 91.6)	36/45	80.0 (65.4, 90.4)
Week 24	1/2	50.0 (1.3, 98.7)	41/43	95.3 (84.2, 99.4)	42/45	93.3 (81.7, 98.6)
Week 48	1/2	50.0 (1.3, 98.7)	40/43	93.0 (80.9, 98.5)	41/45	91.1 (78.8, 97.5)

Approach to handling missing values: FDA Snapshot approach under which all missing values were counted as failure.
Due to low specimen volume, some participants' plasma samples were diluted by a factor of 1.5 or 5 before being tested. This dilution increased the assay's limit of quantification (LoQ) from 40 to 60 or 200 copies/mL respectively. 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 4, three participants at Week 16 and one participant at Week 24 were diluted by a factor of 5, whereas samples for two participants at Week 48 were diluted by a factor of 1.5.
N = Number of participants in each group; n = Number of participants in each subcategory; 95% CI = Exact 95% confidence interval.

The proportion of participants with HIV-1 RNA **<50 Copies/mL** over time using the FDA Snapshot Approach in Cohort 2 All Treated Population Weeks 0 to 48 was the same as for HIV-1 RNA <40 Copies/mL over time, see table above.

Table 15 – Proportion of Participants With HIV-1 RNA < 200 Copies/mL Over Time FDA Snapshot Approach All Treated Population, Cohort 2 Weeks 0 to 48

	Treatment-Naive		Virologically-Suppressed		Total	
Week	n/N	% [95% CI]	n/N	% [95% CI]	n/N	% [95% CI]
Week 0	0/2	0.0 (0.0, 84.2)	43/43	100.0 (91.8, 100.0)	43/45	95.6 (84.9, 99.5)
Week 2	0/2	0.0 (0.0, 84.2)	39/43	90.7 (77.9, 97.4)	39/45	86.7 (73.2, 94.9)
Week 4	0/2	0.0 (0.0, 84.2)	43/43	100.0 (91.8, 100.0)	43/45	95.6 (84.9, 99.5)
Week 8	0/2	0.0 (0.0, 84.2)	40/43	93.0 (80.9, 98.5)	40/45	88.9 (75.9, 96.3)
Week 12	1/2	50.0 (1.3, 98.7)	41/43	95.3 (84.2, 99.4)	42/45	93.3 (81.7, 98.6)
Week 16	2/2	100.0 (15.8, 100.0)	38/43	88.4 (74.9, 96.1)	40/45	88.9 (75.9, 96.3)
Week 24	1/2	50.0 (1.3, 98.7)	42/43	97.7 (87.7, 99.9)	43/45	95.6 (84.9, 99.5)
Week 48	1/2	50.0 (1.3, 98.7)	42/43	97.7 (87.7, 99.9)	43/45	95.6 (84.9, 99.5)

Approach to handling missing values: FDA Snapshot approach under which all missing values were counted as failure.
N = Number of participants in each group; n = Number of participants in each subcategory; 95% CI = Exact 95% confidence interval.

Table 16 – Change From Baseline in Log10 Plasma HIV-1 RNA Over Time for Treatment-Naive Participants Observed Failure Approach All Treated Population, Cohort 2 Weeks 0 to 48

		Change from Baseline in Log10 Plasma HIV-1 RNA	
Visit	n	Baseline Mean	Mean Change (95% CI)
Week 2	2	5.8	-2.0 (-3.8, -0.3)
Week 4	2	5.8	-2.2 (-5.8, 2.3)
Week 8	2	5.8	-2.8 (-5.8, 6.7)
Week 12	2	5.8	-3.6 (-5.8, 1.2)
Week 16	2	5.8	-3.9 (-5.8, 1.7)
Week 24	2	5.8	-2.6 (-5.8, 19.0)
Week 48	2	5.8	-2.1 (-5.8, 26.1)

Observed Failure approach: baseline values were carried forward for participants who have discontinued the study treatment due to lack of efficacy or for non-treatment related reasons with last available HIV-1 RNA ≥ 200 copies/mL; otherwise participants with missing values are excluded.
n = Number of participants in each subcategory; 95% CI = 95% confidence interval calculated based on t-distribution.

One discontinued from the study due to pregnancy after 8 weeks of treatment but had HIV-1 RNA <40 copies/mL at discontinuation and 1 had missing data for <50 copies/mL and <40 copies/mL due to low specimen volume at 24-weeks.

One of the 2 treatment naïve participants in Cohort 2 achieved HIV-1 RNA levels below each cutoff at 24 weeks and 1 had protocol-defined virologic failure. No participant met the criteria for protocol-defined virologic failure between Week 24 and Week 48.

Both at Week 24 and 48, the majority of the participants that were virologically suppressed at baseline in Cohort 2 maintained HIV-1 RNA levels below each cut-off, which is anticipated in this population.

The one treatment-naïve participant with protocol-defined virologic failure had records indicated noncompliance to study treatment, see additional information below.

Ancillary analyses

Change from Baseline in CD4 Cell Count (Cells/mm3)

The mean change from baseline CD4 cell count using the OF approach was maintained over time with small increases observed in virologically suppressed participants in Cohort 2. Increases from baseline in CD4 cell count were observed through Week 48 for the 2 treatment-naïve participants in Cohort 2.

Table 17 – Summary of Changes From Baseline in CD4 Absolute Count (Cells/mm3) Over Time Observed Failure Approach All Treated Population, Cohort 2 Weeks 0 to 48

						Change from Baseline				
ART Classification at Entry	N	Actual Relative Time	n	Baseline Median	Baseline Mean	Mean [95% CI]	SD	Median [Q1, Q3]	Min	Max
Treatment-Naive	2	Baseline	2	99.0	99.0					
		Week 4	2	99.0	99.0	251.5 [-99.0, 677.2]	47.4	251.5 [218.0, 285.0]	218	285
		Week 12	2	99.0	99.0	251.0 [162.1, 339.9]	9.9	251.0 [244.0, 258.0]	244	258
		Week 24	2	99.0	99.0	203.5 [-99.0, 578.3]	41.7	203.5 [174.0, 233.0]	174	233
		Week 48	2	99.0	99.0	175.0 [-99.0, 937.4]	84.9	175.0 [115.0, 235.0]	115	235
Virologically-Suppressed	43	Baseline	42	715.0	747.2					
		Week 4	42	715.0	747.2	27.0 [-26.2, 80.2]	170.8	10.4 [-86.0, 140.0]	-339	517
		Week 12	41	714.0	739.3	-6.5 [-58.2, 45.1]	163.7	-4.0 [-80.0, 99.0]	-441	318
		Week 24	41	714.0	739.3	79.0 [12.7, 145.3]	210.1	88.0 [-34.0, 216.0]	-422	459
		Week 48	41	714.0	739.3	75.5 [6.7, 144.3]	217.9	59.0 [-63.0, 177.0]	-297	620
Total	45	Baseline	44	713.0	717.8					
		Week 4	44	713.0	717.8	37.2 [-15.5, 90.0]	173.5	17.0 [-80.0, 162.0]	-339	517
		Week 12	43	712.0	709.5	5.4 [-46.6, 57.4]	169.0	-4.0 [-80.0, 129.0]	-441	318
		Week 24	43	712.0	709.5	84.8 [21.1, 148.4]	206.8	101.0 [-34.0, 217.0]	-422	459
		Week 48	43	712.0	709.5	80.1 [14.2, 146.0]	214.1	64.0 [-63.0, 217.0]	-297	620

Observed Failure approach: baseline values were carried forward for participants who have discontinued the study treatment due to lack of efficacy or for non-treatment related reasons with last available HIV-1 RNA ≥ 200 copies/mL; otherwise participants with missing values are excluded.
Calculations of baseline mean, median and change from baseline statistics are based on participants with measurements both at baseline and the timepoint assessed.
N = Number of participants in each group; n = Number of participants in each subcategory; SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum value; Max = Maximum value; 95% CI = 95% confidence interval calculated based on t-distribution.

Change from Baseline in CD4 Percent

Table 18 – Summary of Changes From Baseline in CD4 Percent Over Time Observed Failure Approach All Treated Population, Cohort 2 Weeks 0 to 48

						Change from Baseline			
ART Classification at Entry	N	Actual Relative Time	n	Baseline Median	Baseline Mean	Mean [95% CI]	SD	Median [Q1, Q3]	Min	Max
Treatment-Naive	2	Baseline	2	7.6	7.6					
		Week 4	2	7.6	7.6	5.1 [-7.6, 20.9]	1.8	5.1 [3.8, 6.3]	3.8	6.3
		Week 12	2	7.6	7.6	7.9 [-7.6, 25.7]	2.0	7.9 [6.5, 9.3]	6.5	9.3
		Week 24	2	7.6	7.6	7.3 [-7.6, 23.1]	1.8	7.3 [6.0, 8.5]	6.0	8.5
		Week 48	2	7.6	7.6	9.1 [-7.6, 29.4]	2.3	9.1 [7.5, 10.7]	7.5	10.7
Virologically-Suppressed	43	Baseline	42	34.4	34.3					
		Week 4	42	34.4	34.3	-0.6 [-1.8, 0.7]	3.9	0.0 [-3.4, 1.9]	-11.1	9.3
		Week 12	41	34.3	34.1	-2.5 [-3.7, -1.4]	3.7	-2.1 [-3.2, -0.1]	-16.1	4.5
		Week 24	41	34.3	34.1	-1.9 [-3.2, -0.7]	3.9	-1.9 [-3.2, 0.6]	-10.1	8.6
		Week 48	41	34.3	34.1	-0.9 [-2.1, 0.3]	3.8	-0.6 [-2.7, 1.4]	-9.7	5.0
Total	45	Baseline	44	34.2	33.1					
		Week 4	44	34.2	33.1	-0.3 [-1.5, 0.9]	4.0	0.2 [-2.8, 2.3]	-11.1	9.3
		Week 12	43	34.1	32.9	-2.1 [-3.4, -0.8]	4.2	-2.0 [-3.2, 0.0]	-16.1	9.3
		Week 24	43	34.1	32.9	-1.5 [-2.8, -0.2]	4.3	-1.7 [-3.2, 1.1]	-10.1	8.6
		Week 48	43	34.1	32.9	-0.4 [-1.7, 0.9]	4.2	-0.6 [-2.7, 2.6]	-9.7	10.7

Observed Failure approach: baseline values were carried forward for participants who have discontinued the study treatment due to lack of efficacy or for non-treatment related reasons with last available HIV-1 RNA ≥ 200 copies/mL; otherwise participants with missing values are excluded.
Calculations of baseline mean, median and change from baseline statistics are based on participants with measurements both at baseline and the timepoint assessed.
N = Number of participants in each group; n = Number of participants in each subcategory; SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum value; Max = Maximum value; 95% CI = 95% confidence interval calculated based on t-distribution.

Protocol-defined Virologic Failure and Development of Viral Drug Resistance

One treatment-naïve participant in Cohort 2 had protocol-defined virologic failure (defined as 2 consecutive plasma HIV-1 RNA test results ≥200 copies/mL) by Week 24.

The participant had no evidence of baseline resistance and showed a consistent decrease in HIV-1 RNA levels achieving virologic suppression (HIV-1 RNA <200 copies/mL) by Week 16 of DOR/3TC/TDF treatment. However, this suppression was not maintained at Week 24, and the participant was counted as a protocol-defined virologic failure in the Week 24 analysis. The participant had no emergence of phenotypic or genotypic resistance to DOR, 3TC, or TDF. The participant's records indicated noncompliance to study treatment based on 7 missed doses and plasma levels BLQ (reported as <1.00 µg/L) for DOR, 3TC, and TFV at Week 8. The participant was allowed to continue on the study with counseling to improve adherence to treatment and was still in the study as of week 64, however, there was no re-suppression of viral RNA.

Palatability and Acceptability Assessment

Most participants reported that the overall taste, tablet size, and shape of DOR and DOR/3TC/TDF were acceptable and manageable, with no problems swallowing either tablet. All participants in Cohort 2 were offered the choice of oral tablet or oral granule formulation of DOR/3TC/TDF. However, no participants opted to take the oral granule formulation.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19 – Summary of Efficacy for trial P027V01MK1439 up to week 24

Title: 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. Efficacy results are reported in the Clinical Study Report [Ref. 5.3.5.2: P027V01MK1439: 11.2].		
Study Identifier	Protocol Number: P027V01MK1439 IND: 137,041 EudraCT: N/A	
Design	Phase 1/2 multicenter, open-label study of the PK, safety, and tolerability of DOR and DOR/3TC/TDF in children and adolescents with HIV-1 infection (age 12 to <18 years, who weigh at least 35 kg). The study is ongoing through Week 96; results from Week 24 (primary endpoint) and from Week 48 analyses are presented.	
	Duration of Main Phase:	• First Participant First Visit: 02-JUL-2018 • Last participant's last visit for primary endpoint (Week 24) analysis: 19-AUG-2020 • Last participant's last visit for Week 48 analysis: 20 JAN-2021
	Duration of Run-in Phase:	Not Applicable
	Duration of Extension Phase:	Not Applicable
Primary Efficacy Objective	**Objective:** Efficacy was not a primary objective for this study.	
Secondary Efficacy Objective	**Objective:** Secondary efficacy objectives were evaluated for Cohort 2 only, as follows: Evaluate the 24-, 48-, and 96-week virologic efficacy of DOR/3TC/TDF in children and adolescents with HIV-1 infection. Evaluate the 24-, 48-, and 96-week immunologic response (CD4+ T-cell count and percentage change from baseline) of children and adolescents with HIV-1 infection.	
Treatment Groups	Cohort 1	A single dose of DOR (100 mg) added to their current regimen of DTG or RAL plus 2 NRTIs. All participants received the adult tablet. Participants were followed up for 2 weeks. Eleven participants were screened, 10 were allocated, and 9 received DOR and completed the study through Week 2.
	Cohort 2	DOR/3TC/TDF (100 mg/300 mg/300 mg) QD. Oral granule formulation was offered in Cohort 2 but was not chosen by any participant. All participants received the adult tablet. Participants were followed up for 96 weeks. Fifty-two participants were screened, 45 were allocated and received DOR/3TC/TDF, 44 completed through Week 24, and 1 discontinued (due to pregnancy at Week 8).

Endpoints and Definitions	Virologic Efficacy at Weeks 24, 48, and 96	Plasma HIV-1 RNA<200 copies/mL Plasma HIV-1 RNA<50 copies/mL Plasma HIV-1 RNA<40 copies/mL Log10 drop from baseline in plasma HIV-1 RNA (ART-naïve participants)
	Immunologic Response at Weeks 24, 48, and 96	Change in CD4+ T-cell count and CD4+ T-cell percent from baseline
Database Lock	Database lock date for Week 24: 30-SEP-2020 The efficacy tables for Week 48 to respond to the Agency were generated from the database lock: 07-JUL-2021	

Statistical Analysis and Methods:

Efficacy Analysis: Efficacy for Cohort 2 was assessed based on the proportion of participants with HIV-1 RNA levels at 3 cutoff levels (<40 copies/mL, <50 copies/mL, <200 copies/mL) at Week 24 and 48. Immunologic response was assessed based on mean change in CD4+ T-cell count and mean change in CD4+ T-cell percent from baseline.

Missing values were addressed using 2 approaches:

- The FDA Snapshot approach, which considered participants with missing data to be failures regardless of reason.
- The OF approach, which considered participants who prematurely discontinued assigned treatment due to lack of efficacy to be failures. Participants with other types of missing data were excluded from the analysis.

The FDA Snapshot approach was the primary approach for the analysis of the proportion of participants maintaining virologic suppression based on the 3 HIV-1 RNA cutoff levels. The OF approach was applied as a sensitivity analysis. Immunologic response was analyzed using the OF Approach.

Subgroup analyses for efficacy responses were conducted using both the OF and FDA Snapshot approaches. Subgroup analyses for immunologic response were conducted using the OF approach.

Results and Analyses

Analysis Description	**Primary Analyses**
Analysis population and time point description	Efficacy analyses were conducted using the All-Treated Population, which included participants who took at least 1 dose of study intervention. Timepoint: Week 24 In Cohort 2, a total of 45 participants were allocated to treatment (enrolled). All participants allocated to treatment received at least 1 dose of study intervention. A total of 44 participants completed treatment through Week 24, and 1 discontinued due to pregnancy after 8 weeks of treatment. Timepoint: Week 48 All participants allocated to treatment received at least 1 dose of study intervention. A total of 44 participants completed treatment through Week 48, and 1 discontinued due to pregnancy after 8 weeks of treatment.

Results	**Efficacy and Immunologic Response through Week 24 for Cohort 2** The majority (>95%) of virologically suppressed participants in Cohort 2 maintained HIV-1 RNA levels below each cutoff (<40 copies/mL, <50 copies/mL, and <200 copies/mL) at Week 24 based on the FDA Snapshot approach. One of the 2 treatment-naïve participants achieved HIV-1 RNA levels below each cutoff. Based on small sample sizes, limited conclusions can be drawn from an examination of virologic responses by demographic factors. However, virologic responses for virologically suppressed participants in Cohort 2 at Week 24 were generally consistent across subgroups of sex, race, region, and ethnicity. Mean log10 plasma HIV-1 RNA decreased from baseline through Week 24 for treatment-naïve participants in Cohort 2. The mean change from baseline CD4 cell count was maintained over time with small increases observed in virologically suppressed participants in Cohort 2. Increases from baseline in CD4 cell count were observed through Week 24 for the 2 treatment naïve participants in Cohort 2. **Efficacy and Immunologic Response through Week 48 for Cohort 2** At Week 48, 93% (40/43) participants who switched to DOR/3TC/TDF in Cohort 2 remained virologically suppressed (HIV-1 RNA <50 copies/mL) at Week 48, based on the FDA Snapshot approach. Similar to Week 24 the mean change from baseline CD4 cell count using the OF approach was maintained over time with small increases observed in virologically suppressed participants in Cohort 2 up to Week 48. Increases from baseline in CD4 cell count were observed through Week 48 for the 2 treatment-naïve participants in Cohort 2. **Protocol-defined Virologic Failure and Development of Viral Drug Resistance for Cohort 2** One out of 45 participants in Cohort 2 had protocol-defined virologic failure. This treatment-naïve participant had no evidence of baseline resistance and no emergence of genotypic or phenotypic resistance to DOR, 3TC, or TDF. No participant met the criteria for protocol-defined virologic failure (defined as 2 consecutive plasma HIV-1 RNA test results ≥200 copies/mL) between Week 24 and Week 48. **Palatability and Acceptability** The majority of participants reported that the overall taste, tablet size, and shape of the DOR and DOR/3TC/TDF tablets were acceptable and manageable and that they had no problems swallowing the tablet.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The study is not powered for a precise estimate of efficacy and no control arm is available for comparison. Rather, given that exposure is comparable, efficacy will be extrapolated through a PK/PD-bridge which is in line with EMA guidance.

Efficacy data and additional analyses

The results of the study show that the majority of the virologically suppressed participants maintained suppression of HIV-1 RNA viral load with 41/43 (95.3 %) of the participants below 40 copies/mL at week 24 and 40/43 (93%) of the participants below 40 copies/mL at week 48. One participant discontinued from the study due to pregnancy after 8 weeks of treatment but had HIV-1 RNA <40 copies/mL at discontinuation and 1 had missing data at week 24 for <50 copies/mL and <40 copies/mL due to low specimen volume.

Viral suppression was also achieved in 1 of the treatment-naïve subjects, the other had treatment failure linked to noncompliance. Up to week 48 de novo resistance was not reported. The mean change from baseline CD4 cell count was maintained over time with small increases observed in virologically suppressed participants. In the 2 treatment naïve participants increases from baseline in CD4 cell count were also observed through Week 48. The included adolescents were treated with the approved Delstrigo tablet, none of the participant opted for the oral granules (TDF/3TC/DOR).

2.4.4. Conclusions on the clinical efficacy

Given that exposure is comparable, DOR or DOR/3TC/TDF is effective in the treatment of HIV in adolescent patients weighing at least 35 kg.

2.5. Clinical safety

Introduction

P027V01MK1439 evaluated the safety and tolerability of DOR and DOR/3TC/TDF in adolescents based on assessment of AEs, vital signs, clinical laboratory values of all 54 participants exposed to study intervention (the All Treated Population). Primary safety analyses were conducted with data through Week 2 for Cohort 1, and through Week 24 for Cohort 2. In addition, all available safety data for Cohort 2 (through a database lock 07-JUL-2021) including week 48 has been submitted.

Patient exposure

In Cohort 1, a total of 9 participants received a single dose of DOR.

In Cohort 2, a total of 45 participants received at least 1 dose of DOR/3TC/TDF. The mean (SD) duration of days on study intervention was 296.4 (58.5) days.

Adverse events

Most common adverse events

Cohort 1

In Cohort 1, AEs were reported in 4 of 9 participants (44.4%) through Week 2 following single-dose administration of DOR 100 mg. Two participants had Grade 1 (mild) increased aspartate aminotransferase (1 of these participants also had Grade 1 diarrhoea); 1 participant had Grade 1 decreased neutrophil count; and 1 participant had Grade 2 (moderate) increased blood alkaline phosphatase, Grade 2 increased blood glucose, and Grade 1 increased blood phosphorus. None of these AEs were considered serious or drug-related based on investigator assessment.

Cohort 2

One or more AEs were reported for all participants during the first 24 weeks of the study. The most frequently reported AEs (≥20% overall) during the first 24 weeks of the study were increased alanine aminotransferase, increased aspartate aminotransferase, increased blood creatinine, decreased carbon dioxide, and decreased glomerular filtration rate, see table below. Most of these were Grade 1 or 2 AEs, were not considered serious or drug-related based on investigator assessment, had an outcome of 'recovered/resolved' or 'recovering/resolving' at the time of database lock, and had no action taken with regard to study intervention. No AE led to discontinuation of study intervention.

One participant had a reported drug-related AE (Grade 1 dizziness in a treatment-naïve participant). No participants permanently discontinued treatment due to an AE. One participant discontinued from the study due to pregnancy after 8 weeks of treatment. No participants in Cohort 2 died during this study.

Table 20 – Participants With Adverse Events (Incidence >0%) All Treated Population, Cohort 2 Weeks 0 to 24

System Organ Class Preferred Term	Treatment-Naive (N=2) n (%)	Virologically-Suppressed (N=43) n (%)	Total (N=45) n (%)
Number of participants with one or more adverse events	2 (100.0)	43 (100.0)	45 (100.0)
Blood and lymphatic system disorders	0 (0)	2 (4.7)	2 (4.4)
Iron deficiency anaemia	0 (0)	2 (4.7)	2 (4.4)
Lymphadenitis	0 (0)	1 (2.3)	1 (2.2)
Lymphadenopathy	0 (0)	1 (2.3)	1 (2.2)
Eye disorders	0 (0)	1 (2.3)	1 (2.2)
Conjunctival pallor	0 (0)	1 (2.3)	1 (2.2)
Gastrointestinal disorders	0 (0)	5 (11.6)	5 (11.1)
Abdominal pain	0 (0)	1 (2.3)	1 (2.2)
Abdominal pain upper	0 (0)	1 (2.3)	1 (2.2)
Aphthous ulcer	0 (0)	2 (4.7)	2 (4.4)
Diarrhoea	0 (0)	2 (4.7)	2 (4.4)
Dyspepsia	0 (0)	1 (2.3)	1 (2.2)
Flatulence	0 (0)	1 (2.3)	1 (2.2)
Nausea	0 (0)	1 (2.3)	1 (2.2)
Salivary gland mucocoele	0 (0)	1 (2.3)	1 (2.2)
Vomiting	0 (0)	1 (2.3)	1 (2.2)
General disorders and administration site conditions	0 (0)	3 (7.0)	3 (6.7)
Malaise	0 (0)	2 (4.7)	2 (4.4)
Pyrexia	0 (0)	1 (2.3)	1 (2.2)
Hepatobiliary disorders	0 (0)	2 (4.7)	2 (4.4)
Hyperbilirubinaemia	0 (0)	2 (4.7)	2 (4.4)
Infections and infestations	0 (0)	10 (23.3)	10 (22.2)
Bronchitis viral	0 (0)	2 (4.7)	2 (4.4)
Gastroenteritis	0 (0)	1 (2.3)	1 (2.2)
Nasopharyngitis	0 (0)	4 (9.3)	4 (8.9)
Pharyngitis	0 (0)	1 (2.3)	1 (2.2)
Pharyngitis bacterial	0 (0)	1 (2.3)	1 (2.2)
Urinary tract infection	0 (0)	2 (4.7)	2 (4.4)
Injury, poisoning and procedural complications	0 (0)	3 (7.0)	3 (6.7)

System Organ Class Preferred Term	Treatment-Naive (N=2) n (%)	Virologically-Suppressed (N=43) n (%)	Total (N=45) n (%)
Procedural pain	0 (0)	1 (2.3)	1 (2.2)
Skin abrasion	0 (0)	1 (2.3)	1 (2.2)
Thermal burn	0 (0)	1 (2.3)	1 (2.2)
Investigations	2 (100.0)	41 (95.3)	43 (95.6)
Alanine aminotransferase increased	0 (0)	18 (41.9)	18 (40.0)
Aspartate aminotransferase increased	0 (0)	12 (27.9)	12 (26.7)
Blood albumin decreased	0 (0)	3 (7.0)	3 (6.7)
Blood alkaline phosphatase increased	0 (0)	7 (16.3)	7 (15.6)
Blood bicarbonate decreased	1 (50.0)	6 (14.0)	7 (15.6)
Blood cholesterol increased	0 (0)	4 (9.3)	4 (8.9)
Blood creatinine increased	1 (50.0)	11 (25.6)	12 (26.7)
Blood glucose decreased	0 (0)	3 (7.0)	3 (6.7)
Blood glucose increased	1 (50.0)	4 (9.3)	5 (11.1)
Blood phosphorus decreased	0 (0)	2 (4.7)	2 (4.4)
Blood potassium decreased	0 (0)	6 (14.0)	6 (13.3)
Blood potassium increased	0 (0)	1 (2.3)	1 (2.2)
Blood pressure increased	0 (0)	6 (14.0)	6 (13.3)
Blood sodium decreased	0 (0)	4 (9.3)	4 (8.9)
Blood triglycerides increased	0 (0)	1 (2.3)	1 (2.2)
Carbon dioxide decreased	0 (0)	9 (20.9)	9 (20.0)
Glomerular filtration rate decreased	1 (50.0)	18 (41.9)	19 (42.2)
Haemoglobin decreased	1 (50.0)	3 (7.0)	4 (8.9)
Lipase increased	1 (50.0)	5 (11.6)	6 (13.3)
Low density lipoprotein increased	0 (0)	1 (2.3)	1 (2.2)
Platelet count decreased	0 (0)	1 (2.3)	1 (2.2)
Metabolism and nutrition disorders	1 (50.0)	8 (18.6)	9 (20.0)
Decreased appetite	0 (0)	1 (2.3)	1 (2.2)
Hypercholesterolaemia	0 (0)	1 (2.3)	1 (2.2)
Hypertriglyceridaemia	0 (0)	3 (7.0)	3 (6.7)
Hypocholesterolaemia	0 (0)	1 (2.3)	1 (2.2)
Hypokalaemia	1 (50.0)	3 (7.0)	4 (8.9)
Obesity	0 (0)	1 (2.3)	1 (2.2)
Musculoskeletal and connective tissue disorders	0 (0)	2 (4.7)	2 (4.4)
Arthralgia	0 (0)	1 (2.3)	1 (2.2)
Joint swelling	0 (0)	1 (2.3)	1 (2.2)
Myalgia	0 (0)	1 (2.3)	1 (2.2)
Nervous system disorders	1 (50.0)	6 (14.0)	7 (15.6)
Dizziness	1 (50.0)	0 (0)	1 (2.2)

System Organ Class Preferred Term	Treatment-Naive (N=2) n (%)	Virologically-Suppressed (N=43) n (%)	Total (N=45) n (%)
Headache	0 (0)	6 (14.0)	6 (13.3)
Lethargy	0 (0)	1 (2.3)	1 (2.2)
Renal and urinary disorders	0 (0)	4 (9.3)	4 (8.9)
Dysuria	0 (0)	1 (2.3)	1 (2.2)
Proteinuria	0 (0)	3 (7.0)	3 (6.7)
Reproductive system and breast disorders	0 (0)	2 (4.7)	2 (4.4)
Dysmenorrhoea	0 (0)	1 (2.3)	1 (2.2)
Oligomenorrhoea	0 (0)	1 (2.3)	1 (2.2)
Respiratory, thoracic and mediastinal disorders	0 (0)	14 (32.6)	14 (31.1)
Cough	0 (0)	7 (16.3)	7 (15.6)
Dysphonia	0 (0)	1 (2.3)	1 (2.2)
Nasal congestion	0 (0)	6 (14.0)	6 (13.3)
Oropharyngeal discomfort	0 (0)	1 (2.3)	1 (2.2)
Oropharyngeal pain	0 (0)	3 (7.0)	3 (6.7)
Pharyngeal erythema	0 (0)	2 (4.7)	2 (4.4)
Productive cough	0 (0)	5 (11.6)	5 (11.1)
Rhinorrhoea	0 (0)	5 (11.6)	5 (11.1)
Tonsillar hypertrophy	0 (0)	1 (2.3)	1 (2.2)
Skin and subcutaneous tissue disorders	1 (50.0)	4 (9.3)	5 (11.1)
Acne	1 (50.0)	2 (4.7)	3 (6.7)
Papule	1 (50.0)	1 (2.3)	2 (4.4)
Pruritus	1 (50.0)	1 (2.3)	2 (4.4)
Rash	0 (0)	1 (2.3)	1 (2.2)
Rash erythematous	0 (0)	1 (2.3)	1 (2.2)
Seborrhoeic dermatitis	0 (0)	1 (2.3)	1 (2.2)
Urticaria	0 (0)	1 (2.3)	1 (2.2)
Vascular disorders	0 (0)	4 (9.3)	4 (8.9)
Hypertension	0 (0)	4 (9.3)	4 (8.9)

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory.
Adverse event terms are from MedDRA Version 23.0.

Grade 3 or Greater Adverse Events up to week 24

In Cohort 1 there were no Grade 3 (severe) or greater AEs reported, using DAIDS AE grading for severity.

In Cohort 2 Grade 3 AEs were reported in 9 (20.0%) virologically suppressed participants during the first 24 weeks of the study. No Grade 4 (potentially life-threatening) or Grade 5 (death) AEs were reported.

Table 21 – Participants With Grade 3 or Greater Adverse Events (Incidence >0%) All Treated Population, Cohort 2 Weeks 0 to 24

	Treatment-Naive (N=2)			Virologically-Suppressed (N=43)			Total (N=45)		
	Grade			Grade			Grade		
	3	4	3 or 4	3	4	3 or 4	3	4	3 or 4
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of participants with one or more grade 3 or greater adverse events	0 (0)	0 (0)	0 (0)	9 (20.9)	0 (0)	9 (20.9)	9 (20.0)	0 (0)	9 (20.0)
Gastrointestinal disorders	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)	1 (2.3)	1 (2.2)	0 (0)	1 (2.2)
Diarrhoea	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)	1 (2.3)	1 (2.2)	0 (0)	1 (2.2)
Infections and infestations	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)	1 (2.3)	1 (2.2)	0 (0)	1 (2.2)
Gastroenteritis	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)	1 (2.3)	1 (2.2)	0 (0)	1 (2.2)
Investigations	0 (0)	0 (0)	0 (0)	6 (14.0)	0 (0)	6 (14.0)	6 (13.3)	0 (0)	6 (13.3)
Alanine aminotransferase increased	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)	1 (2.3)	1 (2.2)	0 (0)	1 (2.2)
Blood creatinine increased	0 (0)	0 (0)	0 (0)	2 (4.7)	0 (0)	2 (4.7)	2 (4.4)	0 (0)	2 (4.4)
Blood pressure increased	0 (0)	0 (0)	0 (0)	2 (4.7)	0 (0)	2 (4.7)	2 (4.4)	0 (0)	2 (4.4)
Glomerular filtration rate decreased	0 (0)	0 (0)	0 (0)	3 (7.0)	0 (0)	3 (7.0)	3 (6.7)	0 (0)	3 (6.7)
Vascular disorders	0 (0)	0 (0)	0 (0)	2 (4.7)	0 (0)	2 (4.7)	2 (4.4)	0 (0)	2 (4.4)
Hypertension	0 (0)	0 (0)	0 (0)	2 (4.7)	0 (0)	2 (4.7)	2 (4.4)	0 (0)	2 (4.4)

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory; Grade 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Potentially Life-Threatening.
The worst grade for each participant in each subcategory was reported.
Adverse event terms are from MedDRA Version 23.0.

Serious adverse event/deaths/other significant events

There were no SAEs reported in Cohort 1.

In Cohort 2 one SAE (gastroenteritis) was reported in a virologically suppressed participant during the first 24 weeks of the study. This SAE was considered Grade 3 (severe) and not related to study intervention based on investigator assessment, had an outcome of 'recovered/resolved', and no action was taken with regard to study intervention. One SAE of lip injury Grade 2 was also reported in the same patient which resolved.

There were no deaths in either cohort in the study.

Laboratory findings

In Cohort 1 laboratory values that met the predefined limits of change were observed in 1 participant in Cohort 1 who had a Grade 1 change in neutrophils. No participant developed liver toxicities based on the liver chemistry criteria used in this study (i.e., Grade 2 or higher AST or ALT AND Grade 2 or higher total bilirubin AND, at the same time, alkaline phosphatase less than Grade 2).

In Cohort 2 the most frequently reported laboratory values that met the predefined limits of change (>10% of the total participants) in Cohort 2 during the first 24 weeks of the study were Grade 1 changes in alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase, and Grade 2 changes in creatinine. Changes in liver parameters were mild and asymptomatic and not associated with bilirubin increases. No participant developed liver toxicities based on the liver chemistry criteria used in this study (ie, Grade 2 or higher AST or ALT AND Grade 2 or higher total bilirubin AND, at the same time, alkaline phosphatase less than Grade 2).

Table 22 – Participants With Central Laboratory Findings That Met Predetermined Criteria All Treated Population, Cohort 2 Weeks 0 to 24: Creatinine

	Treatment-Naive (N=2)		Virologically-Suppressed (N=43)		Total (N=45)	
Criteria	n/N	(%)	n/N	(%)	n/N	(%)
Creatinine (mg/dL)						
Grade 1: 1.1 to 1.3 x ULN	0/2	0	0/43	0	0/45	0
Grade 2: >1.3 to 1.8 x ULN OR Increase to 1.3 to <1.5 x baseline	1/2	50.0	9/43	20.9	10/45	22.2
Grade 3: >1.8 to <3.5 x ULN OR Increase to 1.5 to <2.0 x baseline	0/2	0	2/43	4.7	2/45	4.4
Grade 4: ≥3.5 x ULN OR Increase of ≥2.0 x baseline	0/2	0	0/43	0	0/45	0

n/N = Number of participants in each subcategory/number of participants in each group.
The worst grade per laboratory test for each participant was used in analysis.
For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present.
Only events with a worse grade than baseline were included.
Criteria based on Division of AIDS (DAIDS) 2017 Table for Grading the Severity of Adult and Pediatric Adverse Events.
[a]Severity grading for hemoglobin (g/dL) for participants 57 days of age to <13 (male and female): Grade 1: 9.5 to 10.4, Grade 2: 8.5 to <9.5, Grade 3: 6.5 to <8.5, Grade 4: <6.5.

Table 23 – Summary of Changes From Baseline in Laboratory Test Results All Treated Population, Cohort 2 Weeks 0 to 24: Creatinine

ART Classification at Entry	Laboratory Test	N	Actual Relative Time	n	Baseline Mean	Mean Change [95% CI]	SD
	Creatinine (mg/dL)	45	Baseline	45	0.6		
			Week 2	41	0.6	0.0 [-0.0, 0.0]	0.1
			Week 4	45	0.6	0.0 [-0.0, 0.1]	0.1
			Week 8	42	0.6	0.0 [-0.0, 0.0]	0.1
			Week 12	43	0.6	0.0 [0.0, 0.1]	0.1
			Week 16	39	0.7	0.0 [0.0, 0.1]	0.1
			Week 24	44	0.6	0.0 [0.0, 0.1]	0.1

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory.
[a]Number of participants with non-missing data.

Glomerular filtration rate decreased was reported in 42.2% of the participants and was the most frequently reported Grade 3 AE reported in 3 (6.7%) participants up to week 24.

Blood creatinine increased was reported in 26.7% of the participants, 10/45 participants had Grade 2 and 2/45 had Grade 3 increase in creatinine, however there was no relevant change in mean creatinine values over time, the mean baseline value was within normal limits. The incidence of renal related AEs is likely due to TDF exposure as renal toxicity is a known issue with TDF.

Moreover, the known bone toxicity associated with TDF exposure is a particular matter of concern in growing children. The Applicant has not addressed this issue and no new data on bone density is provided with this application, hence this study does not shed any further light on this safety concern of TDF.

According to the Applicant none of the Grade 3 AEs were considered related to study intervention by the investigators or led to discontinuation of study intervention.

Vital Signs, Physical Examinations, and Other Observations Related to Safety

There were no clinically meaningful findings based on vital sign measurements or physical examination assessments in this study.

Discontinuation due to adverse events

In Cohort 1 there were no discontinuations due to AEs reported.

In Cohort 2 no participants permanently discontinued treatment due to an AE in Cohort 2 during the first 24 weeks of the study. However, 1 participant discontinued from the study after 8 weeks of treatment with the study intervention due to pregnancy and decided to electively terminate the pregnancy.

Cumulative safety data for Cohort 2

The cumulative safety data includes all data available from Study Day 1 through database lock 07-JUL-2021 of the safety update report (SUR). Forty-four participants completed study treatment through Week 48 in the cumulative SUR period.

Most frequently reported adverse events

The most frequently reported AEs (≥20% overall) in Cohort 2 by decreasing frequency were decreased glomerular filtration rate, increased ALT, increased blood creatinine, increased AST, decreased blood bicarbonate, increased blood ALP, decreased carbon dioxide, decreased blood potassium, and headache. The majority (77.8%) of AEs were Grade 1 or Grade 2 in severity and the results are consistent with the week 24 data.

The median (range) time on study intervention in Cohort 2 for the cumulative SUR period was 590 days (57 to 651 days).

Table 24 Table - Participants With Adverse Events (Incidence ≥5% in Total Column) All Treated Population, Cohort 2 All Data Available as of SUR Database Lock

System Organ Class Preferred Term	Treatment-Naive (N=2) n (%)	Virologically-Suppressed (N=43) n (%)	Total (N=45) n (%)
Number of participants with one or more adverse events	2 (100.0)	43 (100.0)	45 (100.0)
Eye disorders	0 (0)	4 (9.3)	4 (8.9)
Conjunctival pallor	0 (0)	3 (7.0)	3 (6.7)
Gastrointestinal disorders	1 (50.0)	7 (16.3)	8 (17.8)
Diarrhoea	1 (50.0)	4 (9.3)	5 (11.1)
General disorders and administration site conditions	0 (0)	8 (18.6)	8 (17.8)
Pyrexia	0 (0)	3 (7.0)	3 (6.7)
Infections and infestations	1 (50.0)	12 (27.9)	13 (28.9)
Nasopharyngitis	0 (0)	4 (9.3)	4 (8.9)
Injury, poisoning and procedural complications	0 (0)	5 (11.6)	5 (11.1)
Investigations	2 (100.0)	42 (97.7)	44 (97.8)
Alanine aminotransferase increased	0 (0)	20 (46.5)	20 (44.4)
Aspartate aminotransferase increased	0 (0)	13 (30.2)	13 (28.9)
Blood albumin decreased	0 (0)	3 (7.0)	3 (6.7)
Blood alkaline phosphatase increased	0 (0)	11 (25.6)	11 (24.4)
Blood bicarbonate decreased	1 (50.0)	11 (25.6)	12 (26.7)
Blood cholesterol increased	0 (0)	6 (14.0)	6 (13.3)
Blood creatinine increased	1 (50.0)	17 (39.5)	18 (40.0)
Blood glucose decreased	0 (0)	4 (9.3)	4 (8.9)
Blood glucose increased	1 (50.0)	6 (14.0)	7 (15.6)
Blood phosphorus decreased	0 (0)	4 (9.3)	4 (8.9)
Blood potassium decreased	0 (0)	9 (20.9)	9 (20.0)
Blood pressure increased	0 (0)	8 (18.6)	8 (17.8)
Blood sodium decreased	0 (0)	6 (14.0)	6 (13.3)
Carbon dioxide decreased	0 (0)	11 (25.6)	11 (24.4)
Glomerular filtration rate decreased	1 (50.0)	21 (48.8)	22 (48.9)
Haemoglobin decreased	1 (50.0)	6 (14.0)	7 (15.6)
Lipase increased	1 (50.0)	5 (11.6)	6 (13.3)
Metabolism and nutrition disorders	1 (50.0)	9 (20.9)	10 (22.2)
Hypertriglyceridaemia	0 (0)	3 (7.0)	3 (6.7)
Hypokalaemia	1 (50.0)	3 (7.0)	4 (8.9)

Musculoskeletal and connective tissue disorders	0 (0)	6 (14.0)	6 (13.3)
Nervous system disorders	1 (50.0)	9 (20.9)	10 (22.2)
Headache	1 (50.0)	8 (18.6)	9 (20.0)
Renal and urinary disorders	1 (50.0)	9 (20.9)	10 (22.2)
Dysuria	1 (50.0)	2 (4.7)	3 (6.7)
Proteinuria	0 (0)	8 (18.6)	8 (17.8)
Reproductive system and breast disorders	0 (0)	5 (11.6)	5 (11.1)
Respiratory, thoracic and mediastinal disorders	0 (0)	16 (37.2)	16 (35.6)
Cough	0 (0)	7 (16.3)	7 (15.6)
Nasal congestion	0 (0)	6 (14.0)	6 (13.3)
Oropharyngeal pain	0 (0)	5 (11.6)	5 (11.1)
Productive cough	0 (0)	5 (11.6)	5 (11.1)
Rhinorrhoea	0 (0)	6 (14.0)	6 (13.3)
Skin and subcutaneous tissue disorders	1 (50.0)	8 (18.6)	9 (20.0)
Acne	1 (50.0)	3 (7.0)	4 (8.9)
Papule	1 (50.0)	2 (4.7)	3 (6.7)
Pruritus	1 (50.0)	3 (7.0)	4 (8.9)
Vascular disorders	0 (0)	3 (7.0)	3 (6.7)
Hypertension	0 (0)	3 (7.0)	3 (6.7)

N = Number of participants in each group; n (%) = Number (percent) of participants in each subcategory.
Adverse event terms are from MedDRA Version 24.0.

Grade 3 or Greater Adverse Events

Ten participants had Grade 3 or greater AEs in the cumulative SUR period, including 9 participants with Grade 3 AEs that were previously reported in the week 24 data set and 1 additional participant with a Grade 3 AE (scrotal abscess). No Grade 3 or greater AEs were considered drug-related per investigator assessment. Two participants with Grade 3 AEs reported in the week 24 data set had additional Grade 3 or greater AEs as follows:

- One participant with previous Grade 3 AEs (diarrhoea and gastroenteritis) had additional AEs of Grade 3 increased AST and Grade 4 increased ALT that led to discontinuation of study intervention. The AEs were considered 'not recovered/not resolved' at the end of the cumulative SUR period. The participant also had a Grade 2 hepatitis C infection,
- One participant had previous Grade 3 AEs of increased blood creatinine (resolved) and decreased glomerular filtration rate reported (improved to Grade 2). This participant had additional AEs of Grade 3 increased blood creatinine and decreased glomerular filtration rate during the SUR period.

Other Serious Adverse Events

One participant with an SAE of gastroenteritis and Grade 2 lip injury that was previously reported in the 24 week data set had additional SAEs of Grade 1 COVID-19 and Grade 4 increased ALT as of the SUR database lock. The Grade 1 COVID-19 had outcomes of 'recovered/resolved'; no action was taken with regard to the study intervention. The Grade 4 increased ALT was considered 'not recovered/not resolved'

at the time of the SUR database lock; this participant had subsequent AEs of increased ALT and increased AST with hepatitis C infection that led to discontinuation of study intervention.

One participant had an SAE (Grade 3 scrotal abscess, mentioned above) with an outcome of 'recovered/resolved'; no action was taken with the study intervention in response to the event.

Adverse Events Leading to Discontinuation of Study Intervention

Four participants discontinued study intervention in the cumulative SUR period. One due to AEs of increased AST and ALT. Two participants discontinued due to pregnancy. One has been described in the Week 24 data set above, the second pregnant participant discontinued after week 50 of study intervention and the pregnancy resulted in a live birth with no reported congenital anomalies. Another participant discontinued due to noncompliance with the study intervention. The latter 3 participants also discontinued from the study.

Laboratory findings

In the cumulative SUR period, in addition to previously reported laboratory findings in the week 24 dataset (one with Grade 3 ALT increases, two with Grade 3 creatinine increases), one participant had Grade 4 ALT increases and Grade 3 AST increases.

The 3 most common (>20%) laboratory findings that met predetermined criteria in the cumulative SUR period were increased creatinine, increased ALT, and increased AST. Most creatinine elevations were Grade 2 (defined as >1.3 to 1.8 x ULN or an increase of 1.3 to 1.5 x baseline). The majority were intermittent or documented on a single visit, and all except 2 remained within normal limits of 0.5-1 mg/dL (1 participant had an increase from 0.8 mg/mL at baseline to 1.06 mg/dL, which subsequently decreased to 1.0 mg/dL, and one had an increase from 0.81 mg/dL at baseline to 1.01 mg/dL, which subsequently returned to baseline). Of the 2 participants with Grade 3 creatinine elevations (defined as >1.8 to <3.5 x ULN or an increase to 1.5 to <2.0 x baseline), one remained within normal limits and one was 1.05 mg/dL (slightly above the ULN; baseline 0.72); both resolved while continuing study intervention. None were assessed as drug-related by the investigator or resulted in study intervention discontinuation.

Table 25 – Participants With Central Laboratory Findings That Met Predetermined Criteria All Treated Population, Cohort 2 All Data Available as of SUR Database Lock

Creatinine (mg/dL)

	Treatment-Naive (N=2)		Virologically-Suppressed (N=43)		Total (N=45)	
Criteria	**n/N**	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Grade 1: 1.1 to 1.3 x ULN	0/2	0	2/43	4.7	2/45	4.4
Grade 2: >1.3 to 1.8 x ULN OR Increase to 1.3 to <1.5 x baseline	1/2	50.0	13/43	30.2	14/45	31.1
Grade 3: >1.8 to <3.5 x ULN OR Increase to 1.5 to <2.0 x baseline	0/2	0	2/43	4.7	2/45	4.4
Grade 4: ≥3.5 x ULN OR Increase of ≥2.0 x baseline	0/2	0	0/43	0	0/45	0

n/N = Number of participants in each subcategory/number of participants in each group.
The worst grade per laboratory test for each participant was used in analysis.
For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present.
Only events with a worse grade than baseline were included.
Criteria based on Division of AIDS (DAIDS) 2017 Table for Grading the Severity of Adult and Pediatric Adverse Events.
[a]Severity grading for hemoglobin (g/dL) for participants 57 days of age to <13 (male and female): Grade 1: 9.5 to 10.4, Grade 2: 8.5 to <9.5, Grade 3: 6.5 to <8.5, Grade 4: <6.5.

Table 26 – Summary of Changes From Baseline in Estimated Glomerular Filtration Rate (eGFR) All Treated Population, Cohort 2 All Data Available as of SUR Database Lock

ART Classification at Entry	Laboratory Test	N	Actual Relative Time	n	Baseline Mean	Mean Change [95% CI]	SD
Treatment-Naive	eGFR from Creatinine Adjusted for BSA[a] (mL/min/1.73m^2)	2	Baseline	2	168.3		
			Week 2	2	168.3	-8.8 [-156.4, 138.8]	16.4
			Week 4	2	168.3	-17.3 [-106.2, 71.5]	9.9
			Week 8	2	168.3	-13.1 [-168.3, 153.5]	18.5
			Week 12	2	168.3	-14.9 [-168.3, 174.9]	21.1
			Week 16	2	168.3	-7.5 [-102.9, 87.9]	10.6
			Week 24	2	168.3	-30.5 [-168.3, 225.3]	28.5
			Week 36	2	168.3	-30.1 [-168.3, 132.9]	18.1
			Week 48	2	168.3	-22.5 [-71.0, 26.1]	5.4
			Week 64	1	181.4	-22.6	
			Week 80	1	181.4	-16.6	
Virologically-Suppressed	eGFR from Creatinine Adjusted for BSA[a] (mL/min/1.73m^2)	43	Baseline	43	158.4		
			Week 2	39	160.0	-2.0 [-9.2, 5.2]	22.3
			Week 4	43	158.4	-1.5 [-10.5, 7.4]	29.0
			Week 8	40	159.3	-2.0 [-10.2, 6.2]	25.6
			Week 12	41	158.0	-8.1 [-15.3, -0.8]	22.9
			Week 16	37	156.4	-6.2 [-14.9, 2.4]	26.0
			Week 24	42	158.1	-5.3 [-14.2, 3.5]	28.4
			Week 36	41	158.7	-11.4 [-19.2, -3.5]	24.9
			Week 48	42	158.1	-10.7 [-18.5, -2.9]	25.1
			Week 64	40	159.2	-8.5 [-16.6, -0.5]	25.1
			Week 80	27	146.7	-12.8 [-20.5, -5.2]	19.3
Total		45	Baseline	45	158.8		
	eGFR from Creatinine Adjusted for BSA[a] (mL/min/1.73m^2)		Week 2	41	160.4	-2.3 [-9.2, 4.6]	21.9
			Week 4	45	158.8	-2.2 [-10.8, 6.4]	28.6
			Week 8	42	159.7	-2.5 [-10.4, 5.4]	25.3
			Week 12	43	158.5	-8.4 [-15.4, -1.4]	22.6
			Week 16	39	157.0	-6.3 [-14.5, 1.9]	25.3
			Week 24	44	158.5	-6.5 [-15.2, 2.2]	28.6
			Week 36	43	159.2	-12.2 [-19.9, -4.6]	24.8
			Week 48	44	158.5	-11.3 [-18.7, -3.8]	24.6
			Week 64	41	159.8	-8.9 [-16.7, -1.0]	24.9
			Week 80	28	148.0	-13.0 [-20.3, -5.6]	19.0

N = Number of participants in each group; n = Number of participants with a result for that time point; SD = Standard deviation; BSA = Body Surface Area.
Calculations of baseline mean and change from baseline statistics are based on participants with measurements both at baseline and the timepoint assessed.
[a]Calculated using Modified Schwartz equation

Of the 26 participants with a Grade 2 and/or 3 creatinine and eGFR changes, 11 had an eGFR that was Grade 2 at the pre-treatment screening visit compared to baseline. Of the three participants with Grade 3 decreases in eGFR at any time point, two had pre-treatment eGFR that was Grade 2 compared to baseline and the creatinine value was within normal limits through week 48 (participant creatinine ranges were 0.43 to 0.65 mg/dL and 0.46 to 0.74 mg/dL). The third participant's pre-treatment eGFR was Grade 2 compared to baseline and the GFR was Grade 3 at day 34 and returned to Grade 2 for all visits thereafter.

2.5.1. Discussion on clinical safety

The P027 study is not powered to generate a comprehensive safety database in children and no control arm is available for comparison. Rather, given that exposure is comparable, safety will be extrapolated through a PK/PD-bridge.

A single dose of doravirine (100 mg tablet) was generally well tolerated in study P027 (Cohort 1) through 2 weeks of follow-up. There were no Grade 3 AE, SAE or deaths reported.

Delstrigo is a fixed dose combination that in addition to doravirine and lamivudine contains tenofovir disoproxil as fumarate (TDF). Tenofovir impacts renal handling of calcium and phosphate, and secondary to this, may impact bone turnover. This is generally considered manageable in adults, but the impact of tenofovir on growing bone has remained a concern and uncertainty which has not been resolved. With regards to treatment of adolescents, it should be noted that TDF containing products are "indicated for the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years". The background for this restricted indication is the potential for renal/bone toxicity overall, which may be more worrisome in growing individuals. The restricted TDF indication in adolescents stands in contrast to the adult indication of Delstrigo, which is not restricted due to any safety concerns related to growing bone.

The Applicant has not addressed bone toxicity associated with TDF and no new data on bone density is provided with this application, hence this study does not shed any further light on this safety concern of tenofovir.

Twenty-eight participants were identified as either having an adverse event of glomerular filtration rate decreased and/or blood creatinine increased. The majority of the changes to creatinine and eGFR were transient and intermittent and none were considered related to the study medication.

There was no death in the study, one participant had multiple SAEs (Grade 3 gastroenteritis, Grade 2 lip injury, Grade 1 COVID-19 and Grade 4 increased ALT) and had subsequent AEs of increased ALT and increased AST with hepatitis C infection that led to discontinuation of study intervention. Another participant had an SAE of Grade 3 scrotal abscess with an outcome of 'recovered/resolved'.

A total of four participants discontinued study intervention in the cumulative SUR period. One due to AEs of increased AST and ALT. Two participants discontinued due to pregnancy and another participant discontinued due to noncompliance with the study intervention. The latter 3 participants also discontinued from the study.

2.5.2. Conclusions on clinical safety

The safety of doravirine in adolescents is mainly extrapolated from the adult setting based on PK bridging. The safety of lamivudine in adolescents has since long been established. It is not clear whether tenofovir is a safe drug in subjects with growing bone, due to its impact on bone formation via renal tubular toxicity and the same restrictions of indication as for previously approved combination products with tenofovir are applied to Delstrigo.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA submitted an updated Risk Management Plan (RMP) versions 3.0 (DLP for this version: 02 April 2021) for Pifeltro and Delstrigo with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the RMP version 3.0 is acceptable dated 15 February 2022.

However, for Delstrigo RMP only, the WSA should take the following into consideration at the end of the procedure:

- The final wording of the indication is pending on the final outcome of the CHMP Rapporteur's assessment of this variation procedure No. EMEA/H/C/WS2065, as the final wording in the RMP has to be in line with the final wording agreed for the SmPC.

- The reference "[Ref. 5.4: 05NM0X]" should be replaced by the reference "[Ref. 5.4: 07XP7W]", that corresponds to the latest version of the EU guidelines, in section SVII.2 and deleted from section "References").

The CHMP endorsed this advice.

The CHMP endorsed the Risk Management Plan version 3.0 with the following content:

- Reflect the extension of the indication to include the treatment of HIV-1 infection in adolescents and children weighing at least 35 kg;

- Update in accordance with EU guidelines and GVP module V (rev.2), including a proposal to remove the following safety concerns:

Important Identified Risks (Delstrigo)

- Severe acute exacerbations of hepatitis B

- New onset or worsening renal impairment/Renal toxicity

- Decreases in bone mineral density (BMD)/bone events due to proximal renal tubulopathy

Missing Information (Pifeltro and Delstrigo)

- Long-term safety

- Safety during lactation

- Safety in elderly patients

Safety concerns

MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Pifeltro:

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety during pregnancy

Delstrigo:

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety during pregnancy

Risk minimisation measures

Pifeltro:

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk		
None	N/A	N/A
Important Potential Risk		
None	N/A	N/A
Missing Information		
Safety during pregnancy	Routine risk minimization measures: • Section 4.6 and Section 5.3 of the Product Information • What you need to know before you take PIFELTRO section of Package Leaflet	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • APR Additional pharmacovigilance activities: • None

Delstrigo:

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
None	N/A	N/A
Important Potential Risk		
None	N/A	N/A
Missing Information		
Safety during pregnancy	Routine risk minimisation measures: • Section 4.6 and Section 5.3 of the Product Information. • What you need to know before you take DELSTRIGO section of Patient Information Additional risk minimisation measures: • None	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • APR Additional pharmacovigilance activities: • None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated for Delstrigo and Pifeltro to include the new indication for the paediatric population weighing at least 35 kg. The Package Leaflet (PL) has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial corrections and the list of local representatives in the Package Leaflet has been revised.

- DELSTRIGO

4.1 Therapeutic indications

Delstrigo is indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir (see sections 4.4 and 5.1).

Delstrigo is also indicated for the treatment of adolescents aged 12 years and older weighing at least 35 kg who are infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Paediatric population
Safety and efficacy of Delstrigo in children aged less than 12 years or weighing less than 35 kg have not been established.

~~Safety and efficacy of Delstrigo have not been established in patients younger than 18 years of age. No data are available.~~

- PIFELTRO

4.1 Therapeutic indications

Pifeltro is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults**, and adolescents aged 12 years and older weighing at least 35 kg** infected with HIV-1 without past or present evidence of resistance to the NNRTI class (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Paediatric population
Safety and efficacy of Pifeltro in children aged less than 12 years or weighing less than 35 kg have not been established.

~~Safety and efficacy of Pifeltro have not been established in patients younger than 18 years of age. No data are available.~~

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable for the following reasons:

These proposed revisions do not constitute significant changes that would require the need to conduct a new user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Delstrigo and Pifeltro are indication for the treatment of HIV.

The goal of combination antiretroviral therapy in paediatric patients is to achieve and sustain HIV-1 virologic suppression, preserve/restore immune function, minimize drug toxicity, prevent drug resistance, and ultimately lead to normal growth and neurocognitive development.

The applicant is seeking an extension of indication as follows (boldface italic indicates the extension:

Pifeltro is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults, **and adolescents aged 12 years and older weighing at least 35 kg** infected with HIV-1 without past or present evidence of resistance to the NNRTI class (see sections 4.4 and 5.1).

Delstrigo is indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir (see sections 4.4 and 5.1)

Delstrigo is also indicated for the treatment of adolescents aged 12 years and older weighing at least 35 kg who are infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil (see sections 4.4 and 5.1).

3.1.2. Available therapies and unmet medical need

The recommended initial treatment of HIV-1 infection for paediatric patients is therapy with 2 NRTIs in combination with an InSTI or an NNRTI (≥3 years of age) or a boosted PI (<3 years of age). The choice of

HIV-1 therapy depends on various factors including the availability of age-appropriate formulation, ease of use, age/developmental stage of the patient, prior exposure (maternal or prevention), adherence, and in adolescent girls, the risk of pregnancy.

3.1.3. Main clinical studies

The application is based on a single arm cohort where virologically suppressed participants aged 12-18 (n=43) were switched to DOR/3TC/TDF (100/300/300 mg) QD; and treatment-naïve participants (n=2) were initiated on DOR/3TC/TDF (100/300/300 mg) QD.

3.2. Favourable effects

The clinical benefits of treatment with DOR or DOR/3TC/TDF in HIV-1-infected, treatment-naïve or virologically suppressed adults, has been established. The efficacy demonstration in adolescents is based on a PK bridge, whereby efficacy is inferred through similar exposure in adults.

The results of the study show that the majority of the virologically suppressed patients, maintained suppression of HIV-1 RNA viral load with 41/43 (95.3 %) of the participants below 40 Copies/mL at week 24 and 40/43 (93%) of the participants below 40 copies/mL at week 48. One participant discontinued from the study due to pregnancy after 8 weeks of treatment but had HIV-1 RNA <40 copies/mL at discontinuation and another participant discontinued due to pregnancy after 50 weeks of treatment and the pregnancy resulted in a live birth with no reported congenital anomalies. One participant had missing data for <50 copies/mL and <40 copies/mL due to low specimen volume. Viral suppression was also achieved in 1 of the treatment-naïve subjects, the other had treatment failure linked to noncompliance.

3.3. Uncertainties and limitations about favourable effects

It is well known that adherence is on average lower in adolescents than in adults, resulting in less favourable outcomes in terms of virological suppression.

3.4. Unfavourable effects

The safety of DOR and DOR/3TC/TDF is mainly bridged from adults, based on similar exposure.

In the adolescent cohort, the most frequently reported AEs (≥20% overall) during the first 24 weeks of the study were increased alanine aminotransferase, increased aspartate aminotransferase, increased blood creatinine, decreased carbon dioxide, and decreased glomerular filtration rate. Most of these were Grade 1 or 2 AEs, were not considered serious or drug-related based on investigator assessment, had an outcome of 'recovered/resolved' or 'recovering/resolving' at the time of database lock, and had no action taken with regard to study intervention. No AE led to discontinuation of study intervention during the first 24 weeks. During the reporting period for the cumulative safety update including week 48 the majority (77.8%) of AEs were Grade 1 or Grade 2 in severity and the results are consistent with the week 24 data. One participant discontinued study intervention due to AEs of increased AST and ALT.

3.5. Uncertainties and limitations about unfavourable effects

Delstrigo is a fixed dose combination that in addition to doravirine and lamivudine contains tenofovir disoproxil as fumarate (TDF). Tenofovir impacts renal handling of calcium and phosphate, and secondary to this, may impact bone turnover. This is generally considered manageable in adults, but the impact of

tenofovir on growing bone has remained a concern and uncertainty which has not been resolved. The Applicant has not addressed bone toxicity associated with TDF and no new data on bone density is provided with this application, hence this study does not shed any further light on this safety concern of tenofovir.

3.6. Effects Table

Table 27 Favourable effects of Delstrigo in paediatric patients 12 y / ≥ 35 kg

Favourable effects Delstrigo (Tenofovir disoproxil, lamivudine, doravirine)					
		Mean (%CV)		%GMR (90% CI)	
Analyte	PK Parameter	Adolescent Subjects ≥ 35 kg	Adults Phase 2/3	Adolescent Subjects vs Adult Population	Uncertainties / Strength of evidence
Tenofovir	AUC_{0-24} (mcg•h/mL)	2.57 (14.1%)[a]	3.324 (41.2%)[b]	77%[d]	Adolescent: Semi-intensive NCA from P027 (N=10); Adult: VIREAD SmPC
	C_{max} (mcg/mL)	0.31 (36.8%)[a]	0.326 (36.6%)[b]	95%[d]	Adolescent: Semi-intensive NCA from P027 (N=10); Adult: VIREAD SmPC
lamivudine	AUC_{0-24} (mcg•h/mL)	11.7 (28.2%)[a]	8.9 (21%)[c]	131%[d]	Adolescent: Semi-intensive NCA from P027 (N=10); Adult: EPIVIR SmPC
	C_{max} (mcg/mL	2.16 (23.8%)[a]	2.0 (26%)[c]	108%[d]	Adolescent: Semi-intensive NCA from P027 (N=10); Adult: EPIVIR SmPC
Doravirine	AUC_{0-24} (mcg•h/mL)	16.4 (24%)[e]	16.1 (29%)[e]	102% (97%, 108%)[f]	*Adolescent: Model predicted from P027 (n=54); Adult: Model predicted from treatment naïve Phase 3 (N=730)*
	C_{max} (mcg/mL	1.03 (16%)[e]	0.962 (19%)[e]	107% (103%, 111%)[f]	*Adolescent: Model predicted from P027 (n=54); Adult: Model predicted from treatment naïve Phase 3 (N=730)*
	C_{24} (mcg/mL)	0.379 (42%)[e]	0.396 (63%)[e]	96% (87%, 105%)[f]	*Adolescent: Model predicted from P027 (n=54); Adult: Model predicted from treatment naïve Phase 3 (N=730)*

[a] Arithmetic mean and %CV (calculated as SD/mean) based on intensive PK sampling at Week 1 (N=10) following administration of DOR/3TC/TDF
[b] 245 mg TD multiple dose with food in adults, VIREAD SmPC
[c] 300 mg once daily in adults, EPIVIR SmPC
[d] Calculated as adolescent arithmetic mean/adult arithmetic mean
[e] Geometric mean and %GCV
[f] Model-based GMR and 90% CI

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy and safety of doravirine and the combination of doravirine with lamivudine and tenofovir disoproxil fumarate (TDF) is based on PK equivalence with adults, in accordance with regulatory practice in the field of HIV.

The previous concerns regarding the PK bridging exercise have been adequately addressed by the company.

The exception to the rule above, pertain to age specific safety concerns. Regarding treatment of adolescents, it should be noted that TDF containing combination products are "indicated for the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years", or similar formulas. The background for this restricted indication is the potential for renal/bone toxicity overall, which may be more worrisome in growing individuals. The restricted TDF indication in adolescents would stand in contrast to the adult indication of Delstrigo, which is not restricted due to any safety concerns related to growing bone.

There is no place in therapy for Delstrigo in patients that have limited treatment options due to resistance. The indication for Delstrigo is restricted to adolescents without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil.

Some minor changes are proposed in both SmPC to reflect the 48-week data and a minor update of Table 6 of steady state PK in the Delstrigo SmPC.

3.7.2. Balance of benefits and risks

The B/R balance is positive for Pifeltro and Delstrigo in the sought indication.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Delstrigo and Pifeltro are positive provided general statement on conditions.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the new indication to the paediatric population weighing at least 35 kgs for PIFELTRO and DELSTRIGO. Sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3 of the RMP for each product have also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial corrections and to update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Worksharing applicant (WSA) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0177/2021 for Pifeltro and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0176/2021 for Delstrigo and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.