Amsterdam, 26 January 2023
EMA/73505/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Delstrigo

International non-proprietary name: doravirine/lamivudine/tenofovir disoproxil

Procedure no.:EMEA/H/C/004746/P46/003.1

Marketing authorisation holder (MAH): Merck Sharp & Dohme BV

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	28 Nov 2022	28 Nov 2022	☐
☐	CHMP Rapporteur Assessment Report	03 Jan 2023	16 Dec 2022	☐
☐	CHMP members comments	16 Jan 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	19 Jan 2023	n/a	☐
☒	CHMP adoption of conclusions:	26 Jan 2023	26 Jan 2023	☐

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1. Introduction

On 10th of November 2022 , the MAH submitted the 96-week study results for the paediatric study MK-1439-027 (P027) – "Study MK-1439-027, a Phase 1/2 multisite, open-label study of the PK, safety, and tolerability of DOR and DOR/3TC/TDF in adolescent participants (12 to <18 years of age, ≥35 kg) with HIV-1", in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This submission includes the final analysis of the efficacy and immunologic response data at Weeks 48 and 96, safety and tolerability data through Weeks 48 and 96, and sparse pharmacokinetics (PK) data through Week 48, for participants in Cohort 2. As the adolescent data through Week 96 do not provide any clinically meaningful new information, no update to the EU SmPC was proposed.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study MK-1439-027 is part of the agreed Paediatric Investigation Plan:

- EMEA-001695-PIP01-14-M04 (decision P/0176/2021)

2.2. Information on the pharmaceutical formulation used in the study

The approved formulation 100 gm/300 mg/245 mg tablet Delstrigo (DOR/3TC/TDF), for adults and paediatric patients (from 12 years of age) weighing at least 35 kg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study MK-1439-027, a Phase 1/2 multisite, open-label study of the PK, safety, and tolerability of DOR and DOR/3TC/TDF in adolescent participants (12 to <18 years of age, ≥35 kg) with HIV-1 (Cohort 2 of study MK-1439-027 (P027))

2.3.2. Clinical study MK-1439-027 (P027)

This study was conducted in 2 cohorts: Cohort 1 (DOR single 100-mg dose) and Cohort 2 (DOR/3TC/TDF [100/300/300 mg] administered once daily [QD] for 96 weeks). In Cohort 1the PK and safety of a single, oral dose of DOR 100 mg was assessed, with intensive PK evaluation completed on Day 1; this information was reported previously in the Article 46 procedures EMEA/H/C/004747/P46/002 and EMEA/H/C/004746/P46/003. The present report is based on the final analysis of the efficacy and immunologic response data at Weeks 48 and 96, safety and tolerability data through Weeks 48 and 96, and sparse pharmacokinetics (PK) data through Week 48, for participants in Cohort 2.

Methods

An overview of the study design for MK-1439-027 is presented in the table below:

Table 2.5-hivwk96adol: 1
Overview of MK-1439-027

Study Number, Status, Countries, [CTD Location]	Study Design	Study Population	Primary Endpoints	Secondary and Other Endpoints
MK-1439-027 **Status:** Completed **Countries:** Thailand, South Africa, and US **CTD Location:** [Ref. 5.3.5.2: P027MK1439]	**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 adult tablet **Cohort 2**: DOR/3TC/TDF (100 mg/300 mg/300 mg) QD. Oral granule formulation was offered in Cohort 2, but was not opted by any participant. All participants received the adult tablet. **Follow-up Duration:** Cohort 1: 2 weeks Cohort 2: 96 weeks	**Cohort 1 (N=9)** Virologically suppressed participants Male: 7 Female: 2 Median Age, (Range): 15.0 years (12.0 to 16.0 years) Median Weight (Range): 48.7 kg (40.3 to 90.8 kg) **Cohort 2 (N=45)** Virologically suppressed (N=43) and ART-naïve (N=2) participants Male: 19 Female: 26 Median Age (Range): 15.0 years (12.0 to 17.0 years) Median Weight (Range): 51.6 kg (45.1 to 79.8 kg)	**Cohort 1** ***Pharmacokinetics*** Single dose AUC0-∞, Cmax., and C24hr of DOR ***Safety and Tolerability through Week 2*** • Safety Outcome: All AEs, 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 AEs, 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*** Single dose AUC0-24hr Cmax., and C24hr of DOR, 3TC, and TFV ***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 percent change from baseline ***Safety and Tolerability through Week 24*** • Safety Outcome: All AEs, 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)** • PK of DOR, 3TC, and TFV through Week 48 • Genotypic and phenotypic measures of resistance at baseline and at virologic failure • Self-reported measures of acceptability, palatability, and adherence

Sources: [Ref. 5.3.5.2: P027MK1439: 16.1.1], [Ref. 5.3.5.2: P027MK1439]

Study participants/sample size

In cohort 2 from which data are presented in this final report, 45 adolescents participated from 5 sites in the US, Thailand and South Africa.

Treatments

The adult DOR/3TC/TDF tablet (100/300/300 mg) was administered QD to all participants in Cohort 2.

Objective(s) for cohort 2 in the MK-1439-027 study

The primary objective was to evaluate the 24-week safety and tolerability of DOR/3TC/TDF in HIV-1-infected children and adolescents.

The secondary objectives were to:

- Evaluate the pharmacokinetics of DOR, 3TC, and tenofovir using intensive (tenofovir and 3TC) and semi-intensive (DOR) PK sampling at Week 1.
- Evaluate the 24-, 48-, and 96-week virologic efficacy and immunologic response (CD4 cell count and percentage change from baseline).
- Evaluate the 48- and 96-week safety and tolerability.

The other objectives were to:

- Evaluate the pharmacokinetics of DOR, 3TC, and tenofovir using sparse PK sampling through Week 48.
- Assess changes in HIV-1 genotype and phenotype to DOR and other components of the regimen in patients experiencing virologic failure.
- Evaluate acceptability, palatability, and adherence to DOR/3TC/TDF through Week 96.

Outcomes/endpoints

Primary endpoint

Safety and Tolerability through Week 24
- Safety Outcome: All AEs, 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

Pharmacokinetics
Single dose AUC0-24hr Cmax., and C24hr of DOR, 3TC, and TFV

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 percent change from baseline

Safety and Tolerability through Week 48 and 96
- Safety Outcome: All AEs, 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
Plasma concentration of DOR, 3TC, and TFV through Week 48

Genotypic and phenotypic measures of resistance at baseline and at virologic failure
Self-reported measures of acceptability, palatability, and adherence

Analyses

Safety and tolerability of DOR and DOR/3TC/TDF were evaluated for Cohort 2 through Weeks 48 and 96 based on assessment of adverse events (AEs), vital signs, and clinical laboratory values of all participants exposed to study intervention (All Treated Population).

Efficacy was, evaluated in Cohort 2 only. All efficacy analyses were conducted using the All Treated Population, comprising participants who took at least 1 dose of study intervention during the study. Missing values were addressed using 2 approaches as follows:

- 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 3 cutoffs of HIV-1 RNA <40 copies/mL, <50 copies/mL, and <200 copies/mL. The OF approach was applied as a sensitivity analysis.

Immunologic response (change from baseline in CD4+ T-cell count and percent) was a secondary endpoint analysed using the OF Approach. Efficacy by subgroup was analyzed using both the OF and FDA Snapshot approaches.

2.3.3. Results

Baseline data

A total of 42 participants completed the study; 2 discontinued due to pregnancy and 1 discontinued due to a Grade 4, nonserious AE of increased ALT.

Of the 45 participants, 43 were virologically suppressed with CD4+ T-cell counts >700 cells/mm3, and 2 were treatment-naïve (both with baseline HIV-1 RNA levels >500,000 copies/mL and CD4+ T-cell counts <120 cells/mm3.

Efficacy results

At Week 96, the majority of virologically suppressed participants maintained HIV-1 RNA levels below each cutoff (83.7% <40 copies/mL, 83.7% <50 copies/mL, and 88.4% <200 copies/mL) based on the FDA Snapshot approach. Results obtained using the OF approach were consistent with the FDA Snapshot approach. One virologically suppressed participant developed protocol defined virological failure (PVDF) at Week 96 (HIV-1 RNA 286,040 copies/mL).

One of the 2 treatment-naïve participants achieved HIV-1 RNA levels <40 copies/mL at Week 96 and the other participant had PDVF at Week 24 and discontinued from the study and study treatment at Week 62 due to noncompliance.

Table 14.2-5
Efficacy Analysis at Week 96
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)	36/38	94.7 (82.3, 99.4)	37/40	92.5 (79.6, 98.4)
Proportion of participants with HIV-1 RNA <50 copies/mL	1/2	50.0 (1.3, 98.7)	36/38	94.7 (82.3, 99.4)	37/40	92.5 (79.6, 98.4)
Proportion of participants with HIV-1 RNA <200 copies/mL	1/2	50.0 (1.3, 98.7)	38/40	95.0 (83.1, 99.4)	39/42	92.9 (80.5, 98.5)
FDA Snapshot Approach						
Proportion of participants with HIV-1 RNA <40 copies/mL	1/2	50.0 (1.3, 98.7)	36/43	83.7 (69.3, 93.2)	37/45	82.2 (67.9, 92.0)
Proportion of participants with HIV-1 RNA <50 copies/mL	1/2	50.0 (1.3, 98.7)	36/43	83.7 (69.3, 93.2)	37/45	82.2 (67.9, 92.0)
Proportion of participants with HIV-1 RNA <200 copies/mL	1/2	50.0 (1.3, 98.7)	38/43	88.4 (74.9, 96.1)	39/45	86.7 (73.2, 94.9)
	Mean [n]	(95% CI)	Mean [n]	(95% CI)	Mean [n]	(95% CI)
Change from baseline in CD4 cell count (cells/mm3)	455.0 [1]		31.4 [37]	(-40.7, 103.4)	42.5 [38]	(-31.1, 116.1)
Change from baseline in CD4 percent	19.9 [1]		-1.0 [37]	(-2.7, 0.7)	-0.5 [38]	(-2.5, 1.5)

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 two participants at Week 96 were diluted (by a factor of 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 14.2-23
Summary of CD4 Absolute Count (Cells/mm3) Over Time
Observed Failure Approach
All Treated Population, Cohort 2
Weeks 0 to 96

ART Classification at Entry	N	Study Visit	n	Mean [95% CI]	SD	Median [Q1, Q3]	Min	Max
Treatment-Naive	2	Baseline	2	99.0 [0.0, 289.6]	21.2	99.0 [84.0, 114.0]	84	114
		Week 4	2	350.5 [0.0, 966.8]	68.6	350.5 [302.0, 399.0]	302	399
		Week 12	2	350.0 [248.4, 451.6]	11.3	350.0 [342.0, 358.0]	342	358
		Week 24	2	302.5 [0.0, 867.9]	62.9	302.5 [258.0, 347.0]	258	347
		Week 48	2	274.0 [0.0, 1227.0]	106.1	274.0 [199.0, 349.0]	199	349
		Week 64	1	368.0		368.0 [368.0, 368.0]	368	368
		Week 80	1	603.0		603.0 [603.0, 603.0]	603	603
		Week 96	1	569.0		569.0 [569.0, 569.0]	569	569
Virologically-Suppressed	43	Baseline	42	747.2 [668.1, 826.4]	254.0	715.0 [539.0, 891.0]	315	1397
		Week 4	43	775.6 [693.7, 857.4]	265.9	699.0 [542.0, 967.9]	347	1337
		Week 12	42	744.6 [665.5, 823.7]	253.8	715.5 [546.0, 902.0]	345	1493
		Week 24	42	822.5 [745.1, 899.9]	248.4	795.5 [664.0, 975.0]	398	1463
		Week 48	42	814.7 [729.2, 900.2]	274.3	814.5 [595.0, 1021.0]	401	1535
		Week 64	41	696.4 [625.9, 766.8]	223.2	685.0 [516.0, 829.0]	226	1291
		Week 80	41	768.6 [688.2, 849.0]	254.7	747.0 [575.0, 941.0]	354	1357
		Week 96	38	785.4 [690.9, 879.9]	287.4	679.5 [596.0, 980.0]	227	1442
Total	45	Baseline	44	717.8 [631.7, 803.8]	283.1	713.0 [527.0, 886.0]	84	1397
		Week 4	45	756.7 [674.1, 839.2]	274.7	681.0 [534.0, 967.0]	302	1337
		Week 12	44	726.6 [647.2, 806.1]	261.4	695.5 [521.0, 898.5]	342	1493
		Week 24	44	798.9 [717.9, 879.9]	266.3	784.5 [630.0, 974.0]	258	1463
		Week 48	44	790.1 [701.5, 878.7]	291.5	788.5 [569.0, 1013.0]	199	1535
		Week 64	42	688.6 [618.1, 759.1]	226.2	680.0 [504.0, 829.0]	226	1291
		Week 80	42	764.6 [685.9, 843.4]	252.8	746.0 [575.0, 941.0]	354	1357
		Week 96	39	779.9 [687.2, 872.5]	285.7	665.0 [592.0, 980.0]	227	1442

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 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.

Source: [P027MK1439: adam-adeffout]

The mean change from baseline in CD4+ T-cell count and percent was stable through Week 96 with small increases in CD4+ T-cell cell count observed for virologically suppressed participants in Cohort 2. An increase in CD4+ T-cell count was observed in the treatment-naïve participant who completed 96 weeks of treatment.

Clinical Virology

Two of the 45 participants in Cohort 2 (one treatment-naïve and 1 virologically suppressed) had PDVF. The treatment-naïve participant had virologic failure at Week 24, linked to noncompliance, and mutations associated with resistance to DOR at Week 53 (V106A and P225H). The participant was discontinued from the study at week 62 due to non-compliance. The virologically suppressed participant had virologic failure at Week 96 with no genotypic data available for DOR, 3TC, or TDF.

Neither participant with PDVF had evidence of phenotypic resistance to DOR, 3TC, or TDF at the time of failure; paired baseline and postbaseline genotypic resistance data were not available for either participant.

Safety results

AEs were reported for all participants in Cohort 2 through Week 96.

Four participants had AEs assessed by the investigator as drug-related, including dizziness, hyperbilirubinemia, decreased neutrophil count, and hypoglycaemia. One participant discontinued study intervention due to an AE of increased alanine aminotransferase.

Grade 3/4 AEs were reported for 11 (24.4%) participants with the most frequently reported being increased blood creatinine (n=5); no Grade 3/4 AEs were assessed by the investigator as related to the study intervention. SAEs were reported for 2 participants. None of the SAEs were assessed by the investigator as being related to the study intervention and none led to the discontinuation of the study intervention. No serious drug-related AEs were reported and no participants had discontinuation of study intervention due to a drug-related AE.

Three pregnancies were reported during the study. Two participants reported pregnancy at Week 8 and Week 50 and discontinued from the study. A third participant reported a pregnancy at Week 113 and completed the study.
No deaths occurred during this study.

2.3.4. Discussion on clinical aspects

The results from the P027 study through Week 96 demonstrate that DOR/3TC/TDF is generally well tolerated with no new safety concerns identified in HIV-1-infected adolescent participants 12 to <18 years of age weighing at least 35 kg. 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. No new data on bone density is provided with this application. The study results also indicate that DOR/3TC/TDF is efficacious in the treatment of HIV-1-infected adolescents 12 to < 18 years of age. Moreover, DOR/3TC/TDF exhibits favourable immunological response in adolescent participants at Week 96.

Overall, the safety and efficacy of DOR/3TC/TDF at week 96 were generally consistent with that observed in Phase 3 studies in adult participants with HIV-1 infection.

3. Rapporteur's overall conclusion and recommendation

The safety profile in adolescent participants was generally consistent with the established safety profiles in adults. Although with a limited number of participants in the MK 1439-027 study, the results presented in the final report indicate that DOR/3TC/TDF is efficacious in treatment of HIV-1-infected adolescents aged 12 years and older weighing at least 35 kg. The MAH has not proposed an update to the EU SmPC, which is agreed upon.

☒ **Fulfilled:**
No regulatory action required.