European Union Risk Management Plan (EU-RMP)
EDURANT (Rilpivirine)

Data lock point for current RMP	17 February 2023	Version number	10.3

CHMP Opinion Date = 25 July 2024

QPPV Sign-off Date:	19 June 2024
RMP Version Number:	10.3
Supersedes Version:	9.0
EDMS Number:	EDMS-RIM-1338830, 1.0

PPD

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	10.3
Rationale for submitting an updated RMP	To broaden the pediatric indication for HIV-1 treatment and to include a new pharmaceutical form and strength (age-appropriate formulation).
Summary of significant changes in this RMP	The indication for the treatment of HIV-1 infection has been broadened to adults and pediatric patients ≥2 to <18 years of age and weighing at least 14 kg without known mutations associated with resistance to the NNRTI class, and with a viral load ≤100,000 HIV-1 RNA copies/mL. All relevant sections of the EU-RMP are updated with the data of the final analysis including the 48-week initial treatment and post-Week-48 extension periods of trial TMC278-TiDP38-C213 (Cohort 2) and of the Week-48 final analysis of trial TMC278HTX2002.

Other RMP Versions Under Evaluation:

RMP Version Number	**Submitted on**	**Procedure Number**
Not applicable		

Details of the Currently Approved RMP:

Version number of last agreed RMP	Version 9.0
Approved within procedure	EMEA/H/C/002264/II/0037
Date of approval (Competent authority opinion date)	16 January 2020

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Rilpivirine (INN: rilpivirine hydrochloride, TMC278)
Pharmacotherapeutic group(s) (ATC Code)	Antiviral for systemic use Non-nucleoside reverse transcriptase inhibitor (NNRTI) J05AG05
Marketing Authorization Holder	Janssen-Cilag International, NV
Medicinal products to which the RMP refers	1
Invented name(s) in the European Economic Area (EEA)	EDURANT® (further referred to as EDURANT)
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class** NNRTI
	Summary of mode of action Rilpivirine (RPV) is a diarylpyrimidine NNRTI of human immunodeficiency virus type 1 (HIV-1). Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular deoxyribonucleic acid (DNA) polymerases alpha (α), beta (β), and gamma (γ).
	Important information about its composition Not applicable
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet
Indication(s) in the EEA	**Current:** **<u>25-mg film-coated tablet</u>** EDURANT, in combination with other ARV medicinal products, is indicated for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg without known mutations associated with resistance to the NNRTI class, and with a viral load ≤100,000 HIV-1 RNA copies/mL. **<u>2.5-mg dispersible tablet</u>** EDURANT, in combination with other ARV medicinal products, is indicated for the treatment of HIV-1 infection in pediatric patients ≥2 to <18 years of age and weighing at least 14 kg to less than 25 kg without known mutations associated with resistance to the NNRTI class, and with a viral load ≤100,000 HIV-1 RNA copies/mL. Genotypic resistance testing should guide the use of EDURANT.

<table>
<tr><td></td><td>Proposed:
Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
Therapy should be initiated by a physician experienced in the management of HIV infection. EDURANT is available as a 25-mg film-coated tablet and as a 2.5-mg dispersible tablet. A difference in bioavailability of 1 x 25-mg film-coated tablets and 10 x 2.5-mg dispersible tablets was observed, therefore they are not interchangeable.
<u>25-mg film-coated tablet</u>
<u>Posology</u>
The recommended dose of EDURANT in adults and pediatric patients weighing at least 25 kg is one 25-mg tablet taken once daily.
Dose adjustment
For patients concomitantly receiving rifabutin, the EDURANT dose should be increased to 50 mg (2 tablets of 25 mg each) taken once daily. When rifabutin coadministration is stopped, the EDURANT dose should be decreased to 25 mg once daily.
Missed dose
If the patient misses a dose of EDURANT within 12 hours of the time it is usually taken, the patient must take the medicine with a meal as soon as possible and resume the normal dosing schedule. If a patient misses a dose of EDURANT by more than 12 hours, the patient should not take the missed dose, but resume the usual dosing schedule. If a patient vomits within 4 hours of taking the medicine, another EDURANT tablet should be taken with a meal. If a patient vomits more than 4 hours after taking the medicine, the patient does not need to take another dose of EDURANT until the next regularly scheduled dose.
<u>Method of administration</u>
EDURANT must be taken orally, once daily with a meal.
It is recommended that the film-coated tablet be swallowed whole with water and not be chewed or crushed.
<u>2.5-mg dispersible tablet</u>
<u>Posology</u>
The recommended dosage of EDURANT in pediatric patients aged 2 to less than 18 years is based on body weight (see Table below). EDURANT 2.5 mg dispersible tablets should only be given to pediatric patients weighing at least 14 kg and less than 25 kg.
<table>
<tr><th colspan="2">Recommended dose for pediatric patients</th></tr>
<tr><td>Body Weight</td><td>Dose (once daily with food)</td></tr>
<tr><td>≥14 kg to <20 kg</td><td>12.5 mg once daily (five 2.5-mg tablets)</td></tr>
<tr><td>≥20 kg to <25 kg</td><td>15 mg once daily (six 2.5-mg tablets)</td></tr>
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	Missed dose The same is applicable as for the 25-mg tablet. Method of administration EDURANT dispersible tablets must be dispersed in water and must be taken with a meal. The patient should not chew or swallow EDURANT dispersible tablets whole. To aid with administration, the dispersed mixture can be further diluted with the following beverages or soft food: water, milk, orange juice or applesauce.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** **25-mg film-coated tablet** White to off-white, round, biconvex, film-coated tablet with a diameter of 6.4 mm, debossed with "TMC" on one side and "25" on the other side. Each film-coated tablet contains RPV hydrochloride equivalent to 25 mg RPV. **2.5-mg dispersible tablet** White to almost white, round 6.5 mm, dispersible tablet, debossed with "TMC" on one side and "PED" on the other side. Each dispersible tablet contains RPV hydrochloride equivalent to 2.5 mg RPV.
	Proposed: Not applicable

Is/will the product be subject of additional monitoring in the European Union?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: Human immunodeficiency virus type 1 (HIV-1) infection

Global HIV Statistics (Adults and Pediatrics)

Incidence:

The 2022 report from the Joint United Nations Programme on HIV/acquired immunodeficiency syndrome (AIDS) (UNAIDS) on the global AIDS epidemic states that approximately 1.5 million (range: 1.1-2.0 million) individuals (all ages) were newly infected with HIV in 2021, 58% of whom were in sub-Saharan Africa (UNAIDS 2022b). Among the sub-Saharan African regions, the Eastern and Southern African region was most heavily affected by HIV in 2021. However, the number of new cases in the region significantly decreased compared to previous years. From 2010 to 2021, the number of new HIV infections among all ages declined by 44% (38% among women versus 52% among men) in this region (UNAIDS 2022a). On the contrary, the region Eastern Europe and Central Asia has the fastest growing HIV epidemic in the world. In 2021, 160,000 (range: 130,000-180,000) new HIV infections were reported, representing a 48% increase since 2010 (UNAIDS 2022a). Incidence estimates for 2021 (all ages) by region are presented in the below table (UNAIDS 2022b).

Regional HIV incidence estimates for adults and children in the year 2021

Region	Approximate number of new cases of HIV [range]
Eastern and Southern Africa	670,000 [530,000–900,000]
Western and Central Africa	190,000 [140,000–270,000]
Middle East and North Africa	14,000 [11,000–38,000]
Asia and the Pacific	260,000 [190,000–360,000]
Latin America	110,000 [68,000–150,000]
Caribbean	14,000 [9500–18,000]
Eastern Europe and Central Asia	160,000 [130,000–180,000]
Western Europe, Central Europe, North America	63,000 [51,000–76,000]

Source: UNAIDS 2022b

In 2021, there were 16,624 new HIV diagnoses in 29 European Union /EEA countries, with a rate of 4.3 per 100,000 population when adjusted for reporting delay. Cyprus and Latvia were the 2 countries with the highest rates of new HIV diagnoses: 16.5 and 11.2 per 100,000 population, respectively (ECDC 2022). The table below shows the number of new HIV cases (N) and incidence rate (IR) per 100,000 population by country for Europe in 2021 (ECDC 2022).

New HIV diagnoses (N) and incidence rates (IR) per 100 000 population, by country in EU/EEA

Country	N	IR per 100,000
Austria	175	2.0
Belgium	781	6.8
Bulgaria	238	3.4
Croatia	77	1.9
Cyprus	148	16.5
Czech Republic	233	2.2
Denmark	137	2.3
Estonia	125	9.4
Finland	163	2.9
France	3,513	5.2
Germany	2,234	2.7
Greece	526	4.9
Hungary	223	2.3
Iceland	20	5.4
Ireland	403	8.0
Italy	1,770	3.0
Latvia	212	11.2
Liechtenstein	1	2.6
Lithuania	110	3.9
Luxembourg	54	8.5
Malta	45	8.7
Netherlands	396	2.3
Norway	102	1.9
Poland	1,096	2.9
Portugal[a]	-	-
Romania	560	2.9
Slovakia	113	2.1
Slovenia	32	1.5
Spain	2,785	5.9
Sweden	352	3.4
Total European Union/EEA	**16,624**	**3.7**

Source: ECDC 2022

[a] Data from Portugal not published at country request.

IR: Incidence rate expressed as a ratio of the number of new cases to the size of the population at risk for the year 2021

Prevalence:

The global prevalence of HIV in 2021 for all ages was estimated at 38.4 million (range: 33.9-43.8 million), of which 54% were women and girls (UNAIDS 2022b). In 2021, about 75% of all people with HIV (28.7 million people) were accessing antiretroviral therapy (ART), a significant increase from 2010 (7.8 million people), while 5.9 million people did not know they were living with HIV in 2021 (UNAIDS 2022b). Approximately 20.6 million (range: 18.9-23.0 million) people, representing 54% of the global HIV-infected population in 2021, lived in Eastern and Southern Africa (UNAIDS 2022a). Western and Central Europe and North America had 2.3 million (range: 1.9-2.6 million) people with HIV in 2021 (UNAIDS 2022a).

Adult Population (>15 years of age)

Incidence:

In 2021, about 1.3 million (range: 990,000-1.8 million) people (>15 years of age) were newly infected with HIV. Among the sub-Saharan African regions, the region Eastern and Southern

Africa was most heavily affected with 590,000 (range: 460,000-790,000) new cases. However, the number of new cases in this region for this age group (>15 years of age) was much lower than in 2010 (1 million [range: 780,000-1.3 million]). On the contrary, Eastern Europe and Central Asia has the fastest growing HIV epidemic in the world. In 2021, there were 150,000 (range: 130,000-180,000) adults newly infected with HIV compared to 100,000 (range: 85,000-120,000) in 2010. Incidence estimates for 2021 (>15 years of age) by region are presented in the table below (UNAIDS 2022b).

HIV incidence estimates with uncertainty bounds for the adult population (>15 years of age)

Region	Adults (15+) newly infected with HIV
Western and Central Africa	140,000 [90,000-210,000]
Eastern and Southern Africa	590,000 [460,000-790,000]
Eastern Europe and Central Asia	150,000 [130,000-180,000]
Asia and the Pacific	250,000 [180,000-350,000]
Latin America	100,000 [65,000-150,000]
Caribbean	13,000 [9000-17,000]
Western and Central Europe and North America	63,000 [51,000-76,000]
Middle East and North Africa	12,000 [9800-16,000]

Source: UNAIDS 2022b

Prevalence:

In 2021, 36.7 million (range: 32.3-41.9 million) people living with HIV worldwide were adults (>15 years of age), representing around 95% of the total number of people living with HIV worldwide (38.4 million) (UNAIDS 2022b). Eastern and Southern Africa accounted for the highest number of people (>15 years of age) living with HIV in 2021 (19.6 million [range: 17.9-21.8 million]) (UNAIDS 2022b). The below table presents the number of adults (>15 years of age) living with HIV by geographic region in 2021.

HIV prevalence estimates with uncertainty bounds for the adult population (>15 years of age)

Region	Estimated adults (15+) living with HIV
Western and Central Africa	4,500,000 [4,100,000-5,200,000]
Eastern and Southern Africa	19,600,000 [17,900,000-21,800,000]
Eastern Europe and Central Asia	1,800,000 [1,600,000-2,000,000]
Asia and the Pacific	5,900,000 [4,800,000-7,100,000]
Latin America	2,100,000 [1,500,000-2,700,000]
Caribbean	320,000 [280,000-370,000]
Western and Central Europe and North America	2,300,000 [1,900,000-2,600,000]
Middle East and North Africa	170,000 [150,000-200,000]

Source: UNAIDS 2022b

Demographics of the Population in the Authorized Indication and Risk Factors for the Disease

Of those people more than 15 years of age who were living with HIV in 2021, around 53% (19.7 million [range: 17.6-22.4 million]) were women (UNAIDS 2022b). In adults between 15 and 49 years of age, the global HIV prevalence rate was 0.7% in 2021. In younger adults between 15 and 24 years of age, the global HIV prevalence rate was 0.4% in women and 0.2% in men. The

HIV prevalence rates by region for the adult population (15-49 years of age) in 2021 were 6.2% (range: 5.5%-6.9%) in Eastern and Southern Africa, followed by 1.3% (range: 1.1%-1.4%) in Western and Central Africa and 1.2% (range: 1.0%-1.3%) in the Caribbean (UNAIDS 2022a).

Risk factors for acquiring HIV include geography, sex, injection drug use, and sexual activity.

Geography

In 2021, Sub-Saharan Africa accounted for 66% of the total population living with HIV globally and 58% of the total number of new HIV infections (all ages). Eastern and Southern Africa had the highest IR for adults between 15 to 49 years of age (2.39 [range: 1.87-3.18] per 1,000 population) (UNAIDS 2022b). In Eastern Europe and Central Asia, new HIV infections have continued to rise with an IR per 1,000 population of 0.63 (range: 0.53-0.70) in 2010 to 1 (range: 0.83-1.11) in 2021 for adults between 15 to 49 years of age. (UNAIDS 2022a, 2022b). The largest proportion of newly diagnosed people in the European Union/EEA belonged to the age group 30 to 39 years of age (30%), 10% were young people aged 15 to 24 years and 21% were older adults aged 50 years or above at diagnosis (ECDC 2022). Based on data from 26 European Union/EEA countries, 5,961 diagnoses (36% of total diagnoses and 42% of those with known information on region of origin) were reported among people originating from outside the reporting country. Of these, 1,983 (12% of total diagnoses and 14% of those with known information on region of origin), irrespective of transmission mode, were reported among people originating from countries with generalized HIV epidemics in sub-Saharan Africa. Among the European Union/EEA countries, Belgium, Cyprus, Denmark, Finland, France, Iceland, Ireland, Luxembourg, Norway, and Sweden had more than half of their new HIV diagnoses among people originating from outside of the reporting country (ECDC 2022).

Sex

Globally, women and girls (all ages) constituted 54% of all people living with HIV (UNAIDS 2022b). The burden of HIV on women was especially high in high-prevalence regions. In Eastern and Southern Africa, women and girls accounted for 63% of the region's new HIV infections in 2021, being 3 times higher among adolescent girls and young women (15-24 years of age) than among males of the same age (UNAIDS 2022a). However, in the European Union/EEA, the male-to-female ratio of new HIV diagnoses in 2021 was 3.6 (ECDC 2022). The IR was 5.8 per 100,000 population among men and 1.6 per 100,000 population among women. The 25- to 29-year-old age group had the highest rate of HIV diagnosis in the European Union/EEA at 9.3 per 100,000 population. Again, the rate for men was higher than for women in this age group; 14.6 per 100,000 population for men, while rates for women were highest in the 30- to 39-year-old age group at 4.0 per 100,000 population (ECDC 2022).

Injection drug use

In low-prevalence regions, injection drug users are a key population of people living with HIV, accounting for 18% of new HIV infections outside of sub-Saharan Africa, 3% in sub-Saharan Africa, and 10% globally (UNAIDS 2022b). The World Health Organization (WHO) strongly

recommends health interventions for injection drug users as a way of HIV prevention (WHO 2022). In the European Union/EEA, transmission due to injection drug use accounted for 4% of new HIV diagnoses with a known route of transmission in 2021 (ECDC 2022).It is highly likely that 24% of HIV cases in Latvia and 20% of cases in Greece were transmitted through injection drug use (ECDC 2022).Sexual activity

Worldwide, median HIV prevalence among sex workers and men who have sex with men (MSM) is higher than in the general population. Globally, these 2 groups accounted for 33% of new HIV infections, and outside sub-Saharan Africa, 9% of new infections occurred in sex workers and 41% in the MSM population (UNAIDS 2022b). In the United States of America, MSM accounted for 68% of new HIV diagnoses in 2020, and 64% in the Western and Central Europe and North America region in 2021.

In the European Union/EEA in 2021, the highest proportion (40%) of HIV diagnoses was reported in the MSM population, while the second highest (29%) was reported in heterosexual men (ECDC 2022). In Europe, MSM accounted for more than 60% of new HIV diagnoses in 11 European countries namely Austria, Croatia, Czechia, Germany, Hungary, Ireland, Malta, Netherlands, Poland, Slovakia and Spain (UNAIDS, 2022a).

The Main Existing Treatment Options:

The HIV treatment guidelines updated by the WHO in 2016 and 2017 recommend ART for the treatment of all adults with HIV regardless of WHO clinical stage and at any CD4+ cell count. ART should also be started immediately for all pregnant and breast- and chest-feeding people living with HIV, even if they are identified late in pregnancy or postpartum (WHO 2022), adolescents (10-19 years of age), and children <10 years of age (WHO 2016, 2017).

Current treatment options include HIV protease inhibitors (PIs), nucleoside/nucleotide reverse transcriptase inhibitor (NRTIs), NNRTIs, entry inhibitors (eg, a C-C chemokine receptor type 5 [CCR5] antagonist and a fusion inhibitor), and integrase strand transfer inhibitors (INSTIs). An ARV regimen for a treatment-naïve patient generally consists of 2 NRTIs in combination with a third active ARV drug from one of 3 drug classes: an INSTI, an NNRTI, or a PI with a pharmacokinetic (PK) enhancer (cobicistat [COBI] or ritonavir [rtv]). Given the large number of options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, comorbid conditions, access, and cost (NIH 2023a).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

HIV is a virus that is transmitted through certain body fluids and attacks the body’s immune system, specifically the CD4+ cells. Over time, HIV can destroy so many of these cells that the body cannot fight off infections and disease. Individuals who become infected with HIV and do not receive treatment will typically progress through 3 stages of disease (CDC 2022).

Stage 1 is the acute HIV infection stage, which occurs within 2 to 4 weeks after infection with HIV. People may experience a flu-like illness, which may last for a few weeks. People with acute HIV infection have a large amount of virus in their blood and are very contagious. These people are often unaware that they are infected because they may not feel sick right away or at all (CDC 2022, NIH 2023c).

Stage 2, the clinical latency period, is sometimes called asymptomatic HIV infection or chronic HIV infection. During this phase, HIV is still active but reproduces at very low levels. People may not have any symptoms or get sick during this time. For people who are not taking medicine to treat HIV, this period usually advances to Stage 3 in about a decade or more, but some may progress faster. On the other hand, people who adhere to HIV treatment can potentially remain in this stage for several decades. At the end of this phase, a person's viral load starts to increase as the CD4+ cell count begins to decrease. As this happens, the person may develop symptoms and progress to Stage 3 (AIDS) (CDC 2022, NIH 2023c).

Stage 3, the most severe stage of HIV infection, is also called AIDS. People with AIDS have such inefficient immune systems that they develop an increasing number of severe illnesses. Without treatment, AIDS patients typically survive about 3 years. People are diagnosed with AIDS when their CD4+ cell count drops below 200 cells/mm^3 or they develop certain opportunistic illnesses. People with AIDS can have a high viral load and be very infectious (CDC 2022, NIH 2023c).

Treatment can slow or prevent progression from one stage to the next. It can also dramatically reduce the chance of transmitting HIV to someone else (NIH 2023c).

Globally, approximately 650,000 (range: 510,000–860,000) AIDS-related deaths occurred in 2021 (all ages), down from 1.4 million in 2010. Of this, 560,000 (range: 430,000- 740,000) were adults >15 years of age. This figure represents a 52% reduction in mortality since 2010 (UNAIDS 2022d). In the European Union/EEA, 558 individuals with AIDS (all ages) were reported to have died during 2021. This figure has been consistently decreasing since 2012 (ECDC 2022). The Antiretroviral Therapy Cohort Collaboration, which includes cohorts of HIV-positive patients from Canada and Europe, reported a mortality rate of 15.5 and 7.4 per 1,000 person-years for men and women, respectively and includes 20,784 patients and 104,649 person-years of follow-up, reported an overall mortality rate of 11.2 (95% CI: 10.6-11.9) per 1,000 person-years (Antiretroviral Therapy Cohort Collaboration 2016).

The mortality rate in the second and third years after initiating ART has declined over time, with an adjusted hazard ratio of 1.12 (range: 0.97-1.28) for those starting ART between 1996 and 1999, and 0.80 (range: 0.66-0.97) for those starting treatment between 2008 and 2010 (Antiretroviral Therapy Cohort Collaboration 2017). The Antiretroviral Therapy Cohort Collaboration also reported that baseline CD4+ count was prognostic for unadjusted cumulative mortality. Patients who started ART with a CD4+ count <50 cells/µL experienced the greatest declines in mortality rates over time on ART, from 88 (95% CI: 78-99) per 1,000 person-years during the first 6 months to 15 (95% CI: 13-17) per 1,000 person-years after 10 years from start of ART (May 2016).

Important Comorbidities:

Important comorbidities in HIV-1-infected ARV treatment-naïve adult patients include chronic hepatitis secondary to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, renal disease, malignancies, tuberculosis, opportunistic infections, lipid abnormalities, coronary artery disease, dementia, peripheral neuropathy, pancreatitis, bleeding disorders, and progressive multifocal leukoencephalopathy.

Pediatric Population (<15 years of age)

Incidence:

The 2021 annual report from UNAIDS on the global AIDS epidemic estimates that worldwide, approximately 160,000 children <15 years of age were newly infected with HIV in 2021, a decrease of 52% from 2010 (UNAIDS 2022a). The Middle East and North Africa is the only region where child infections have failed to decrease since 2010 (UNAIDS, 2022a). Incidence estimates were unavailable for Eastern Europe, Western Europe, Central Europe, North America, and Central Asia from the UNAIDS report. Alternatively, WHO reported lowest age-specific incidence rates in children under 15 years of age (0.1 per 100,000 population) for the European Union/EEA region in 2021 (ECDC 2022). The number of children (0-14 years of age) newly infected with HIV in 2021, by geographic region is as follows:

HIV incidence estimates with uncertainty bounds for the pediatric population (0-14 years)

Region	Children (0-14 years) newly infected with HIV
Western and Central Africa	54,000 [39,000–71,000]
Eastern and Southern Africa	78,000 [49,000– 130,000]
Eastern Europe and Central Asia	Not reported
Asia and the Pacific	14,000 [9400– 20,000]
Latin America	4,000 [2100– 6000]
Caribbean	910 [580– 1300]
Western Europe, Central Europe, North America	Not reported
Middle East and North Africa	1,500 [1,200– 1,800]

Source: UNAIDS 2022b

Prevalence:

In 2021, there were 1.7 million (range:1.3-2.1 million) children (0-14 years of age) living with HIV (UNAIDS 2022b). Globally, only 52% (range: 42%–65%) of children (0-14 years of age) had access to ARV treatment (UNAIDS 2022a). In the Middle East and North Africa only 40% of children living with HIV were accessing HIV treatment services in 2021. Prevalence estimates were unavailable for Western Europe, Central Europe, and North America from the UNAIDS report. The WHO reported the number of HIV diagnoses in 2021 was 89 in the European Union/EEA in children less than 15 years of age. This was highest in France with 24 HIV diagnoses in this age group in 2021 (ECDC 2022). The number of children (0-14 years of age) living with HIV in 2021, by geographic region is as follows:

HIV prevalence estimates with uncertainty bounds for the pediatric population (0-14 years)

Region	Estimated children (0-14 years) living with HIV
Western and Central Africa	420,000 [340,000-500,000]
Eastern and Southern Africa	1 million [830,000- 1.3 million]
Eastern Europe and Central Asia	Not reported
Asia and the Pacific	130,000 [100,000- 160,000]
Latin America	33,000 [22,000-44,000]
Caribbean	9,200 [7800-11000]
Western Europe, Central Europe, North America	Not reported
Middle East and North Africa	9,200 [7,900-11,000]

Source: UNAIDS 2022b

Demographics of the Population in the Authorized Indication and Risk Factors for the Disease

The Collaborative HIV Paediatric Study is a multicenter cohort of HIV-1-infected children under care and included a total of 2,212 children by end of March 2021, comprising virtually all children receiving HIV-related care in the United Kingdom from 2006 onwards and in Ireland from 2006 to 2018 (Collaborative HIV Paediatric Study 2021). Demographic data for 2020 for this cohort are presented in the tables below.

Age of United Kingdom/Irish Cohort of Patients with HIV Acquired in Childhood, 2020

Number*	Median Age (IQR)	<1 year	1-4 years	5-9 years	10-14 years	15-19 years	≥20 years
1,890	22 (18-26)	0 (0%)	13 (1%)	45 (2%)	160 (8%)	359 (19%)	1,313 (69%)

IQR= interquartile range
Source: Collaborative HIV Paediatric Study 2021
* Data for 2019/2020 are incomplete as subject to reporting delay. Republic of Ireland ceased reporting in 2018; those reported up to that date are included here.

Demographics and Disease History of the 489 Children in Follow-up*, 2020

Characteristic	N (%)
Female	283 (58%)
Ethnic Group	Black: 357 (73%)
	White: 31 (6%)
	Mixed: 61 (12%)
	Other: 12 (2%)
	Unknown: 28 (6%)

Source: Collaborative HIV Paediatric Study 2021
* Those who have died, lost to follow-up, left the UK or transferred to adult care are excluded.

Globally in 2021, 41% of children living with HIV (0-14 years of age) are estimated to have suppressed viral loads, up from 26% in 2015. Viral suppression rates in 2021 were highest in Asia and the Pacific (65%) and Eastern and Southern Africa (44%). The lowest rates of viral suppression were in Western and Central Africa (27%). No data were available from Eastern Europe and Central Asia and Western and Central Europe and North America for 2021 (UNAIDS 2022b).

Risk factors for acquiring HIV include geography and mother-to-child transmission.

Globally, in the absence of interventions, vertical transmission (ie, mother-to-child transmission) rates range from 15% to 45% (WHO 2023). Between 2016 and 2021, the rate of new infections through vertical transmission has only decreased by 22%. Although vertical transmission of HIV is common in Africa, it has been virtually eliminated in industrialized countries, accounting for less than 1% of new infections in the European Union/EEA (ECDC 2022). In 2021, almost 85% of the new vertical infections occurred in sub-Saharan Africa (UNAIDS 2022c). These infections are partly due to the lack of prophylactic ART to prevent transmission during pregnancy, delivery, and breast-feeding in the lower income countries of sub-Saharan Africa. It is estimated that the percentage of pregnant women living with HIV who received ART for preventing vertical transmission was only 60% in Western and Central Africa in 2021 (UNAIDS 2022a). However, it is noteworthy that ART coverage was as high as 90% in Eastern and Southern Africa.

The Main Existing Treatment Options:

For treatment-naïve HIV-infected children, combination therapy with 3 ARV drugs is currently recommended. This includes a dual NRTI backbone plus an active drug from one of the following classes: an INSTI, an NNRTI, or a boosted PI. Choice of treatment should be based on several factors, including the patient's age, weight, and other personal factors, as well as the results of drug-resistance testing (NIH 2023b).

In western countries (eg, United States and Europe), the preferred first-line ARV regimen in the pediatric population generally contains 3 drugs, including either a boosted PI, NNRTI or INSTI plus an NRTI backbone (Bamford 2018, NIH 2023b).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Progression of HIV infection in pediatric patients is similar to adults, although surveillance data from the CDC suggest that patients aged 13 to 24 years when diagnosed with AIDS have a longer survival than older individuals. Vertically transmitted HIV can cause rapidly progressive, chronically progressive, or adult-like disease in which a significant clinical latency period occurs before symptoms appear (Rivera 2017).

Infants infected perinatally are usually asymptomatic during the first few months of life, even if no ART is started. Although the median age at symptom onset is about 3 years, some children remain asymptomatic for >5 years and, with appropriate ART, can be expected to survive to adulthood. The most common manifestations of HIV infection in children not receiving ART include generalized lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, oral candidiasis, central nervous system disease (including developmental delay, which can be progressive), lymphoid interstitial pneumonitis, recurrent bacteremia, opportunistic infections, recurrent diarrhea, parotitis, cardiomyopathy, hepatitis, nephropathy, and cancers (Weinberg 2013).

It is estimated that in 2021, only 52% of children (0-14 years of age) living with HIV had access to ART (UNAIDS 2022b). In 2021, 98,000 (range: 67,000-140,000) children less than 15 years of

age died due to AIDS (UNAIDS 2022b). AIDS deaths among children were estimated at approximately 1,600 (range: <1,000-3,000) in 2006 in Eastern Europe and Central Asia (EuroHIV 2007).

Important Comorbidities:

Important comorbidities in pediatric patients with HIV-1 infection include encephalopathy, psychiatric disorders, pain, HBV and/or HCV infection, renal disease, respiratory diseases, cardiomyopathy/ventricular dysfunction, reduced bone density/osteoporosis/osteonecrosis, cytopenias, malignancies, tuberculosis, opportunistic infections, progressive multifocal leukoencephalopathy, lipid abnormalities, and sexual maturity and growth abnormalities.

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
Toxicity findings:	
Single & repeat-dose toxicity	
Hepatotoxicity	
Hepatocellular hypertrophy in mice and rats was associated with liver enzyme (ie, uridine diphosphate glucuronosyltransferase [UDP-GT]) induction and an increase of the organ weight at exposures at least 14-fold higher than the clinical exposure.	Based on results from clinical trials and postmarketing data (including careful clinical monitoring of hepatotoxicity), hepatotoxicity is not considered to be an important potential risk.
Mild to moderate perivascular inflammatory reactions together with fibrosis and single hepatic cell necrosis in the central part of the lobules were seen in dogs and were associated with an increase in cholesterol, bilirubin, alkaline phosphatase, and alanine aminotransferase at exposures at least 10-fold higher than the clinical exposure. Moreover, mononuclear phagocytic system aggregates and multifocal bile duct proliferation were noted.	
Thyroid and pituitary glands	
The thyroid gland effects in rats were characterized by an increased organ weight, hypertrophy of follicular epithelium, and reduced serum concentrations of thyroxine and were associated with liver enzyme (ie, UDP-GT) induction. Effects on the pituitary gland in rats comprised an increase of swollen and vacuolated cells in the pars distalis. These effects are considered secondary to the thyroid gland effects.	As the effects on thyroid and pituitary glands are secondary to the effects of RPV on rodent-specific thyroxine clearance, they are considered not relevant for humans.
Nephrotoxicity	
Minimal to moderate degenerative nephropathy was noted in mice at exposures 320-fold higher than the clinical exposure. Moderate acute nephritis was observed in dogs at exposures 25-fold higher than the clinical exposure.	The kidney effects seen in mice and dogs are not indicative of an effect on glomerular filtration or proximal tubular resorption. For these reasons and in view of the safety margins, the nonclinical kidney effects are considered not relevant for humans.

Key Safety Findings	Relevance to Human Usage
Adrenal glands	
Changes in the serum concentrations of adrenal hormones or their precursors and of adrenocorticotropic hormone in rats, dogs, monkeys and likely the effects in dog testes and ovaries of mice and dogs are due to the apparent inhibition of cytochrome P450 (CYP)21 and CYP17, key enzymes in steroidogenesis.	These findings suggest a potential for changes in adrenal hormones and gonadal effects in humans and eventually for adrenal insufficiency. Based on results from clinical trials and postmarketing data (including careful clinical monitoring of decreased blood cortisol), decreased blood cortisol is not considered to be an important potential risk.
Red blood cells	
A small decrease in red blood cell parameters was seen in mice, rats, and dogs at exposures 277-fold, 30-fold, and 25-fold higher than the clinical exposure, respectively. Signs of regeneration were noted and no signs pointed toward bone marrow suppression.	Given the absence of bone marrow suppression in rats, mice, and dogs, the red blood cell effects are considered not relevant for humans.
Coagulation system	
A mild to moderate increase of coagulation times of both the intrinsic and extrinsic pathways occurred only in male rats at exposures 30-fold higher than the clinical exposure. There were no clinical manifestations of affected coagulation in this species.	Given the absence of clinical manifestations, this effect in rats only is considered not relevant for humans.
Reproductive toxicity	
Rilpivirine did not show a teratogenic potential or effect on reproductive function in rats and rabbits. The reproductive and developmental toxicity studies did not demonstrate any effects on fertility or fecundity, parturition, or maternal behavior.	The results of reproductive toxicity studies (in rats and rabbits) and developmental toxicity studies (in rats) did not suggest a risk for humans.
Developmental toxicity	
The reproductive and developmental toxicity studies in rats did not demonstrate any effects on the development of offspring from dams treated with RPV during pregnancy and lactation. In rats, the placenta was a partial barrier for RPV. Low exposure to RPV in rat pups nourished by dams treated with RPV indicated a low concentration of RPV in milk of rats.	The results of reproductive and developmental toxicity studies in rats did not suggest a risk for humans.

Key Safety Findings	Relevance to Human Usage
Genotoxicity	
No indications of a genotoxic potential of RPV were observed in genotoxicity tests (in vitro and in vivo).	The results of genotoxicity testing did not indicate a safety concern for humans.
Carcinogenicity	
Hepatocellular adenomas and carcinomas seen in mice were associated with induction of CYP4A and peroxisome proliferation. Hepatocellular adenomas and follicular adenomas and carcinomas in the thyroid gland in rats occurred as a result of induction of CYP3A and UDP-GT.	The liver enzyme inductions underlying the carcinogenetic effects in rodents is considered species-specific and therefore considered not relevant for humans.
General safety pharmacology findings:	
Cardiovascular (including potential for QT interval prolongation)	
Rilpivirine demonstrated the potential to inhibit some potassium channels involved in cardiac action potential repolarization and to induce QT interval prolongation in the rabbit ventricular wedge assay. However, the observed mild QT interval prolongation contributed to only a marginal Torsade de Pointes score at unbound drug concentrations much higher than those achieved in humans with the approved 25-mg dose, indicating a low proarrhythmic risk of RPV. In the in vivo animal models, no significant effect on electrophysiological cardiovascular or hemodynamic parameters was noted.	Nonclinical data suggest a potential for QT interval prolongation in humans, as confirmed by the dose-dependent QT prolongation in the thorough QT (TQT) trial with supratherapeutic doses. However, no QT prolongation was observed with the approved 25-mg dose once daily. Based on results from clinical trials and postmarketing data (including careful clinical monitoring of QT interval prolongation), QT interval prolongation is not considered to be an important potential risk.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

EDURANT (RPV, also referred to as TMC278) oral tablet, in combination with other ARV medicinal products, was initially indicated for the treatment of HIV-1 infection in ARV treatment-naïve adult patients with a viral load ≤100,000 HIV-1 RNA copies/mL, based on the adult Phase 3 program.

Based on safety and efficacy analyses through 48 weeks from an open-label, Phase 2 trial in ARV treatment-naïve adolescents aged 12 to <18 years (TMC278-TiDP38-C213, Cohort 1), the indication was further extended to ARV treatment-naïve pediatric patients 12 years of age and older with a viral load ≤100,000 HIV-1 RNA copies/mL.

Based on safety and efficacy results of trial TMC114HIV3015 in pregnant women, the Summary of Product Characteristics (SmPC) was updated to allow use of EDURANT during pregnancy, but only if the potential benefit justifies the potential risk.

The clinical development of RPV started in CCI and includes an extensive program of Phase 1 trials that provided a description of the PK characteristics of RPV and its drug-drug interaction potential, its short-term safety and tolerability profile, as well as recommendations for the administration and dosing regimen.

Two short-term Phase 2a Proof-of-Principle trials (R278474-C201 and R278474-C202) were conducted to provide clinical confirmation in HIV-1-infected subjects of the in vitro findings of antiviral activity of RPV. Due to the short duration of treatment and different population, respectively, these trials do not bring significant additional information and were therefore not included in the exposure tables.

The following trials are included in this EU-RMP, for characterization of exposure and safety:

Two registrational Phase 3 trials and one Phase 2b trial in **adult** subjects:

- TMC278-TiDP6-C209 (C209; also known as Early Capture HIV Cohort Study [ECHO]): A Phase 3, randomized, double-blind trial of TMC278 25 mg once daily versus efavirenz (EFV) 600 mg once daily in combination with a fixed background regimen in ART-naïve HIV-1-infected subjects
- TMC278-TiDP6-C215 (C215; also known as Targeted Highly-Effective Interventions to Reverse the HIV Epidemic [THRIVE]): A Phase 3, randomized, double-blind trial of TMC278 25 mg once daily versus EFV 600 mg once daily in combination with a background regimen in ART-naïve HIV-1-infeced subjects
- TMC278-C204 (C204): A Phase 2b, randomized, active controlled, partially blind, dose-finding trial of TMC278 in ART-naïve HIV-1 infected subjects (long-term data, up to 240 weeks)

One Phase 2 trial in **adolescents**:

- TMC278-TiDP38-C213 (C213), Cohort 1: A Phase 2, open-label, single-arm trial to evaluate the PK, safety, tolerability, and antiviral activity of TMC278 in ART-naïve HIV-1-infected adolescents aged ≥12 to <18 years (long-term data, up to 240 weeks)

Two Phase 2 trials in **children** (2 to <12 years of age):

- TMC278-TiDP38-C213 (C213), Cohort 2: A Phase 2, open-label, single-arm trial to evaluate the PK, safety, tolerability, and antiviral activity of TMC278 in ART-naïve HIV-1-infected children aged ≥6 to <12 years (Week 48 and post-Week 48 final data)
- TMC278HTX2002 (HTX2002): A Phase 2, open-label, single-arm, multicenter study to evaluate the PK, safety, tolerability, and efficacy of switching to RPV plus other ARVs in HIV-1-infected children (aged 2 to <12 years) who are virologically suppressed (Week 48 final data)

One Phase 3b trial in **pregnant women**:

- TMC114HIV3015: A single-arm, open-label trial to assess the PK of darunavir and ritonavir, darunavir and cobicistat, etravirine, and RPV in HIV-1 infected pregnant women

RPV is also formulated as a long-acting parenteral formulation for intramuscular injection. This formulation showed no additional safety concerns of relevance to the oral tablet and is not further discussed in this EU-RMP. The RPV 25 mg oral tablet formulation can be used as an optional oral lead-in and for bridging of missed RPV LA injection visits. Overall, no safety issue was identified for RPV oral from this optional oral lead-in and bridging use.

SIII.2. Clinical Trial Exposure

Overall, 945 healthy adult subjects and 1,997[a] HIV-1 infected subjects (adults and pediatrics) have been enrolled in the RPV oral tablets clinical development program[b], of which 2,061 subjects have received RPV oral tablets (25-mg or 2.5-mg tablets) in Company-sponsored clinical trials (see Table SIII.1). Approximately, 861 subjects received RPV oral tablets in the Phase 1 clinical trials, 431 subjects received RPV oral tablets in the Phase 2 clinical trials, 761 subjects received RPV oral tablets in the Phase 3 clinical trials, and 8 subjects received RPV oral tablets in the Phase 4 clinical trials.

Of the 2,061 subjects who received RPV oral tablets, 1,981 subjects were ≥18 years of age (RPV 25 mg), 36 subjects were ≥12 to <18 years of age (RPV 25 mg), and 44 subjects were <12 years of age (RPV 25, 15, or 12.5 mg).

[a] It is noted that exposure in trial TMC114HIV3015 was limited to single agent RPV (3 subjects) and therefore, 16 subjects receiving the FDC (TDF/FTC/RPV) were not counted.

[b] The subjects in cross-over clinical trials were counted only once for the total number of healthy adult subjects.

More information on oral RPV exposure in adults, adolescents, and children is provided in the following sections.

Table SIII.1: Estimated Cumulative Subject Exposure From Company-sponsored RPV Oral Tablets Clinical Trials[1]

	Number of Subjects (N=2,942)[2]
RPV Oral Clinical Program	
RPV (Oral Tablet)	2,061 (70.1%)[3]
Comparator[4]	771 (26.2%)
Placebo[5]	207 (7.0%)

Note: Data up to 19 May 2022.

1 The following trials are included: R278474-C101, TMC114HIV3015, TMC125-IFD1001; TMC278-X trials, with X = C201, C202, and C204; TMC278-TiDP38-X trials, with X = C145 and C213; TMC278-TiDP6-X trials, with X = C102, C103, C104, C105, C106, C108, C109, C112, C114, C116, C117, C119, C120, C121, C123, C125, C127, C130, C131, C136, C137, C139, C140, C151, C152, C153, C154, C209, C215, CDE101, CDE102, and CDE103; TMC278HIV1001, TMC278HTX2002, TMC278HTX3001, TMC278IFD1001, TMC278IFD1003, TMC278IFD1004, TMC278IFD1005, TMC278IFD4005, TMC435-TiDP16-C114.

2 This is the total number of unique subjects. Subjects who switched between treatment groups (eg, cross-over clinical trials) were counted in each treatment group but were only counted once for the total number of subjects. In addition, subjects who rolled over from the Phase 2b or Phase 3 clinical trials to trial TMC278-TiDP6-C222 and from trial TMC278-TiDP38-C213 to trial TMC278IFD3004 were only counted once. Estimates of cumulative subject exposure, based upon actual exposure data from completed and ongoing clinical trials.

3 It is noted that exposure in clinical trial TMC114HIV3015 was limited to single agent RPV (3 subjects) and therefore, 16 subjects receiving the fixed-dose combination (tenofovir disoproxil fumarate/emtricitabine/RPV) were not counted.

4 Comprised of subjects exposed to comparator in the Phase 2b/3 clinical trials only, excluding subjects exposed to comparator in the Phase 1 clinical trials TMC278-TiDP6-C152 and TMC278IFD1005.

5 Comprised of subjects exposed to placebo in the Phase 1 healthy subject trials (such as TQT/QTc clinical trials TMC278-TIDP6-C131, TMC278-TIDP6-C151, and TMC278-TIDP6-C152) and 1 Phase 2a clinical trial in subjects with HIV-1 infection (TMC278-C201).

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Adult Population

Exposure in Randomized Blinded Trials: Pooled Phase 3 Trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE)

The C209 and C215 trials were double-blinded up to Week 96 (note: for the Week 48 primary analysis, the sponsor was fully unblinded to the treatment groups, but subjects, investigators, and monitors who interacted with site personnel were not unblinded at that time).

The overall pooled exposure data of adult subjects treated with RPV from the 2 registrational Phase 3 trials C209 and C215 up to 96 Weeks are presented in Tables SIII.2 through SIII.5 for all subjects by duration, by age and sex, by race/ethnicity, and variable stratifications relevant to the product (estimated glomerular filtration rate for creatinine as calculated by Modification of Diet in Renal Disease [MDRD] formula [$eGFR_{creat}$] at baseline, coinfection with HBV/HCV). Data from the pooled Phase 3 trials (up to Week 96) were not presented by dose as both trials used RPV at the recommended dose of 25 mg once daily.

Table SIII.2: Exposure BY DURATION (by Indication)

	Persons (n)	Person-Years[1]
INDICATION HIV-1 infection	(N = 686)	
Exposure for at least 4 Weeks	683	52
Exposure for at least 12 Weeks	672	155
Exposure for at least 24 Weeks	637	293
Exposure for at least 48 Weeks	612	563
Exposure for at least 96 Weeks	566	1,041
Total person time		1,277

[1]Overall person-years is calculated based on the individual exposure, while person-years by interval (exposure for at least xx weeks) is calculated based on the formula n*xx*7/365.25 (xx = duration of exposure in weeks).

[TRMPEX01.RTF] [/SAS/Z_TMC278/TMC278ZRMP/FILES/RE/RMP2018/PROGRAMS/TRMPEX01.SAS] 08JUN2018, 14:36

Table SIII.3: Exposure BY AGE GROUP AND SEX (by Indication)

	Men		Women	
	Persons (n)	Person - Years[1]	Persons (n)	Person - Years[1]
INDICATION HIV-1 infection	(N = 518)		(N = 168)	
<18 years	0	0	0	0
18 - 54 years	494	925	159	285
55 - 64 years	22	43	8	17
≥65 years	2	4	1	2
Total	518	972	168	304

[1]Overall person-years is calculated based on the individual exposure (exposure in days/365.25).

[TRMPEX02.RTF] [/SAS/Z_TMC278/TMC278ZRMP/FILES/RE/RMP2018/PROGRAMS/TRMPEX02.SAS] 08JUN2018, 14:40

Table SIII.4: Exposure BY ETHNIC or RACIAL ORIGINS (by Indication)

	Persons (n)	Person - Years[1]
INDICATION HIV-1 infection	(N = 686)	
Race		
White	420	799
Black or African American	165	282
Asian	78	152
Not allowed to ask per local regulations	7	12
Other	14	28
Missing	2	4
Ethnicity		
Hispanic or latino	183	345
Not hispanic or latino	498	923
Not allowed to ask per local regulations	5	9
Total	686	1,277

[1]Overall person-years is calculated based on the individual exposure (exposure in days/365.25).

[TRMPEX03.RTF] [/SAS/Z_TMC278/TMC278ZRMP/FILES/RE/RMP2018/PROGRAMS/TRMPEX03.SAS] 12JUN2018, 09:09

Table SIII.5: Exposure BY SPECIAL POPULATIONS

	Persons (n)	Person - Years[1]
INDICATION HIV-1 infection	(N = 686)	
$eGFR_{creat}$ at baseline		
Stage 1: GFR ≥90 ml/min/1.73m^2	523	967
Stage 2: 60≤ GFR <90 ml/min/1.73m^2	142	268
Stage 3: 30≤ GFR <60 ml/min/1.73m^2	1	2
Stage 4: 15≤ GFR <30 ml/min/1.73m^2	0	0
Stage 5: GFR <15 ml/min/1.73m^2	0	0
Missing	20	40
HBV/HCV coinfection		
Yes	49	82
No	621	1,165
Unknown	16	29
Total	686	1,277

[1]Overall person-years is calculated based on the individual exposure (exposure in days/365.25).
$eGFR_{creat}$ = estimated Glomerular Filtration Rate for creatinine as calculated by Modification of Diet in Renal Disease (MDRD) formula.

[TRMPEX04.RTF] [/SAS/Z_TMC278/TMC278ZRMP/FILES/RE/RMP2018/PROGRAMS/TRMPEX04.SAS] 11JUN2018, 13:19

Exposure in All Clinical Trials Including Open Extensions

Phase 2b Trial TMC278-C204

Exposure to RPV in Phase 2b trial C204 up to Week 240 is summarized in Tables SIII.6 through SIII.10 for all subjects by duration across doses, by duration by dose, by age and sex, by race, and variable stratifications relevant to the product ($eGFR_{creat}$ at baseline, coinfection with HBV/HCV).

There is no pooling of data from the Phase 2b and Phase 3 trials available because of the differences in design and treatment duration between clinical trials.

The C204 trial was partially blinded up to Week 96 (ie, the RPV doses were blinded, while the administration of EFV in the control group was open-label). After Week 96, the trial was open-label.

The intent-to-treat (ITT) population in trial C204 included 279 subjects. However, for one subject (PPD available data did not allow calculation of treatment duration and this subject was therefore not included in the calculation of exposure to RPV.

After Week 240, subjects on RPV were given the option to continue treatment until RPV was commercially available, reimbursed, or could be accessed from another source. The population of 166 RPV-treated subjects included in the post-Week 240 analysis received 166.5 person-years exposure to RPV.

Table SIII.6: Exposure BY DURATION (by Indication) (Week 240 Analysis)

	Persons (n)	Person-Years[1]
INDICATION HIV-1 infection in ARV treatment-naïve adult patients with a viral load ≤100,000 HIV-1 RNA copies/mL	(N = 278*)	
Exposure for at least 4 Weeks	270	21
Exposure for at least 12 Weeks	261	60
Exposure for at least 24 Weeks	248	114
Exposure for at least 48 Weeks	236	217
Exposure for at least 96 Weeks**	218	401
Exposure for at least 144 Weeks	194	535
Exposure for at least 192 Weeks	182	670
Exposure for at least 240 Weeks	168	773
Total person time		985

[1]Overall person-years is calculated based on the individual exposure, while person-years by interval (exposure for at least xx weeks) is calculated based on the formula n*xx*7/365.25 (xx = duration of exposure in weeks).
* Subject PPD was included in the ITT population but was not included in the exposure calculations as available data did not allow calculation of treatment duration for this subject.
** This trial was partially blinded up to Week 96, ie the RPV doses were blinded to each other while the administration of EFV in the control group was open-label. After Week 96 the trial was open-label.

[TRMPEX01_C204.RTF] [/SAS/Z_TMC278/TMC278ZRMP/FILES/RE/RMP2018/PROGRAMS/TRMPEX01_C204.SAS] 15JUN2018, 10:07

Table SIII.7: Exposure BY DURATION (by Dose Level) (Week 240 Analysis)

	Persons (n)	Person-Years[1]
INDICATION HIV-1 infection in ARV treatment-naïve adult patients with a viral load ≤100,000 HIV-1 RNA copies/mL	(N = 278*)	985
Dose of exposure: TMC278 25mg qd		
Exposure for at least 4 Weeks	216	17
Exposure for at least 12 Weeks	207	48
Exposure for at least 24 Weeks	203	93
Exposure for at least 48 Weeks	197	181
Exposure for at least 96 Weeks**	173	318
Exposure for at least 144 Weeks	65	179
Exposure for at least 192 Weeks	58	213
Total	219	503
Dose of exposure: TMC278 75mg qd		
Exposure for at least 4 Weeks	231	18
Exposure for at least 12 Weeks	230	53
Exposure for at least 24 Weeks	223	103
Exposure for at least 48 Weeks	176	162
Exposure for at least 96 Weeks**	74	136
Exposure for at least 144 Weeks	49	135
Exposure for at least 192 Weeks	0	0
Total	233	342
Dose of exposure: TMC278 150mg qd		
Exposure for at least 4 Weeks	87	7
Exposure for at least 12 Weeks	84	19
Exposure for at least 24 Weeks	79	36
Exposure for at least 48 Weeks	75	69
Exposure for at least 96 Weeks**	60	110
Exposure for at least 144 Weeks	0	0
Exposure for at least 192 Weeks	0	0
Total	90	140

qd = once daily.
[1] Overall person-years is calculated based on the individual exposure, while person-years by interval (exposure for at least xx weeks) is calculated based on the formula n*xx*7/365.25 (xx = duration of exposure in weeks).
* Subject PPD was included in the ITT population but was not included in the exposure calculations as available data did not allow calculation of treatment duration for this subject.
** This trial was partially blinded up to Week 96, ie the RPV doses were blinded to each other while the administration of EFV in the control group was open label. After Week 96 the trial was open-label.

[TRMPEX02_C204.RTF] [/SAS/Z_TMC278/TMC278ZRMP/FILES/RE/RMP2018/PROGRAMS/TRMPEX02_C204.SAS] 15JUN2018, 10:07

Table SIII.8: Exposure BY AGE GROUP AND SEX (by Indication) (Week 240 Analysis)

	Men		Women	
	Persons (n)	Person-Years[1]	Persons (n)	Person-Years[1]
INDICATION HIV-1 infection	(N = 186*)		(N = 92)	
<18 years	0	0	0	0
18 - 54 years	179*	636	90	320
55 - 64 years	5	16	1	5
≥65 years	2	5	1	5
Total	186*	656	92	329

[1]Overall person-years is calculated based on the individual exposure (exposure in days/365.25).
* Subject PPD was included in the ITT population but was not included in the exposure calculations as available data did not allow calculation of treatment duration for this subject.

[TRMPEX04_C204.RTF] [/SAS/Z_TMC278/TMC278ZRMP/FILES/RE/RMP2018/PROGRAMS/TRMPEX04_C204.SAS] 15JUN2018, 10:07

Table SIII.9: Exposure BY RACIAL ORIGINS (by Indication) (Week 240 Analysis)

	Persons (n)	Person-Years[1]
INDICATION HIV-1 infection	(N = 278*)	
Race		
Caucasian/White	121*	440
Black or African American	65	190
Oriental/Asian	54	218
Hispanic	29	101
Other	9	36
Total	278*	985

[1]Overall person-years is calculated based on the individual exposure (exposure in days/365.25).
* Subject PPD was included in the ITT population but was not included in the exposure calculations as available data did not allow calculation of treatment duration for this subject.

[TRMPEX05_C204.RTF] [/SAS/Z_TMC278/TMC278ZRMP/FILES/RE/RMP2018/PROGRAMS/TRMPEX05_C204.SAS] 15JUN2018, 10:07

Table SIII.10: Exposure BY SPECIAL POPULATIONS (Week 240 Analysis)

	Persons (n)	Person-Years[1]
INDICATION HIV-1 infection	(N = 278*)	
$eGFR_{creat}$ at baseline		
Stage 1: GFR ≥90 ml/min/1.73m^2	222*	777
Stage 2: 60≤ GFR <90 ml/min/1.73m^2	56	208
Stage 3: 30≤ GFR <60 ml/min/1.73m^2	0	0
Stage 4: 15≤ GFR <30 ml/min/1.73m^2	0	0
Stage 5: GFR <15 ml/min/1.73m^2	0	0
Missing	0	0
HBV/HCV coinfection		
Yes	26*	74
No	232	843
Unknown	20	69
Total	278*	985

$eGFR_{creat}$ = estimated Glomerular Filtration Rate for creatinine as calculated by Modification of Diet in Renal Disease (MDRD) formula.
[1]Overall person-years is calculated based on the individual exposure (exposure in days/365.25).
* Subject PPD was included in the ITT population but was not included in the exposure calculations as available data did not allow calculation of treatment duration for this subject.

[TRMPEX06_C204.RTF] [/SAS/Z_TMC278/TMC278ZRMP/FILES/RE/RMP2018/PROGRAMS/TRMPEX06_C204.SAS] 15JUN2018, 10:07

Phase 3 Trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE): post-Week 96

After the Week 96 cut-off of both Phase 3 trials, all subjects were unblinded and given the option to continue open-label treatment until their final/withdrawal visit.

For C209 this:

- included 268 subjects exposed to RPV;
- resulted in an additional 123,2 person-years exposure to RPV.

For C215 this:

- included 274 subjects exposed to RPV;
- resulted in an additional 120,8 person-years exposure to RPV.

Pediatric Population (≥12 years of age)

Phase 2 Trial TMC278-C213, Cohort 1

In Cohort 1 of this open-label, single arm trial, 36 ART-naïve, HIV-1-infected adolescents aged ≥12 to <18 years weighing ≥32 kg were treated with RPV 25 mg once daily in combination with an investigator-selected background regimen of 2 NRTIs:

- the majority of subjects were Black (32 subjects; 88.9%);
- 20 (55.6%) subjects were female;
- the median (range) age and weight at screening were 14.5 (12-17) years and 45.2 (33-93) kg, respectively. There were 18 (50.0%) subjects in the 2 age subgroups (≥12 to <15 years and ≥15 to <18 years).

At the time of final Week 240 analysis, the mean (standard deviation) duration of exposure to RPV 25 mg once daily was 159.06 (100.62) weeks. The total RPV exposure was 109.74 person-years.

Table SIII.11: Exposure BY DURATION (by Indication) (Week 240 Analysis)

	Persons (n)	Person-Years[1]
INDICATION: HIV-1 infection in ARV treatment-naïve patients 12 years of age and older	(N = 36)	
Exposure for at least 4 Weeks	35	3
Exposure for at least 12 Weeks	34	8
Exposure for at least 24 Weeks	29	13
Exposure for at least 48 Weeks	29	27
Exposure for at least 96 Weeks	23	42
Exposure for at least 144 Weeks	21	58
Exposure for at least 192 Weeks	21	77
Exposure for at least 240 Weeks	18	83
Total person time		110

[1]Overall person-years is calculated based on the individual exposure, while person-years by interval (exposure for at least xx weeks) is calculated based on the formula n*xx*7/365.25 (xx = duration of exposure in weeks).

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Pediatric Population (≥2 to <12 years of age)

Phase 2 Trial TMC278-C213, Cohort 2

In Cohort 2 of this open-label, single arm trial, 13 ART-naïve, HIV-1-infected children aged ≥6 to <12 years were treated with RPV 25 mg once daily (body weight of ≥25 kg), RPV 15 mg once daily (body weight of ≥20 to <25 kg), or RPV 12.5 mg once daily (body weight of <20 kg) in combination with an investigator-selected background regimen of 2 N(t)RTIs (ie, the recommended dose group):

- the majority of subjects were Black (12 subjects; 92.3%);
- 8 (61.5%) subjects were male;

– the median (range) age and weight at screening were 8.0 (6-11) years and 27.0 (17-51) kg, respectively.

At the time of final analysis of Cohort 2 (including the 48-week initial treatment and post-week 48 extension periods), the mean (standard deviation) duration of exposure to RPV was 85.4 (56.48) weeks. The total RPV exposure was 21.3 person-years.

Note that 5 subjects enrolled in the trial are not part of the recommended dose group. These subjects weighing ≥20 to <25 kg were treated with RPV 25 mg once daily. No relevant safety findings have been observed.

Exposure to RPV in the Phase 2 trial TMC278-C213 (Cohort 2) is summarized in Tables SIII.12 through SIII.14 for all subjects by duration across doses, by duration by dose and weight, and by age and weight.

Table SIII.12: Exposure BY DURATION (by Indication) (Week 48 Analysis; Full Analysis Set)

	Persons (n)	Person-Years[1]
INDICATION: HIV-1 infection in ARV treatment-naïve patients aged ≥ 6 to <12 years	(N = 18)	
Number of subjects received RPV recommended dose	13	
Dose of exposure: All RPV recommended dose[2]		
Exposure for at least 4 Weeks	13	1.0
Exposure for at least 12 Weeks	13	3.0
Exposure for at least 24 Weeks	13	6.0
Exposure for at least 48 Weeks	8	7.4
Exposure for at least 96 Weeks	4	7.4
Exposure for at least 144 Weeks	2	5.5
Exposure for at least 192 Weeks	2	7.4
Exposure for at least 240 Weeks	0	0
Total person time		21.3

[1]Overall person-years is calculated based on the individual exposure, while person-years by interval (exposure for at least xx weeks) is calculated based on the formula n*xx*7/365.25 (xx = duration of exposure in weeks).
[2]The summary output including all RPV recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for ≥25kg

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Table SIII.13: Exposure BY DURATION (by Dose Level and Weight) (Week 48 Analysis; Full Analysis Set)

	Persons (n)	Person-Years[1]
INDICATION: HIV-1 infection in ARV treatment-naïve patients aged ≥ 6 to <12 years	18	34.57
Dose of exposure: 12.5 mg qd, < 20 kg		
Exposure for at least 4 Weeks	2	0.2
Exposure for at least 12 Weeks	2	0.5
Exposure for at least 24 Weeks	2	0.9
Exposure for at least 48 Weeks	0	0
Exposure for at least 96 Weeks	0	0
Exposure for at least 144 Weeks	0	0
Exposure for at least 192 Weeks	0	0
Exposure for at least 240 Weeks	0	0
Total	2	1.8

Table SIII.13: Exposure BY DURATION (by Dose Level and Weight) (Week 48 Analysis; Full Analysis Set)

	Persons (n)	Person-Years[1]
Dose of exposure: 15 mg qd, 20 - < 25 kg		
Exposure for at least 4 Weeks	2	0.2
Exposure for at least 12 Weeks	2	0.5
Exposure for at least 24 Weeks	2	0.9
Exposure for at least 48 Weeks	1	0.9
Exposure for at least 96 Weeks	0	0
Exposure for at least 144 Weeks	0	0
Exposure for at least 192 Weeks	0	0
Exposure for at least 240 Weeks	0	0
Total	2	1.9
Dose of exposure: 25 mg qd, ≥ 25kg		
Exposure for at least 4 Weeks	9	0.7
Exposure for at least 12 Weeks	9	2.1
Exposure for at least 24 Weeks	9	4.1
Exposure for at least 48 Weeks	7	6.4
Exposure for at least 96 Weeks	4	7.4
Exposure for at least 144 Weeks	2	5.5
Exposure for at least 192 Weeks	2	7.4
Exposure for at least 240 Weeks	0	0
Total	9	17.5
Dose of exposure: All RPV recommended dose[2]		
Exposure for at least 4 Weeks	13	1.0
Exposure for at least 12 Weeks	13	3.0
Exposure for at least 24 Weeks	13	6.0
Exposure for at least 48 Weeks	8	7.4
Exposure for at least 96 Weeks	4	7.4
Exposure for at least 144 Weeks	2	5.5
Exposure for at least 192 Weeks	2	7.4
Exposure for at least 240 Weeks	0	0
Total	13	21.3

qd = once daily.
[1]Overall person-years is calculated based on the individual exposure, while person-years by interval (exposure for at least xx weeks) is calculated based on the formula n*xx*7/365.25 (xx = duration of exposure in weeks).
[2]The summary output including all RPV recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for ≥25kg

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Table SIII.14: Exposure by AGE GROUP AND WEIGHT (Week 48 Analysis; Full Analysis Set)

	6 - < 9 Years		9 - < 12 Years	
	Persons (n)	Person-Years[1]	Persons (n)	Person-Years[1]
INDICATION: HIV-1 infection in ARV treatment-naïve patients aged ≥ 6 to <12 years	(N = 8)		(N = 10)	
12.5 mg qd, < 20 kg	2	1.8	0	0
15 mg qd, 20 - < 25 kg	2	1.9	0	0
25 mg qd, ≥ 25 kg	3	3.0	6	14.5
All RPV recommended dose[2]	7	6.8	6	14.5

qd = once daily.
[1]Overall person-years is calculated based on the individual exposure (exposure in days/365.25)
[2]The summary output including all RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for ≥25kg

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Phase 2 Trial TMC278HTX2002

In this open-label, single arm trial, 24 virologically suppressed HIV-1-infected children aged ≥2 to <12 years were treated with RPV 25 mg once daily (body weight of ≥25 kg), RPV 15 mg once daily (body weight of ≥20 to <25 kg), or RPV 12.5 mg once daily (body weight of <20 kg) in combination with an investigator-selected background ARV (ie, the recommended dose group):

- half of the subjects were Black (12 subjects; 50%);
- 14 (58.3%) subjects were male;
- the median (range) age and weight at screening were 10.0 (6-12) years and 30.2 (18-60) kg, respectively.

At the time of final Week 48 analysis, the median treatment duration was 48.4 (range 47 to 52) weeks. The total RPV exposure was 22.3 person-years.

Note that 2 subjects enrolled in the trial are not part of the recommended dose group. These subjects weighing <20 kg were treated with RPV 15 mg once daily. No relevant safety findings have been observed.

Exposure to RPV in the Phase 2 trial HTX2002 is summarized in Tables SIII.15 through SIII.17 for all subjects by duration across doses, by duration by dose and weight, and by age and weight.

Table SIII.15: Exposure BY DURATION (by Indication) (Week 48 Analysis; Full Analysis Set)

	Persons (n)	Person-Years[1]
INDICATION: HIV-1 infection in patients 2 to <12 years of age who are virologically suppressed	(N = 26)	
Number of subjects received RPV recommended dose	24	
Dose of exposure: All RPV recommended dose[2]		
Exposure for at least 4 Weeks	24	1.8
Exposure for at least 12 Weeks	24	5.5
Exposure for at least 24 Weeks	24	11.0
Exposure for at least 48 Weeks	20	18.4
Total person time		22.3

[1]Overall person-years is calculated based on the individual exposure, while person-years by interval (exposure for at least xx weeks) is calculated based on the formula n*xx*7/365.25 (xx = duration of exposure in weeks).
[2]The summary output including all RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for ≥25kg

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Table SIII.16: Exposure BY DURATION (by Dose Level and Weight) (Week 48 Analysis; Full Analysis Set)

	Persons (n)	Person-Years[1]
INDICATION: HIV-1 infection in patients 2 to <12 years of age who are virologically suppressed	26	24.20
Dose of exposure: 12.5 mg qd, < 20 kg		
Exposure for at least 4 Weeks	1	0.1
Exposure for at least 12 Weeks	1	0.2

Table SIII.16: Exposure BY DURATION (by Dose Level and Weight) (Week 48 Analysis; Full Analysis Set)

	Persons (n)	Person-Years[1]
Exposure for at least 24 Weeks	1	0.5
Exposure for at least 48 Weeks	0	0
Total	1	0.9
Dose of exposure: 15 mg qd, 20 - < 25 kg		
Exposure for at least 4 Weeks	5	0.4
Exposure for at least 12 Weeks	5	1.1
Exposure for at least 24 Weeks	5	2.3
Exposure for at least 48 Weeks	4	3.7
Total	5	4.6
Dose of exposure: 25 mg qd, ≥ 25kg		
Exposure for at least 4 Weeks	18	1.4
Exposure for at least 12 Weeks	18	4.1
Exposure for at least 24 Weeks	18	8.3
Exposure for at least 48 Weeks	16	14.7
Total	18	16.8
Dose of exposure: All RPV recommended dose[2]		
Exposure for at least 4 Weeks	24	1.8
Exposure for at least 12 Weeks	24	5.5
Exposure for at least 24 Weeks	24	11.0
Exposure for at least 48 Weeks	20	18.4
Total	24	22.3

qd = once daily.
[1]Overall person-years is calculated based on the individual exposure, while person-years by interval (exposure for at least xx weeks) is calculated based on the formula n*xx*7/365.25 (xx = duration of exposure in weeks).
[2]The summary output including all RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for ≥25kg

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Table SIII.17: Exposure by AGE GROUP AND WEIGHT (Week 48 Analysis; Full Analysis Set)

	2 - < 6 Years		6 - < 12 Years	
	Persons (n)	Person-Years[1]	Persons (n)	Person-Years[1]
INDICATION: HIV-1 infection in patients 2 to <12 years of age who are virologically suppressed	(N = 1)		(N = 25)	
12.5 mg qd, < 20 kg	1	0.9	0	0
15 mg qd, 20 - < 25 kg	0	0	5	4.6
25 mg qd, ≥ 25kg	0	0	18	16.8
All RPV recommended dose[2]	1	0.9	23	21.4

qd = once daily.
[1]Overall person-years is calculated based on the individual exposure (exposure in days/365.25.)
[2]The summary output including all RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for ≥25kg

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Pregnant Women

Trial TMC114HIV3015 to Assess the PK in HIV-1-infected Pregnant Women (RPV arm)

A total of 19 pregnant women were included in the RPV arm of trial TMC114HIV3015.

Table SIII.12: Exposure BY DURATION (by Indication) (Final Analysis)

	Persons (n)	Person-Years[1]
INDICATION: HIV-1 infection in ARV treatment-naïve patients 12 years of age and older	(N = 19)	
Exposure for at least 4 Weeks	16	1
Exposure for at least 8 Weeks	12	2
Exposure for at least 12 Weeks	12	3
Exposure for at least 16 Weeks	11	3
Exposure for at least 20 Weeks	9	3
Exposure for at least 24 Weeks	5	2
Exposure for at least 30 Weeks	1	1
Total person time		6

[1]Overall person-years is calculated based on the individual exposure, while person-years by interval (exposure for at least xx weeks) is calculated based on the formula n*xx*7/365.25 (xx = duration of exposure in weeks).

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Subjects with known clinically significant allergy or hypersensitivity to any of the components of EDURANT.**
Reason for being an exclusion criterion	The use of EDURANT is contraindicated in patients with hypersensitivity to any of the components to avoid possible severe and life-threatening allergic/hypersensitivity reactions.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Hypersensitivity to the active substance or to any of the excipients of its final commercial formulation is a contraindication to EDURANT use.
Criterion 2	**Subjects with known or suspected acute (primary) HIV-1 infection.**
Reason for being an exclusion criterion	Evaluation of viral load evolution as marker of disease is confounded during the acute infection given the spontaneous evolution when not treated. Given that viral load is the primary efficacy parameter, this confounding factor should be avoided in clinical trials.
Considered to be included as missing information	No
Rationale (if not included as missing information)	In routine clinical practice, this confounding of the viral load evolution is not relevant as once treatment is started, it must be maintained for life.
Criterion 3	**Subjects with previously documented HIV-2 infection.**
Reason for being an exclusion criterion	NNRTIs such as RPV have no activity against HIV-2, as demonstrated by in vitro data.
Considered to be included as missing information	No
Rationale (if not included as missing information)	EDURANT is indicated only for the treatment of HIV-1 infection.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 4	**Subjects who received any previous treatment with a therapeutic HIV vaccine or ART, with the exception of subjects who received a single dose of NVP to prevent mother-to-child transmission in the TMC278-C213 trial.**
Reason for being an exclusion criterion	The intended indication for EDURANT included only treatment-naïve HIV-1-infected patients (adults and adolescents). Virologically suppressed subjects were excluded from the pivotal trials of the initial EDURANT clinical development program, with the exception of subjects who received a single dose of NVP to prevent mother-to-child transmission in the TMC278-C213 trial. Virologically suppressed pediatric subjects were included later in trial HTX2002.
Considered to be included as missing information	No
Rationale (if not included as missing information)	EDURANT was only indicated for treatment of HIV-1 infection in ARV treatment-naïve patients 12 years of age and older. Based on results of trial HTX2002, including virologically suppressed pediatric patients who were on a stable ARV regimen, and the EMA Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection (EMA 2016), the indication for the treatment of HIV-1 infection has been broadened to adults and pediatric patients ≥2 to <18 years of age and weighing at least 14 kg without known mutations associated with resistance to the NNRTI class, and with a viral load ≤100,000 HIV-1 RNA copies/mL.
Criterion 5	**Subjects with genotypic evidence of NNRTI resistance at screening or from historical data available in the source documents.**
Reason for being an exclusion criterion	Antiretroviral activity of EDURANT in subjects with genotypic evidence of NNRTI resistance could be compromised. Therefore, the use of EDURANT in these subjects increases the risk of virologic failure and emergence of resistance which can result in the loss of treatment options in the NNRTI class and other constituents of the ART. In the double-blinded Phase 3 registrational RPV trials, EFV was used in the control arms. To cover the resistance profile of both EFV and RPV and thus to minimize the risk of virologic failure using either compound, a broad exclusionary list of NNRTI resistance-associated mutations (RAMs) needed to be used.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Considered to be included as missing information	No
Rationale (if not included as missing information)	The resistance profile of EDURANT and its cross-resistance to other NNRTIs is well established. The SmPC states that, as with other ARV medicinal products, genotypic resistance testing should guide the use of EDURANT. A list of RPV RAMs, based on all available in vitro and in vivo data, is provided in SmPC Section 5.1 (Pharmacodynamic properties).
Criterion 6	**Children <12 years old.**
Reason for being an exclusion criterion	The initial indication for EDURANT was sought in ART-naïve HIV-1-infected adult subjects. Subsequently, the indication was extended, based on data obtained in subjects 12 to 17 years of age. The collection of data in younger age groups is completed.
Considered to be included as missing information	No
Rationale (if not included as missing information)	EDURANT was initially only indicated for adults. Subsequently, the indication was extended to pediatric patients (12 to 17 years of age). The indication has been broadened further to pediatric patients ≥2 to <18 years of age and weighing at least 14 kg.
Criterion 7	**Pregnant or breast-feeding female subjects. Female subjects of childbearing potential were requested to use effective birth control methods during and for 30 days after the end of treatment.**
Reason for being an exclusion criterion	Per International Council for Harmonisation (ICH) guidelines, pregnant women should normally be excluded from clinical trials. HIV-infected women should not breast-feed because of the potential for HIV transmission.
Considered to be included as missing information	Yes (Pregnancy)
Rationale (if not included as missing information)	The SmPC (Section 4.6) states that mothers should be instructed not to breast-feed if they are receiving EDURANT because of both the potential for HIV transmission and the potential for adverse reactions in breastfed infants.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 8	**Subjects with any active AIDS-defining illness, Category C conditions, with the exception of stable cutaneous Kaposi's Sarcoma, wasting syndrome due to HIV infection, or *Pneumocystis jiroveci* infection and past occurrence of cryptococcosis that are considered cured and the acute phase ended at least 30 days ago.**
Reason for being an exclusion criterion	These subjects were excluded because these conditions could confound the safety evaluation.
Considered to be included as missing information	No
Rationale (if not included as missing information)	While confounding factors in the evaluation of safety in clinical trials, these conditions are not expected to alter the safety or efficacy of EDURANT.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 9	**One or more risk factors for QT interval prolongation:** • **Confirmed prolongation of QT/corrected QT (QTc) interval in screening electrocardiogram (ECG);** • **Pathological Q-waves;** • **Evidence of ventricular pre-excitation;** • **ECG evidence of complete or incomplete left bundle branch block or right bundle branch block;** • **Evidence of second or third degree heart block;** • **Intraventricular conduction delay with QRS duration >120 ms;** • **Bradycardia as defined by sinus rate <50 beats per minute;** • **Personal or family history of long QT syndrome;** • **Personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, with the exception of sinus arrhythmia;** • **Syncopal episodes;** • **Risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, hypomagnesemia).**
Reason for being an exclusion criterion	This was added to the Phase 3 exclusion criteria after a TQT trial showed that at supratherapeutic doses, RPV was associated with prolongation of the QTc interval of the ECG, and subsequently also added to the exclusion criteria of trial C213.
Considered to be included as missing information	No
Rationale (if not included as missing information)	No QT effect was observed in a TQT trial with the 25-mg dose. The potential for QT prolongation is adequately addressed in Sections 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), and 5.1 (Pharmacodynamic properties) of the SmPC.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 10	**Subjects with renal impairment (calculated creatinine clearance [Cl_{Cr}] <50 mL/min)[1,2]**
Reason for being an exclusion criterion	In patients with severe renal impairment or end-stage renal disease, RPV plasma concentrations may be increased due to alteration of drug absorption, distribution, and/or metabolism secondary to renal dysfunction.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The SmPC states that EDURANT should be used with caution in patients with severe renal impairment or end-stage renal disease.

[1]As per the clinical trial protocols. Terminology was changed to $eGFR_{creat}$ <50 mL/min/1.73 m^2 in the SmPC and in this EU-RMP.
[2] Renal impairment was not an exclusion criterion in the pediatric trial C213.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	**Exposure**
Children and adolescents <18 years	In Cohort 1 of trial C213, 36 ART-naïve, HIV-1-infected adolescents aged ≥12 to <18 years and weighing ≥32 kg were treated with RPV 25 mg once daily for 240 weeks in combination with an investigator-selected background regimen of 2 NRTIs. The total RPV exposure was 109.74 person-years. In Cohort 2 of trial C213, 13 ART-naïve, HIV-1-infected children aged ≥6 to <12 years were treated with RPV 25 mg once daily (body weight of ≥25 kg), RPV 15 mg once daily (body weight of ≥20 to <25 kg), or RPV 12.5 mg once daily (body weight of <20 kg) in combination with an investigator-selected background regimen of 2 N(t)RTIs. The total RPV exposure (based on the

Type of Special Population	Exposure
	recommended RPV dose) was 21.3 person-years. In trial HTX2002, 24 virologically suppressed HIV-1-infected children aged ≥2 to <12 years were treated with RPV 25 mg once daily (body weight of ≥25 kg), RPV 15 mg once daily (body weight of ≥20 to <25 kg), or RPV 12.5 mg once daily (body weight of <20 kg) in combination with an investigator-selected background ARV. The total RPV exposure (based on the recommended RPV dose) was 22.3 person-years. The safety and efficacy of EDURANT in children less than 2 years of age or weighing less than 14 kg have not been established.
Elderly	Of the 686 adult subjects in the pooled Phase 3 trials, only 3 (0.4%) subjects were ≥65 years of age.
Pregnant or breast-feeding women	Pregnant women have been excluded from all clinical trials to date, except for the Phase 3b trial TMC114HIV3015, which assessed the PK in HIV-1-infected pregnant women. In this trial, 19 pregnant women were treated with RPV. Breast-feeding women have been excluded from all clinical trials to date.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	In the Phase 1 trial TMC278-C130, 16 subjects with hepatic impairment were exposed to RPV, of which 8 subjects with mild hepatic impairment (Child-Pugh score A) and 8 subjects with moderate hepatic impairment (Child-Pugh score B). Patients with severe hepatic impairment were not included in the clinical development program.
• Patients with renal impairment	No specific clinical trials have been conducted in patients with renal impairment. Of the 686 adult subjects in the pooled Phase 3 trials, 142 (268 person-years) subjects had mild ($eGFR_{creat}$ ≥60-<90 mL/min/1.73 m²), 1 (2 person-years) subject had moderate ($eGFR_{creat}$ ≥30-<60 mL/min/1.73 m²), and none of the subjects had severe ($eGFR_{creat}$ ≥15-<30mL/min/1.73 m²) renal impairment at baseline. Of the 278 adult subjects in trial C204, 56 (208 person-years) subjects had mild ($eGFR_{creat}$ ≥60-<90 mL/min/1.73 m²), and none of the subjects had moderate or severe renal

Type of Special Population	Exposure
	impairment at baseline.
• Patients with cardiovascular impairment	Not included in the clinical development program
• Immunocompromised patients	Not applicable
• Patients coinfected with HIV and HBV and/or HCV	Of the 686 adult subjects in the pooled Phase 3 trials, 49 (82 person-years) HIV-1-infected subjects were coinfected with HBV and/or HCV. Of the 278 adult subjects in trial C204, 26 (74 person-years) subjects were coinfected with HBV and/or HCV.
• Patients with a disease severity different from inclusion criteria in clinical trials	EDURANT has not been studied in patients with acute primary HIV-1 infection. ART-experienced patients have not been studied in Phase 3 trials and have only been included in a short-term Phase 2a trial and trial HTX2002 (children aged ≥2 to <12 years). Trial C213 only included adolescents aged ≥12 to <18 years (Cohort 1) and children aged ≥6 to <12 years (Cohort 2) who were never treated with ARVs, with the exception of a single dose of NVP at birth to prevent mother-to-child transmission.
Population with relevant different racial and/or ethnic origin	Of the 686 adult subjects in the pooled Phase 3 trials, 420 were white, 165 were black/African American, 78 were Asian, and 14 were of another race. The racial origin of 9 subjects was unknown because it was not allowed to ask per local regulations (7 subjects) or the information was missing (2 subjects). This population mainly included non-Hispanic/Latino subjects (498). Of the 278 adult subjects in the Phase 2b trial, 121 were Caucasian/white, 65 were black/African American, 54 were Oriental/Asian, 29 were Hispanic and 9 were of another race.
Subpopulations carrying relevant genetic polymorphisms	There are no data on subgroup populations with genetic polymorphisms.
Other	Not applicable

Summary of Safety Concerns Due to Limitations of the Clinical Trial Program

Important identified risks	None
Important potential risks	None
Missing information	Pregnancy

PART II: SAFETY SPECIFICATION

Module SV: Post-authorization Experience

SV.1. Post-authorization Exposure

SV.1.1. Method Used to Calculate Exposure

Interval and cumulative patient exposure from marketing experience are provided for RPV (25 mg once daily oral tablet). Product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient. Patient exposure was estimated by calculation from Company distribution data which are available by month. Estimates of exposure are based upon finished product. The recommended dosage is 1 tablet once daily and therefore 1 tablet is equivalent to 1 person-day.

SV.1.2. Exposure

Considering the number of RPV oral tablets distributed worldwide from launch through 30 April 2022, the cumulative postmarketing exposure is estimated to be at least CCI person-years, of which CCI person-years occurred in the European Union.

A total of 1CCI RPV oral tablets were distributed worldwide from launch through 30 April 2022, of which CCI tablets were distributed in the European Union.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

The potential for illegal use is unlikely given that the pharmacodynamic mode of action of EDURANT is virus-specific.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

There are no important identified risks.

There are no important potential risks.

Missing information:

– Pregnancy

MedDRA version 16.1 was used to classify the clinical trials AE information that is summarized in this Module.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2. Presentation of the Missing Information

Missing information: Pregnancy
Evidence source: Data from women on RPV in combination with a background regimen in a PK clinical trial (n=19) indicated that the exposure to total RPV was lower during pregnancy compared with the postpartum period. However, the virologic response was generally preserved throughout the trial period. No mother-to-child transmission occurred in the infants born to the mothers who completed the trial. EDURANT-related pregnancy data are being submitted to the Antiretroviral Pregnancy Registry (APR), an international registry designed to evaluate the rate of congenital abnormalities in pregnant women in a prospective fashion. Sufficient numbers of first trimester exposures to EDURANT have been monitored which would allow detection of at least a 2-fold increase in risk of overall birth defects. There was no increase detected to date. APR interim reports are prepared bi-annually. At the time of Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR) submission, the most recent APR interim report is submitted together with the PBRER/PSUR.
Anticipated risk/consequence of the missing information: Per SmPC, pregnant women should not take EDURANT unless the potential benefit justifies the potential risk.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	Pregnancy

PART III: PHARMACOVIGILANCE PLAN (Including Post-Authorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities		
Activity	Objective/Description	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Study	
Study name and title	Antiretroviral Pregnancy Registry
Rationale and study objectives:	Rationale for inclusion in the pharmacovigilance plan: Pregnancy is missing information. Objective: To collect information on the risk of birth defects in patients exposed to EDURANT during pregnancy.
Safety concerns addressed	Pregnancy
Study design	Voluntary, prospective, exposure-registration, observational study
Study population	Pregnant women
Milestones	Interim reports will be submitted and discussed in the PBRERs/PSURs (data lock point and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.3: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable.				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
Antiretroviral Pregnancy Registry Ongoing	To collect information on the risk of birth defects in patients exposed to EDURANT during pregnancy	- Pregnancy	Submission of interim reports	Interim reports will be submitted and discussed in the PBRERs/PSURs (data lock point and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Post-Authorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Missing information	
Pregnancy	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.6 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation regarding the use of EDURANT during pregnancy is provided in SmPC Sections 4.4 and 4.6 and PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concern of the medicinal product.

V.2.1. Removal of Additional Risk Minimization Activities

Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Pregnancy	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.6 • PL Section 2 • Recommendation regarding the use of EDURANT during pregnancy is provided in SmPC Sections 4.4 and 4.6 and PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Antiretroviral Pregnancy Registry Interim reports will be submitted and discussed in the PBRERs/PSURs (data lock point and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for EDURANT (INN: Rilpivirine hydrochloride, TMC278)

This is a summary of the risk management plan (RMP) for EDURANT. The RMP details important risks of EDURANT, how these risks can be minimized, and how more information will be obtained about EDURANT's risks and uncertainties (missing information).

EDURANT's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) provide essential information to healthcare professionals and patients on how EDURANT should be used.

This summary of the RMP for EDURANT should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of EDURANT's RMP.

I. The Medicine and What it is Used For

EDURANT, in combination with other antiretroviral (ARV) medicinal products, is authorized for the treatment of human immunodeficiency virus (HIV)-1 infection in adults and pediatric patients (≥2 to <18 years of age and weighing at least 14 kg) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, and with a viral load ≤100,000 HIV-1 ribonucleic acid (RNA) copies/mL (see SmPC for the full indication). It contains rilpivirine (RPV) hydrochloride as the active substance and it is given as an oral tablet (RPV 25-mg film-coated tablet or 2.5-mg dispersible tablet).

Further information about the evaluation of EDURANT's benefits can be found in EDURANT's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/edurant

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of EDURANT, together with measures to minimize such risks and the proposed studies for learning more about EDURANT's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

– The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of EDURANT is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of EDURANT are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of EDURANT. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	Pregnancy

II.B. Summary of Important Risks

Missing Information: Pregnancy	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.6 • PL Section 2 • Recommendation regarding the use of EDURANT during pregnancy is provided in SmPC Sections 4.4 and 4.6 and PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None
Additional pharmacovigilance	Additional pharmacovigilance activities:

activities	• Antiretroviral Pregnancy Registry Interim reports will be submitted and discussed in the Periodic Benefit-Risk Evaluation Reports (PBRERs)/PSURs (data lock point and periodicity as described in the List of EU reference dates and frequency of submission of PSURs) See section II.C of this summary for an overview of the post-authorization development plan.

II.C. Post-authorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of EDURANT.

II.C.2. Other Studies in Post-authorization Development Plan

Antiretroviral Pregnancy Registry

Purpose of the study: To collect information on the risk of birth defects in patients exposed to EDURANT during pregnancy.

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable.