Core Risk Management Plan for Kaletra and Aluvia (Lopinavir/Ritonavir)

AbbVie Inc. (AbbVie)

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP:

- Fulfillment of the LEG-121 (including EPPICC Cohort Study P19-106) commitment for the European Medicines Agency (EMA) including removal of the study from additional pharmacovigilance activities.
- Remove Missing Information: Safety of chronic exposure to propylene glycol and ethanol in patients 14 days to 2 years of age.

Summary of significant changes in the RMP: A summary of significant changes is included in RMP Annex 8.

Administrative Information on the RMP

Part Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part 1: Product(s) Overview	March 2019	9.0
Part II: Safety Specification		
SI – Epidemiology of the Indication(s) and Target Population(s)	March 2019	9.0
SII – Non-Clinical Part of the Safety Specification	May 2022	10.0
SIII – Clinical Trial Exposure	March 2019	9.0
SIV – Populations Not Studied in Clinical Trials	May 2022	10.0
SV – Post-Authorization Experience	March 2019	9.0
SVI – Additional European Union (EU) Requirements for the Safety Specification	May 2017	8.2
SVII – Identified and Potential Risks	May 2022	10.0
SVIII – Summary of the Safety Concerns	May 2022	10.0
Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)	May 2022	10.0
Part IV: Plan for Post-Authorization Efficacy Studies	Not applicable	Not applicable
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	May 2022	10.0
Part VI: Summary of the Risk Management Plan	May 2022	10.0
Part VII: Annexes		
Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	May 2022	10.0
Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	December 2019	9.1
Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms	June 2018	8.2
Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV	January 2015	7.0
Annex 6 – Details of Proposed Additional Risk Minimization Activities (If Applicable)	March 2019	9.0
Annex 7 – Other Supporting Data (Including Referenced Material)	March 2019	9.0

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
	Annex 8 – Summary of Changes to the Risk Management Plan Over Time	May 2022	10.0
	Annex 9 – Local Currently-Approved Country Labeling	August 2016	8
	Annex 10 – Local Risk Management/Mitigation Plan	Not applicable	Not applicable

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Qualified person responsible for pharmacovigilance (QPPV) oversight declaration:
The content of the RMP has been reviewed and approved by the marketing authorization holder QPPV through an electronic document system per company standard operating procedure.

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List of Abbreviations

AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	Antiretroviral
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AV	Atrioventricular
BAC	blood alcohol concentration
BID	twice daily
BSA	body surface area
CAD	coronary artery disease
cART	combination antiretroviral therapy
CCDS	company core data sheet
CD4+	cluster of differentiation 4
CHER	Children with HIV Early Antiretroviral Therapy
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CDC	Centers for Disease Control and Prevention
CKD	chronic kidney disease
CNS	central nervous system
CYP	cytochrome P450
CYP3A	cytochrome P450 3A isoform subfamily
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs
DDI	Drug-drug interaction
EACS	European AIDS Clinical Society
EAGA	Expert Advisory Group on AIDS
EC	Ethics Committee
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiography
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration

ESRD	end-stage renal disease
EU	European Union
FDA	Food and Drug Administration
FI	fusion inhibitors
GGT	gamma-glutamyl transpeptidase
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
hERG	human ether à-go-go–related gene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
IBD	international birth date
INN	International Nonproprietary Name
IRIS	Immune reconstitution inflammatory syndrome
IVDU	intravenous drug user(s)
LDL-C	low-density lipoprotein cholesterol
LEG	Legally binding measure
LPV	Lopinavir
LRx	IMS® LRx Germany (database)
MA	Marketing Authorization
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MM	million
MTCT	mother-to-child transmission
MSM	men who have sex with men
NNRTI	non-nucleoside reverse transcriptase inhibitor
NSHPC	National Study of HIV in Pregnancy and Childhood
NRTI	Nucleos(t)ide reverse transcriptase inhibitor
NVP	Nevirapine
PACTG	Paediatric AIDS Clinical Trials Group
PASS	post-authorization safety study
PENTA	Paediatric European Network for Treatment of AIDS
PEP	post-exposure prophylaxis

PI	protease inhibitor
PK	pharmacokinetic(s)
PL	package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT	preferred term(s)
PTD	patient treatment day
PTY	patient-treatment year(s)
PY	person year(s)
PV	Pharmacovigilance
QD	once daily
QPPV	qualified person responsible for pharmacovigilance
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
REMS	risk evaluation and mitigation strategy
RMP	risk management plan
RNA	ribonucleic acid
RTV	Ritonavir
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
TDD	total daily dose
TSH	thyroid-stimulating hormone
UK	United Kingdom
US	United States
USA	United States of America
WEC	Western Europe / Canada

Part I: Product(s) Overview

Table 1. Product Overview

Active substance(s) (INN or common name)	Lopinavir/ritonavir
Pharmacotherapeutic group(s) (ATC Code)	Lopinavir/ritonavir: Antivirals for systemic use, protease inhibitors, ATC code: J05AR10
Marketing Authorization	AbbVie Ltd.
Medicinal products to which this RMP refers	1 (Lopinavir/ritonavir)
Invented name(s) in the European Economic Area (EEA)	Kaletra® Aluvia®
Marketing authorization procedure	Kaletra: Centralized procedure Aluvia: Article 58 of Regulation (EC) No. 726/2004
Brief description of the product	Chemical class: Lopinavir/ritonavir is a co-formulation of 2 protease inhibitors (PI).
	Summary of mode of action: Lopinavir is an inhibitor of the human immunodeficiency virus type 1 (HIV-1) and HIV type 2 proteases. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein, resulting in the production of immature, noninfectious virus whereas ritonavir acts as a pharmacokinetic (PK) enhancer of lopinavir. Ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. Lopinavir provides the antiviral activity of Kaletra and Aluvia.
	Important information about its composition: Lopinavir/ritonavir oral solution is highly concentrated and contains 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v), which could be harmful to preterm neonates.
Hyperlink to the Product Information	SmPC

Indication(s) in the EEA	Current (if applicable): **Lopinavir/ritonavir 200 mg/50 mg film-coated tablets and lopinavir/ritonavir 100 mg/25 mg film-coated tablets**: lopinavir/ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents, and children above the age of 2 years. **Lopinavir/ritonavir (80 mg + 20 mg)/ml oral solution**: Lopinavir/ritonavir is indicated, in combination with other antiretroviral medicinal products, for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children aged from 14 days and older. The choice of lopinavir/ritonavir to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients. Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): Lopinavir/ritonavir oral solution: Adults: 400/100 mg twice daily (BID) Paediatrics: per the Summary of Product Characteristics (SmPC) Lopinavir/ritonavir film-coated tablets Adults: 400/100 mg twice daily (BID) or 800/200 mg once daily (QD) Paediatrics: per the Summary of Product Characteristics (SmPC) Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Film-coated tablet: 200 mg lopinavir/50 mg ritonavir or 100 mg lopinavir/25 mg ritonavir Oral solution: each milliliter contains 80 mg lopinavir + 20 mg ritonavir Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ATC = anatomical therapeutic chemical; INN = International Nonproprietary Name

Part II: Safety Specification

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

Indication:

Lopinavir/ritonavir is indicated in combination with other antiretroviral (ARV) medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infected adults, adolescents and children above the age of 14 days.

Incidence:

The incidence of human immunodeficiency virus (HIV) infections are decreasing globally due to HIV prevention and treatment programs, with an estimated 1.8 million (MM) (95% CI: 1.6 MM – 2.1 MM) new cases globally in 2016, of which 73,000 were among adults and children across Western and Central Europe and North America (UNAIDS 2017). Across the European Union and European Economic Area (EU/EEA), 29,747 new HIV diagnoses were reported across 31 countries in 2016, a rate of 5.8 per 100,000 (no confidence interval [CI] reported). Rates range from a high of 20.6 per 100,000 in Estonia to no reported cases in Liechtenstein (ECDC 2017).

Prevalence:

In 2016, the number of people globally who were living with HIV was estimated as 36.7 MM (95% CI: 30.8 MM – 42.9 MM), of whom 34.5 MM (95% CI: 28.8MM – 40.2MM) were aged 15 and above, 17.8 MM (15.4 MM – 20.3 MM) were woman and 2.1 MM (1.7 MM – 2.6 MM) were children less than 15 (UNAIDS 2017). Across Western and Central Europe and North America 2.1 MM were living with HIV and acquired immune deficiency syndrome (AIDS) in 2016 (UNAIDS 2017). Specifically across the EU/EEA, 0.2%, or 810,000 adults and children aged ≥ 15 years-old were living with HIV in 2015, with an estimated up to 15% of which, based on modeling, were unaware of their HIV infection (Pharris 2016).

Globally, an estimated 1.0 MM (95% CI: 830,000 – 1.2MM) AIDS-related deaths occurred in 2016 of which 18,000 were adults and children across Western and Central Europe and North America (UNAIDS 2017).

Demographics of the target population:

Within the EU/EEA, males constituted 77% of new HIV infections in 2015, a male: female ratio of 3.3:1, and the higher incidence of infection among men was observed across age strata, except among persons under 15 years of age (primarily due to mother-to-child-transmission [MTCT]). Among transmission groups, men who have sex with men (MSM) constituted 42% of new cases, followed by heterosexual contact – 32%, intravenous drug users (IVDU) – 4%, and

MTCT – < 1%. By age, the highest rate of new infection occurred in the 25-29 age group, 14.8 per 100,000 population. The number of MTCT HIV cases in 2015 was 197 (ECDC 2017).

Risk Factors:

Populations at highest risk of HIV infection (UNAIDS 2011)

- Sex workers
- Clients of sex workers
- People who inject drugs
- MSM
- Infants born to HIV-infected mothers

The main treatment options:

The goals of HIV antiretroviral therapy (ART) are to maximally and durably suppress plasma HIV-1 ribonucleic acid (RNA) in order to allow immune system recovery in an overall attempt to prolong the duration and quality of life for persons infected with HIV. Treatment goals in paediatric patients include normal growth and physical, pubertal, neurological, and psychological development and immune reconstitution, while minimizing long-term drug toxicity and viral drug resistance, thus optimizing general health for a full and productive adult life (Paediatric European Network for Treatment of AIDS [PENTA] 2015, European AIDS Clinical Society [EACS] 2018). Combination antiretroviral therapy (cART), consisting of ARV drugs from at least 2 different classes, is typically required to achieve these therapeutic goals. To date, 36 anti-HIV medicines have been centrally authorized in the EU representing 6 different mechanisms of action including nucleoside or nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), PIs with or without ritonavir as a pharmacokinetic(s) (PK) enhancer, fusion inhibitors (FI), chemokine receptor (CCR5) antagonists, and integrase strand transfer inhibitors.

Important co-morbidities:

Liver disease including hepatitis B and C, cardiovascular disease, kidney disease, diabetes, osteoporosis, malignancies, and use of potentially interacting drugs, especially those medicinal products that are highly dependent on cytochrome P450 3A isoform subfamily (CYP3A) for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events.

Module SII Non-Clinical Part of the Safety Specification

A standard battery of nonclinical studies was conducted for lopinavir/ritonavir, and a summary of the findings for lopinavir/ritonavir is provided below.

Key Safety Findings (from Non-Clinical Studies)	**Relevance To Human Usage**
Toxicity	
Single and repeat dose toxicity • Not acutely toxic. • Primary target organ on repeated dosing is the liver (hepatocellular change) in multiple species. • Thyroid hypertrophy: Reduced serum thyroxin led to an increased release of TSH with resultant follicular cell hypertrophy in the thyroid glands of rats. These changes were reversible with withdrawal of the active substance and were absent in mice and dogs. • Mild changes in erythrocytes cell shape and number: Coombs-negative anisocytosis and poikilocytosis were observed in rats, but not in mice or dogs.	The SmPC recommends that appropriate laboratory testing (transaminases and bilirubin) should be conducted prior to initiating therapy with lopinavir/ritonavir and close monitoring should be performed during treatment. Additional details are provided in hepatotoxicity section below. Adverse events pertaining to the thyroid gland with lopinavir/ritonavir have not been identified in humans. Though anemia is a labelled adverse event in the product label for lopinavir/ritonavir, anisocytosis and poikilocytosis are not labelled adverse events in humans.
Reproductive toxicity No evidence for impairment of male or female fertility in rats.	Animal studies have shown no effects on fertility. No human data on the effect of lopinavir/ritonavir on fertility are available.
Developmental toxicity In rats, embryofoetotoxicity (pregnancy loss, decreased foetal viability, decreased foetal body weights, increased frequency of skeletal variations) and postnatal developmental toxicity (decreased survival of pups) was observed at maternally toxic dosages. The systemic exposure to lopinavir/ritonavir at the maternal and developmental toxic dosages was lower than the intended therapeutic exposure in humans. No developmental toxicity observed in rabbits.	Changes in rats were secondary to maternal toxicity and not considered a primary developmental toxicity directly related to treatment. In humans, lopinavir/ritonavir has been evaluated in over 3,000 women during pregnancy, including over 1,000 during the first trimester in the antiretroviral pregnancy registry (APR). In postmarketing surveillance through the APR, established since January 1989, an increased risk of birth defects exposures with lopinavir/ritonavir has not been reported among over 1,000 women exposed during the first trimester. The prevalence of birth defects after any trimester exposure to lopinavir/ritonavir is comparable to the prevalence observed in the general population. No pattern of birth defects suggestive of a common etiology was seen. Based on the data mentioned, birth defects are unlikely in humans. As noted in the product labeling for lopinavir/ritonavir, lopinavir/ritonavir can be used during pregnancy if clinically needed.

Nephrotoxicity Mild increase in cytoplasmic vacuolation only observed in single rodent species. Other than this mild increase in cytoplasmic vacuolation in kidney tissue in a single rodent species in one study, this finding was not reproduced in other animal studies. There were no kidney findings in rat toxicity studies up to 6 months duration or in dog toxicity studies up to 9 months duration (R&D/98/375, R&D/96/574, R&D/98/307, R&D/96/243, R&D/98/371, R&D/96/675, R&D/99/093, R&D/97/752, and R&D/97/069).	The product labeling for humans describes certain uncommon renal adverse events including creatinine clearance decreased, hematuria, and nephritis.
Hepatotoxicity Mild to moderate hepatocellular changes in animals have been accompanied by clinical biomarker changes (e.g., ALT, AST, ALP, GGT, cholesterol, triglycerides).	Safety concerns for hepatotoxicity have been extensively studied in humans and the risk is well defined. Labelled hepatic adverse events from clinical trials and postmarketing experience in adult and paediatric patients for lopinavir/ritonavir include: hepatitis including AST, ALT, and GGT increases (common); hepatic steatosis, hepatomegaly, cholangitis, and hyperbilirubinemia (uncommon); and jaundice (frequency unknown). The SmPC recommends that appropriate laboratory testing should be conducted prior to initiating therapy with lopinavir/ritonavir and close monitoring should be performed during treatment.
Genotoxicity No genetic toxicity observed in either in vivo assays or in vivo studies. Lopinavir/ritonavir was not found to be mutagenic or clastogenic in a battery of in vitro and in vivo assays, including the Ames bacterial reverse mutation assay, the mouse lymphoma assay, the mouse micronucleus test, and chromosomal aberration assays in human lymphocytes.	No safety concern has been observed in humans.
Carcinogenicity A moderate increase in hepatocellular neoplasms observed in mice. No tumor findings in rats.	Hepatocellular tumors were considered secondary to mitogenic stimulation and not reactivity with DNA (supported by negative genotoxicity assays). These tumors in mice are generally considered not to have a human correlate. Thus findings have little human relevance.

General Safety Pharmacology	
Cardiovascular Minimal signals for adverse effects observed. The cardiovascular assessment in conscious male rats instrumented with telemetry transmitters in demonstrated minimal effects on heart rate. Another cardiovascular study in anesthetized instrumented dogs demonstrated minimal effects on heart rate and blood pressure, which may have been related to the pentobarbital anesthetic. In a third cardiovascular study in instrumented conscious dogs, there were no effects on heart rate or blood pressure. Reference for the above is R&D/96/445.	QT prolongation with supratherapeutic doses and PR prolongation at therapeutic doses are important potential risks with lopinavir/ritonavir. Particular caution must be used when prescribing lopinavir/ritonavir and medicinal products known to induce QT interval prolongation. (See Section SVII.1.2 for further details). Other labeled cardiovascular adverse events from clinical trials and postmarketing experience in adult and paediatric patients for lopinavir/ritonavir are (all uncommon): atherosclerosis such as myocardial infarction, atrioventricular block, and tricuspid valve incompetence. In addition, in the product labeling hypertriglyceridaemia and hypercholesterolemia are labelled events. The labeling describes a clinical study on QT prolongation in adults during which no subject experienced an increase in QTcF of 60 ms from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 ms. The label also states that caution must be used when prescribing lopinavir/ritonavir and medicinal products known to induce QT interval prolongation since lopinavir/ritonavir could increase concentrations of the co-administered medicinal products and this may result in an increase of their associated cardiac adverse reactions.
Nervous system Minimal signals for adverse effects observed.	Labeled nervous system events include more common (≥ 1/100 to < 1/10): headache (including migraine), neuropathy (including peripheral neuropathy), dizziness, and insomnia. Uncommon (≥ 1/1000 to < 1/100) adverse events include: cerebrovascular accident, convulsion, dysgeusia, ageusia, and tremor have been reported.
Immune system disorders In preclinical toxicology reports, no signal of adverse effects was seen on the immune system.	In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease) has also been reported. However, as noted in the labeling, the reported time to onset is variable and can occur many months after initiation of treatment.

Mechanisms for drug interactions Lopinavir and ritonavir are both CYP3A4 inhibitors	Drug-drug interaction (DDI) potential in humans have been well studied and described in the product labeling, which notes that lopinavir and ritonavir both are inhibitors of the P450 isoform CYP3A. Lopinavir/ritonavir is likely to increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. These increases of plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events. Current product labeling also indicates that lopinavir/ritonavir should not be coadministered/is contraindicated with certain medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Specific recommendations for individual drugs are provided in the SmPC in Section 4.4.
Other toxicity-related information or data	
Juvenile toxicity. No significant differences in tolerability or target organs observed.	Safety of chronic exposure to propylene glycol and ethanol in patients 14 days to 2 years of age taking lopinavir/ritonavir oral solution was evaluated for 4 years as part of a commitment to EMA (PAM-LEG-121), No new safety concern with propylene glycol and ethanol toxicity was identified in pediatric patients (14 days to 2 years of age). (See Section SVII.1.2 for further details). The current CCDS and SmPC includes safety information on the pediatric population.

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma glutamyl transpeptidase; TSH = thyroid-stimulating hormone

Non-Clinical Safety Findings that are Included as Safety Concerns

The nonclinical safety considerations for lopinavir/ritonavir tablets are characterized and are found to be consistent with the currently approved lopinavir/ritonavir formulations.

Safety Concerns	
Important identified risks	Not applicable.
Important potential risks	QT prolongation with supratherapeutic doses
Missing information	Not applicable

Module SIII Clinical Trial Exposure

Patient exposure during AbbVie lopinavir/ritonavir clinical trials as of 26 January 2018 is provided in Table 2 through Table 6. Phase 2 to 4 trials conducted in adults were to include persons ≥ 18 years of age; trials conducted in paediatric patients were to include persons < 18 years of age. Persons included in the Adult Early Access Program were to be ≥ 12 years of age.

In Phase 1 studies, the exposure was 1164 male subjects and 518 female subjects for a total of 1682 subjects.

Table 2. Duration of Exposure

Adult Phase 2 to 4 Studies		
Duration of Exposure (months)	**Patients (n)**	**Person Time (years)**
≤ 1	78	--
> 1 to ≤ 3	96	--
> 3 to ≤ 6	115	--
> 6 to ≤ 12	683	--
> 12 to ≤ 24	1366	--
> 24	274	--
Total	2612	4186.1
Adult Early Access Program		
Duration of Exposure (months)	**Patients (n)**	**Person Time (years)**
≤ 1	929	--
> 1 to ≤ 3	2359	--
> 3 to ≤ 6	3707	--
> 6 to ≤ 12	4273	--
> 12 to ≤ 24	603	--
> 24	12	--
Total	11883	5535.3

Paediatric Phase 2 to 4 Studies		
Duration of Exposure (months)	**Patients (n)**	**Person Time (years)**
≤ 1	0	--
> 1 to ≤ 3	0	--
> 3 to ≤ 6	1	--
> 6 to ≤ 12	1	--
> 12 to ≤ 24	46	--
> 24	52	--
Total	100	273.1

Paediatric Early Access Program		
Duration of Exposure (months)	**Patients (n)**	**Person Time (years)**
≤ 1	1	--
> 1 to ≤ 3	2	--
> 3 to ≤ 6	1	--
> 6 to ≤ 12	3	--
> 12 to ≤ 24	0	--
> 24	0	--
Total	7	2.6

Note: Available person-time years data have been presented. No further analyses are planned.

Note: Adult and paediatric data are each separated into Phase 2 to 4 studies and Early Access Program and are not combined at this time. No further analyses are planned.

Table 3. Exposure by Age Group and Gender

Adult Phase 2 to 4 Studies						
	Patients (n)			Person Time (years)		
Age Group (years)	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
18 to < 25	86	26	112	163.8	30.0	193.8
25 to < 35	576	187	763	1030.0	262.5	1292.5
35 to < 45	831	210	1041	1414.1	262.4	1676.5
45 to < 55	404	113	517	603.7	142.7	746.5
55 to < 65	119	28	147	183.5	45.2	228.7
65 to < 75	20	9	29	27.9	18.3	46.2
75 to < 85	2	1	3	2.1	0.1	2.2
≥ 85	0	0	0	0	0	0
Total	2038	574	2612	3425.1	761.1	4186.1
Adult Early Access Program						
	Patients (n)[a]			Person Time (years)[a]		
Age Group (years)[a]	**Male**	**Female**	**Total[b]**	**Male**	**Female**	**Total[b]**
< 18[c]	35	29	65	17.8	14.3	32.5
18 to < 25	95	44	139	46.0	22.1	68.1
25 to < 35	1784	663	2449	820.0	312.1	1133.1
35 to < 45	5121	866	5995	2431.9	391.9	2827.8
45 to < 55	2247	238	2486	1037.8	101.4	1139.4
55 to < 65	580	52	633	256.8	22.5	280.3
65 to < 75	92	9	101	43.1	3.4	46.4
75 to < 85	5	3	8	2.1	2.3	4.3
≥ 85	0	0	0	0	0	0
Total[d]	9964	1905	11883	4658.0	870.0	5535.3

Paediatric Phase 2 to 4 Studies						
	Patients (n)			Person Time (years)		
Age Group	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
< 28 days[e]	0	0	0	0	0	0
28 days to < 24 months	8	6	14	24.0	23.8	47.8
24 months to < 12 years	34	51	85	78.7	145.0	223.6
12 years to < 18 years (Maximum age reported was 12.6 years)	1	0	1	1.7	0	1.7
Total	43	57	100	104.4	168.7	273.1
Paediatric Early Access Program						
	Patients (n)			Person Time (years)		
Age Group	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
< 28 days	0	0	0	0	0	0
28 days to < 24 months	0	0	0	0	0	0
24 months to < 12 years	2	5	7	0.3	2.4	2.6
≥ 12 years to < 18 years	0	0	0	0	0	0
Total	2	5	7	0.3	2.4	2.6

a. Age data not reported for 7 persons. Gender data not reported for 14 persons.

b. Total includes those with missing gender data.

c. Minimum age reported was 11 years.

d. Total includes those with missing age data.

e. Data in this table are from studies conducted by AbbVie. AbbVie Study M98-940 (N = 100) did not enroll subjects < 28 days of age. PACTG Studies P1030 and P1060 and the CHER study were supportive studies not conducted by AbbVie and are not included in this table. Paediatric AIDS Clinical Trials Group (PACTG) Study P1030 enrolled subjects in the 14 days to < 6 months age range.

Table 4. Exposure by Dose Regimen

Adult Phase 2 to 4 Studies		
Dose Regimen	**Patients (n)**	**Person Time (years)**
QD	767	991.6
BID	1845	3194.5

QD = once daily; BID = twice daily

Table 5. Exposure by Ethnic Origin

Exposure by Study Type and Race						
	Patients (n)			Person Time (years)		
Study Type	**White**	**Black**	**Other**	**White**	**Black**	**Other**
Adult Phase 2 to 4 Studies	1755	664	193	2908.6	1001.4	276.1
Adult Early Access Program	9511	1288	1084	4610.1	488.5	436.7
Paediatric Phase 2 to 4 Studies	12	57	31	30.4	180.8	61.9
Paediatric Early Access Program	3	2	2	1.4	0.3	0.9

Exposure by Study Type and Ethnicity				
	Patients (n)		Person Time (years)	
Study Type	**Hispanic**	**Not Hispanic**	**Hispanic**	**Not Hispanic**
Adult Phase 2 to 4 Studies	421	2191	567.5	3618.6
Adult Early Access Program	956	10927	412.2	5123.1
Paediatric Phase 2 to 4 Studies	33	67	73.7	199.4
Paediatric Early Access Program	1278	6	0.1	2.5

Table 6. Exposure for Special Populations

Special Population	Patients (n)
Mild or Moderate Hepatic Impairment[a]	24

a. Mild or moderate hepatic impairment defined as Child-Pugh Class A or B. Study was a Phase 1 study conducted in adults (Study M01-347).

Module SIV Populations Not Studied in Clinical Trials

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

Criterion 1: Severe hepatic insufficiency
Reason for exclusion: Patients with severe underlying liver disease should not be administered lopinavir/ritonavir as indicated in the product label.
Is it considered to be included as missing information? No
Rationale: Use in patients with severe hepatic insufficiency (but not in those with mild to moderate hepatic insufficiency) is contraindicated in the label. The steady state PK parameters of lopinavir in HIV-infected patients with mild to moderate hepatic impairment were compared with those of HIV-infected patients with normal hepatic function in a multiple dose study with lopinavir/ritonavir 400/100 mg twice daily. A limited increase in total lopinavir concentrations of approximately 30% has been observed, which is not expected to be of clinical relevance. However, no PK data are available in patients with severe hepatic impairment.

Criterion 2: Co-administration of medications metabolised by CYP3A
Reason for exclusion: Clinically important drug-drug interactions through CYP3A can result in serious and important adverse outcomes.
Is it considered to be included as missing information? No
Rationale: Current product labeling indicates that lopinavir/ritonavir should not be coadministered/is contraindicated with certain medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Specific recommendations for individual drugs are provided in the SmPC in Section 4.4.

Criterion 3: Pregnant or lactating women
Reason for exclusion: Lack of clinical trial data in pregnant women. It is not known whether lopinavir is excreted in human milk.
Is it considered to be included as missing information? No
Rationale: At the time of the pivotal clinical trials for lopinavir/ritonavir, the effects on the fetus were unknown Since then, the safety of lopinavir/ritonavir is supported by literature reports and postmarketing surveillance that includes the surveillance of the APR and the AbbVie postmarketing safety database. Most treatment guidelines from national, regional, and global organizations and agencies recommend lopinavir/ritonavir as a preferred or alternative or other PI during pregnancy. The guideline recommendations (e.g., Department of Health and Human Services (Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States 2017 [DHHS 2018]); World Health Organization [2016]; British HIV Association [de Ruiter 2014]) are supported by published clinical studies in pregnant HIV-infected patients. Based on postmarketing surveillance data from the APR, the prevalence of birth defects after exposure to lopinavir/ritonavir is comparable to the prevalence observed in the general population. Analysis of the AbbVie postmarketing safety database demonstrates that the safety profile of lopinavir/ritonavir in pregnant women is similar to the safety profile of nonpregnant women. As requested by the EMA, APR data has been submitted together with recent PSURs, and APR updates will continue to be included in the PSURs going forward (letter from EMA dated 20 January 2015 ref: EMA/44360/2015).

Criterion 4: Significant renal impairment identified by abnormal value of serum creatinine > 1.5 × upper limit of normal laboratory range
Reason for exclusion: Lack of PK data for lopinavir/ritonavir patients with renal insufficiency.
Is it considered to be included as missing information? No
Rationale: As stated in the product labeling, renal clearance of lopinavir/ritonavir is negligible. A decrease in total body clearance is not expected in patients with renal insufficiency.

SIV.2 Limitations to Detect Adverse Reactions in the Clinical Development Program

A clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged use.

Limitations of the Clinical Trial Database with Reference to Adverse Drug Reaction Detection

Not applicable.

SIV.3 Limitations in Respect to Populations Typically Under Represented in Clinical Development Program

Table 7. Exposure of Special Populations Included or Not in the Clinical Development Program

Type of special population	Exposure	Implications
Children < 2 years of age	Approximately 500 subjects below 2 years of age treated with a lopinavir/ritonavir-based regimen have been assessed for safety and efficacy in AbbVie Study M98-940, PACTG Study P1030, PACTG Study P1060, and the CHER study. In Study P19-106, a total of 42 pediatric patients aged 14 days to 2 years from 8 cohorts in 7 European Union countries were included (EPPICC Cohort study conducted by PENTA). This study was conducted as part of a Legally Binding Measure (LEG-121).	The results of Study P1060, Study P1030, and the CHER study reflect the virologic and immunologic benefits of lopinavir/ritonavir-based regimens, including a high-level barrier to the development of resistance known to be a characteristic of lopinavir/ritonavir, in children < 2 years of age. Results from Study P1030 showed that 60% of subjects in the younger cohort (≥ 14 days to < 6 weeks of age) and 76% of subjects in the older cohort (≥ 6 weeks to < 6 months of age) achieved reduction of viral load to < 400 copies/mL at Week 48. The proportion of subjects with an HIV-1 RNA < 400 copies/mL increased from 55% at Week 24 to 71% at Week 48 across the 2 cohorts combined. There were significant increases in CD4+ T cell count and CD4+ T cell percentage across the 2 cohorts combined. The clinical data from these studies, including antiviral activity and the safety profile in children older than 14 days and younger than 2 years of age, are consistent with the significant body of safety and efficacy information available in older children and adults receiving lopinavir/ritonavir -based therapy and was included as supporting data to the application for a Type II variation to extend the dosing of paediatric patients to those who are 2 weeks of age and older. Post-marketing surveillance for lopinavir/ritonavir includes weekly literature review and global safety database case report review, as well as regular case series review of reports of lack of efficacy, medication errors including overdose, and AEs in paediatric patients < 2 years old taking the lopinavir/ritonavir Oral Solution (propylene glycol and ethanol-containing dosage form). Since the labeling changes regarding propylene glycol and ethanol toxicity were made, no new safety signals in the age group < 2 years have been confirmed. In addition, a post-authorization safety study (PASS) P19-106 was completed in 2021, with no new confirmed

Type of special population	Exposure	Implications
		safety signals in the age group 14 days to 2 years (see section SVII.2).
Children (continued) 2 years of age and older	A total of 140 subjects ≥ 2 years of age were studied in the clinical development program. A total of 86 subjects ≥ 2 years of age were enrolled in Study M98-940. A total of 54 subjects ≥ 2 years of age were enrolled in Study P1060.	In addition to the postmarketing surveillance activities discussed above, regular case series of AEs in paediatric patients < 18 years of age, with subgroup analyses for patients aged > 2 years is conducted. No safety concerns in this particular age group have emerged from this surveillance.
Elderly	The use of lopinavir/ritonavir in elderly patients has not been studied. Exposure to lopinavir/ritonavir, presented as number of patients (and patient treatment years [PTYs]), is 29 (46.2), 3 (2.2), and 0 (0) in the age groups 65 to < 75 years, 75 to < 85 years, and ≥ 85 years, respectively, from Phase 2 to 4 clinical trials.	The use of lopinavir/ritonavir in this population is important because of the increasing use of lopinavir/ritonavir by an aging HIV population, who potentially could have developed concurrent conditions and illnesses (e.g., renal insufficiency, hepatic impairment) and could be on other concomitant medications that could affect the metabolism of lopinavir/ritonavir. Postmarketing surveillance includes quarterly review of a case series of AEs in elderly patients ≥ 65 years. No safety concerns in this particular age group have emerged from this surveillance.

Type of special population	Exposure	Implications
Pregnant or breastfeeding women	The MAH has not conducted clinical trials in pregnant women. However, lopinavir/ritonavir has been evaluated in over 3,000 women during pregnancy, including over 1,000 first trimester exposures.	The safety of lopinavir/ritonavir is also supported by literature reports and postmarketing surveillance that includes the APR and the AbbVie postmarketing safety database. The APR is a prospective, international, voluntary, exposure-driven pregnancy registry designed to monitor for potential increased birth defects following fetal exposure to antiretrovirals. Pregnant women are registered by their caregivers before pregnancy outcome is known. In postmarketing surveillance through the APR established since January 1989, an increased risk of birth defects exposures with lopinavir/ritonavir has not been reported among over 1,000 pregnant women exposed during the first trimester. Analysis of the APR data has been and shall continue to be provided with the lopinavir/ritonavir Periodic Safety Update Reports PSUR (letter from EMA dated 20 January 2015 ref: EMA/44360/2015). In addition to the APR, the MAH conducted a detailed analysis from animal toxicology data, major clinical publications, data from the APR and the National Study on HIV in Pregnancy and Childhood, epidemiological literature, and an analysis of postmarketing reports describing prematurity coincident with Lopinavir/ritonavir-based therapy. The potential signal for premature birth for lopinavir/ritonavir was not confirmed (May 2012). Lopinavir/ritonavir is a potential treatment option during pregnancy in treatment guidelines from national, regional, and global organizations and agencies (US Department of Health and Human Services [Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission 2018]; World Health Organization [2016]; British HIV Association [de Ruiter 2014]). These guideline recommendations are supported by published clinical studies in pregnant HIV-infected patients.

Type of special population	Exposure	Implications
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	**Patients with Hepatic Impairment** The use of lopinavir/ritonavir in patients with severe hepatic impairment, defined according to Child-Pugh criteria, has not been studied. The use of lopinavir/ritonavir in patients with mild or moderate hepatic impairment defined as Child-Pugh Class A or B was studied in 24 adult patients in Study M01-347. **Patients with Renal Impairment** The use of lopinavir/ritonavir in patients with renal impairment has not been formally studied.	**Patients with Hepatic Impairment** The product label indicates that lopinavir/ritonavir should not be used in subjects with severe hepatic impairment. **Patients with Renal Impairment** Renal impairment is not expected to impact the PKs of lopinavir/ritonavir because of its negligible renal clearance. In addition, population PK analysis from Study M05-730 did not result in changes in lopinavir PK in HIV-1–infected subjects with mild renal impairment. Product labeling indicates no dose adjustment is needed in subjects with renal impairment. The SmPC states that patients taking the oral solution, particularly those with renal impairment or with decreased ability to metabolise propylene glycol (e.g., those of Asian origin), should be monitored for adverse reactions potentially related to propylene glycol toxicity (i.e., seizures, stupor, tachycardia, hyperosmolarity, lactic acidosis, renal toxicity, and haemolysis).

AbbVie = AbbVie Inc.; AE = adverse event; APR = Antiretroviral Pregnancy Registry; CD4+ = cluster of differentiation 4; CHER = Children with HIV Early Antiretroviral Therapy; EMA = European Medicines Agency; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; MAH = marketing authorisation holder; PACTG = Paediatric AIDS Clinical Trials Group; PK = pharmacokinetic(s); PSUR = periodic safety update report; PTYs = patient treatment years; RNA = ribonucleic acid; SmPC = Summary of Product Characteristics; US = United States

Module SV Post-Authorization Experience

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

Two separate exposure analyses were conducted to estimate usage characteristics and distribution of lopinavir/ritonavir. Methods for the respective exposure estimates are presented prior to data presentation.

SV.1.2 Exposure

An estimate of the number of patients treated with lopinavir/ritonavir capsules, tablets, half tablets, and oral solution worldwide by country was calculated from internal AbbVie distribution data. PTYs are given by formulation for the entire postmarketing timeframe of 15 September 2000 through 26 January 2018.

Using the total number of capsules/tablets or milliliters sold and dividing by the total daily dose (TDD) (800 mg daily, 300 mg daily for the 100/25 mg formulation), estimates of the number of patient-treatment days (PTDs) were obtained. The estimated numbers of PTYs were obtained by dividing the PTDs by 365.25. Following this calculation, the estimated PTYs for each dosing regimen per formulation were calculated by EU country and rest of world, aggregated (Table 8).

Table 8. Lopinavir/ritonavir Patient-treatment year(s) (PTY) Exposure by EU Country/Rest of World – 15 September 2000 through 26 January 2018

PTYs Per Dosing Regimen/Formulation					
Country/Region	**Capsule - 133/33 mg**	**Oral Solution - 80 mg/ml**	**Tablet - 100/25 mg**	**Tablet - 200/50 mg**	**Grand Total**
EU Total	248,162	14,614	6,587	548,959	818,322
Austria	[redacted]				
Belgium					
Bulgaria					
Croatia					
Cyprus					
Czech Republic					
Denmark					
Estonia					
Finland					
France					
Germany					
Greece					
Hungary					
Ireland					
Italy					
Latvia					
Lithuania					
Malta					
Netherlands					
Poland					
Portugal					
Romania					
Slovakia					
Slovenia					
Spain					
Sweden					
United Kingdom					

PTYs Per Dosing Regimen/Formulation					
Country/Region	**Capsule - 133/33 mg**	**Oral Solution - 80 mg/ml**	**Tablet - 100/25 mg**	**Tablet - 200/50 mg**	**Grand Total**
Non-EU Total	548,161	260,496	297,453	4,603,901	5,710,011
Overall Total	796,323	275,110	304,040	5,152,860	6,528,332

EU = European Union

Module SVI Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Lopinavir/ritonavir is an ARV medicinal product for which the chemical structure and/or mode of action are not known to pose a potential for illegal use.

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/Missing Information Considered Important for Inclusion in the RMP

Important Identified Risks

Identified risk 1: Toxicity in preterm neonates of lopinavir/ritonavir oral solution

Reason for Inclusion:

When present in high concentrations, propylene glycol increases osmolality, especially in preterm neonates with diminished renal function. Symptoms of ethanol and propylene glycol toxicity include lactic acidosis, renal failure, CNS depression, heart block, and heart failure or cardiomyopathy. Lopinavir/ritonavir oral solution is highly concentrated and contains 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v). Each 1 mL of lopinavir/ritonavir oral solution contains 356.3 mg of alcohol and 152.7 mg of propylene glycol.

Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients.

Identified risk 2: Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)

Reason for Inclusion:

The FDA in the US notified AbbVie of a class labeling change for protease inhibitors in October 2011 to add to the information that was already in the label for IRIS that "autoimmune disorders such as Graves' disease, polymyositis, and Guillain-Barre syndrome have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment." The labeling at that time already had information on IRIS describing inflammatory response to indolent or residual opportunistic infections. The MAH performed a medical safety assessment at the time confirming the signal and the labeling was updated. Due to the potentially serious nature of some of the events, this was subsequently included as an important identified risk in the RMP.

The likelihood and severity of IRIS correlates with 2 interrelated factors: 1) the extent of CD4+ T cell immune suppression prior to the initiation of highly active antiretroviral therapy (HAART) and 2) the degree of viral suppression and immune recovery following the initiation of HAART.

The syndrome of IRIS in HIV patients has been recognized in the setting of treatment of an opportunistic infection and initiation of ART; that is, with rapid improvement in immune function, systemic or local inflammatory reactions may occur at the site or sites of the pre-existing infection. This inflammatory reaction is usually self-limiting, especially if the pre-existing infection is effectively treated. However, long-term sequelae and fatal outcomes may occur rarely, particularly when neurologic structures are involved. In addition to exacerbation of infections, autoimmune disorders have also been reported in the setting of IRIS.

Identified risk 3: Lipid elevations

Reason for Inclusion:

Treatment with lopinavir/ritonavir has resulted in large increases in the concentration of total cholesterol and triglycerides of 7.4% and 6.2%, respectively, in adult patients receiving lopinavir/ritonavir in the combined Phase 2/4 Studies (N = 2,612). Lipid elevations can cause the patient to experience life-threatening events, such as cardiac disorders, pancreatitis, liver disorders, or abnormal liver enzymes.

Important Potential Risks

Potential risk 1: QT prolongation with supratherapeutic doses

Reason for Inclusion:

In AbbVie Study M06-809, a Phase 1, randomized, open-label, placebo- and active-control, multiple-dose crossover study in healthy volunteers, the upper bound of the 95% (CI) for the drug effect of lopinavir/ritonavir 400/100 mg BID on QTcF, when compared with placebo, was 6.3 ms (mean values of −2.3 ms to 3.6 ms). When lopinavir/ritonavir was administered at the supratherapeutic dose of 800/200 mg BID (resulting in exposures 3-fold higher than those achieved by the recommended dose of lopinavir/ritonavir at steady state), the 10 ms threshold was exceeded for the upper bound of the 95% CI around the mean QT interval effect. The upper bound of the 95% CI for lopinavir/ritonavir 800/200 mg BID, when compared with placebo, ranged from 11.1 ms to 15.8 ms (mean point estimates of 8.4 ms to 13.1 ms). However, no subject experienced an increase in QTcF of ≥ 60 ms from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 ms.

QT interval prolongation is a risk factor for life-threatening ventricular arrhythmias leading to sudden death. Potential risk is low at standard doses of lopinavir/ritonavir. The potential for prolongation of QTcF may exist with supratherapeutic doses.

Potential risk 2: PR prolongation at therapeutic dosing

Reason for Inclusion:

In AbbVie Study M06-809, a Phase 1, randomized, open-label, placebo- and active-control, multiple-dose crossover study in healthy volunteers, there was an increase in PR interval at 400/100 mg BID of lopinavir/ritonavir on Day 3, when lopinavir concentrations were approximately 30% to 50% higher than those observed at steady state. Maximum PR interval was 286 ms and no second or third degree heart block was observed. While first-degree atrioventricular (AV) block can be clinically nonsignificant, third-degree AV block may require interventions such as pacemaker implantation.

Potential risk 3: Risks of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg

Reason for Inclusion:

Lopinavir/ritonavir oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). Based on the results of the 2 mL syringe/device risk assessment, infants from 2 to 9 weeks of age and weighing less than 3.8 kg may be at risk of exceeding the blood alcohol concentration (BAC) limit in the context of overdose when the 2 mL syringe is used (in view of the residual capacity of the 2 mL syringe), leading to toxicity.

Missing information

Information 1: Safety of chronic exposure to propylene glycol and ethanol in patients 14 days to 2 years of age
Reason for Inclusion: The effect of long-term exposure, even to low levels of ethanol and propylene glycol, in medicines on the health and development of children has not been evaluated. Ethanol and propylene toxicity may cause hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis.
Data to be Collected Post-Authorization: PV Cohort study such as European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC).

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

There are no new safety concerns or reclassification of safety concerns during this RMP revision period. One safety concern (missing information of Safety of chronic exposure to propylene glycol and ethanol in patients 14 days to 2 years of age) has been removed, as follows:

Removed Missing Information

Missing Information 1: Safety of chronic exposure to propylene glycol and ethanol in patients 14 days to 2 years of age

Reason for Removal:

The effect of long-term exposure, even to low levels of ethanol and propylene glycol, in medicines on the health and development of children was evaluated as part of a commitment to EMA (Post-Authorization Measure – Legally Binding Measure-121 [PAM-LEG-121]), including the EPPICC Cohort Study P19-106 and annual reviews of literature and the post-marketing safety database. The EMA Legally Binding Measure (LEG) was a condition of approval for the extension of the indication of Kaletra Oral Solution to include children aged 14 days and older in the treatment of HIV-1 on 26 July 2017 (Type II variation EMEA/H/C/000368/II/0161/G). The LEG commitment required the sponsor to provide an annual safety review focused on AEs in children 14 days to 2 years of age that may suggest toxicity with ethanol or propylene glycol. Four such annual reports were submitted to EMA. No cases suggesting propylene glycol or ethanol toxicity and no medication errors leading to overdose were identified in children 14 days to 2 years of age with Kaletra oral solution during the study. In addition, no new safety signals arose regarding use in pediatric patients aged 14 days to 2 years during the PAM-LEG-121 reviews. The LEG-121.4 assessment report of 27 January 2022 (EMA reference: EMA/PRAC/CHMP/23418/2022) indicated that this commitment was fulfilled (Procedure no.: EMA/H/C/000368).

The updates made to the list of safety concerns in previous RMP versions are listed below:

Updates Made in RMP version 9.0

Two safety concerns (1 important potential risk [Drug interaction with HCV PIs boceprevir and telaprevir] and 1 missing information safety concern [Use of lopinavir/ritonavir in elderly patients]) were removed, as follows:

Removed Important Potential Risks

Potential risk 1: Drug interaction with HCV PIs boceprevir and telaprevir

Reason for Removal:

The marketing authorisation holder (MAH) recommended the removal of the "Important Potential Risk" of drug-drug interaction (DDI) with the HCV drugs telaprevir/boceprevir for several reasons. First, many newer drugs for HCV treatment are now available, and telaprevir and boceprevir are now used infrequently, especially in developed countries. Second, boceprevir and telaprevir have both been removed from the market in several countries such as the United States (US); in the EU, telaprevir has been withdrawn and boceprevir is still centrally authorized but only with minimal use.

As part of a drug utilization study to determine in which countries boceprevir and telaprevir are used, the MAH reviewed boceprevir use in western Europe/Canada (WEC) Countries (01 June 2017 to 31 Dec 2017). During this time interval in WEC countries, the drug was used only in the United Kingdom (UK) and in very small quantities, treating fewer than 10 patients. There was no expected use of boceprevir in the UK for 2018.

In addition, the MAH searched the global safety database for numbers of case reports from 01 January 2008 to 31 December 2017 in which boceprevir or telaprevir was used concomitantly with lopinavir/ritonavir for all countries. The MAH found only a few reports of either boceprevir (2 reports, 1 each from Spain (2013) and Switzerland [2016]) or telaprevir (1 report in the UK in 2013) together with lopinavir/ritonavir in that time interval.

EMA agreed to this RMP update.

Removed Missing Information

Missing Information 1: Use of lopinavir/ritonavir in elderly patients

Reason for removal:

The MAH recommended to remove "Use of Lopinavir/ritonavir in elderly patients" from the missing information sections of the RMP. Recent EU guidance recommends to include use of lopinavir/ritonavir in elderly patients in missing information only if there is a specific safety concern in the elderly population. In elderly patients, consideration must be given to the possibility of decreased hepatic or renal function; lopinavir/ritonavir is metabolized by the liver

and is not eliminated by the kidney. However, in over 6.5 million PYs of lopinavir/ritonavir exposure over nearly 20 years (IBD 15 September 2000), no specific safety concerns in the elderly population have emerged.

To support the removal of this risk from the RMP, the MAH searched the global safety database for numbers of case reports per year, in elderly (≥ 65 years) and not elderly (< 65 years) patients, for case reports where age was provided. The results are shown in Figure 1. Use in patients ≥ 65 years of age is minimal.

Figure 1. Numbers of Case Reports Per Year, in Elderly (≥ 65 Years) and Not Elderly (< 65 Years) Patients (For Global Safety Database Case Reports Where Age Was Provided)

Age range (years)	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	Grand Total
≥85	0	0	0	0	0	0	0	0	1	0	1
75-84	1	3	3	2	3	3	2	5	4	2	28
65-74	5	4	14	17	28	23	19	13	17	18	158
<65	189	522	348	558	908	724	511	550	791	700	5801
Grand Total	195	529	365	577	939	750	532	568	813	720	5988

In summary, the MAH recommended removing "Use of Lopinavir/ritonavir in elderly patients" from the missing information sections of the RMP because no specific safety concerns in the elderly population have emerged in nearly 2 decades of use and because there is minimal use of lopinavir/ritonavir in this population. EMA agreed to this RMP update.

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

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

Important Identified Risk 1: Toxicity in preterm neonates of lopinavir/ritonavir oral solution
MedDRA preferred terms (PTs): Lactic acidosis, Renal failure acute, Blood creatinine increased, Blood osmolality increased, Coma, Stupor, Central nervous system depression not otherwise specified, Seizure, Hypotonia, Apnoea, Bradycardia, Atrioventricular block complete, Cardiac failure, and Cardiomyopathy. Potential Mechanisms: Lopinavir/ritonavir oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). Theoretically, through competitive inhibition, the ethanol contained in lopinavir/ritonavir oral solution may inhibit the metabolism of propylene glycol, leading to elevated concentrations of propylene glycol due to the long half-life of propylene glycol in the premature neonate. Due to their diminished ability to metabolise propylene glycol, preterm neonates may be at an increased risk of propylene glycol toxicity. The mechanism of toxicity for propylene glycol has been well characterized (Ellenhorn 1997). Approximately 55% of propylene glycol is metabolised to lactic acid by hepatic alcohol dehydrogenase. The lactic acid is then metabolised to pyruvic acid and shunted to the glycolytic pathway. The remaining 45% is excreted by the kidneys. In adults, the half-life for propylene glycol is 5 hours (Yu 1985). In contrast, in neonates, the half-life is 19.3 hours (Glasgow 1983).
Evidence Source and Strength of Evidence: Postmarketing surveillance and literature (Glasgow 1983, Yu 1985, Ellenhorn 1997, Boxwell 2011, FDA Drug Safety Communication 2011).
Characterization of the Risk: When present in high concentrations, propylene glycol increases osmolality, especially in preterm neonates with diminished renal function. Symptoms of ethanol and propylene glycol toxicity include lactic acidosis, renal failure, central nervous system (CNS) depression, heart block, and heart failure or cardiomyopathy. Postmarketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death have been reported predominantly in preterm neonates receiving lopinavir/ritonavir oral solution. Specifically, in March 2011, FDA described 10 case reports of such events of which 7 of these case reports included events of cardiac toxicity. The MAH became aware of an 11th published case in 2011 (Karydes 2011) for which a premature neonate received an unintentional overdose of lopinavir/ritonavir and did not have significant cardiovascular compromise. The labeling was updated to include warnings regarding the risk of such events in preterm neonates, and since then the MAH has not become aware of further such case reports. Frequency in AbbVie clinical trials cannot be calculated because no infants younger than the approved age were evaluated in these trials.

Risk Factors and Risk Groups: Preterm neonates of 42 weeks and before a postnatal age of at least 14 days.
Preventability: Lopinavir/ritonavir is not approved for use in children < 14 days of age, as noted in product labeling available to health care providers. Health care providers have also been provided information through the product information for lopinavir/ritonavir, which notes that total amounts of alcohol and propylene glycol from all medicines, including lopinavir/ritonavir oral solution, that are to be given to infants should be taken into account in order to avoid toxicity from these excipients. The product information also notes that infants should be monitored closely for toxicity related to lopinavir/ritonavir oral solution.
Impact on the Risk-Benefit Balance of the Product: The product labeling contains adequate language that lopinavir/ritonavir oral solution is not approved for use in children < 14 days of age. The benefit-risk balance remains positive for the approved use in approved paediatric age groups.
Public Health Impact: HIV-1 infection has been associated with morbidity and mortality in HIV-exposed premature infants. Lopinavir/ritonavir solution has been used in the past in a small population of preterm infants 0.04% to < 0.1% of lopinavir/ritonavir users, with rare cases of ethanol or propylene glycol toxicities reported. The product labeling currently notes that lopinavir/ritonavir oral solution is not approved for use in children < 14 days of age, so the public health impact is minimal.

Important Identified Risk 2: Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)
MedDRA Terms: Immune reconstitution inflammatory syndrome, Immune reconstitution inflammatory syndrome associated tuberculosis, Immune reconstitution inflammatory syndrome associated Kaposi's sarcoma, Basedow's disease, Polymyositis, and Guillain-Barre syndrome.
Potential Mechanisms: The mechanism for these paradoxical reactions is not well understood, but it appears to be immune mediated. A few autoimmune and other noninfectious conditions may appear after HAART is begun i.e., Graves' disease, suggesting that inflammation induced by an IRIS-like syndrome is responsible. Whether such associations represent a causal or a coincidental finding is unproven at present.

Evidence Source and Strength of Evidence:

Clinical Trial reports (Combined phase 2 to 4 studies)

Literature reports:

Chen F, et al. Medicine (Baltimore). 2005;84(2):98-106.

French MA, et al. HIV Med. 2000;1(2):107-15.

Grant PM, et al. PloS ONE. 2010;5(7)e11416.

Murdoch DM, et al. AIDS. 2008;22(5):601-10.

Ratnam I, et al. Clin Infect Dis. 2006;42(3):418-27.

Shelburne SA, et al. AIDS. 2005;19(4):399-406.

Vos F, et al. Scand J Infect Dis. 2006;38(2):124-6.

Characterization of the Risk:

Frequency:

Searches for the PTs listed above, MedDRA version 16.0, were performed separately for adult and paediatric subjects in Phase 2 to 4 clinical trials. 20/2612 or 0.77% (95% CI: 0.47%, 1.18%) of adult subjects and 0/100 paediatric subjects had PTs in the search.

Seriousness/outcomes:

The syndrome of IRIS in HIV patients has been recognized in the setting of treatment of an opportunistic infection and initiation of ART; that is, with rapid improvement in immune function, systemic or local inflammatory reactions may occur at the site or sites of the pre-existing infection. This inflammatory reaction is usually self-limited, especially if the pre-existing infection is effectively treated. However, long-term sequelae and fatal outcomes may occur rarely, particularly when neurologic structures are involved.

In adult clinical trials, 21 PTs (events) in the SMQ search were reported by 20 subjects; 1 of the 21 events was serious and led to hospitalization. No adult subjects died from such an event.

There were no events in paediatric subjects. The details for the hospitalized patient are presented below:

Subject [redacted] (Study M99-049) was a [redacted]-year-old [redacted] [redacted] with a history of proteinuria in the past and hypertension who experienced glomerulonephritis (focal segmental glomerulosclerosis diagnosed by biopsy) twice while on 11 months of study drug (Day 186 and Day 239), with the first event classified as an SAE of moderate severity, requiring hospitalization and treatment with Cozaar (losartan, given for 59 days). Study drug was not discontinued for either event. The first event resolved in 54 days. Both events were assessed as not related by both the investigator and sponsor, and attributed to underlying disease.

Severity and nature of risk:

In combined Phase 2 to 4 Studies (N = 2,612) for lopinavir/ritonavir, treatment-emergent adverse reactions of moderate or severe intensity occurring in at least 0.1% of adult patients included immune reconstitution syndrome (also known as immune reconstitution inflammatory syndrome) in only 0.115%, as noted in the company core data sheet (CCDS).

There were no events in paediatric subjects.

Risk Factors and Risk Groups: Patients with pre-existing opportunistic infections and low baseline CD4 cell counts are at risk. The likelihood and severity of IRIS correlates with 2 interrelated factors: 1) the extent of CD4+ T cell immune suppression prior to the initiation of HAART and 2) the degree of viral suppression and immune recovery following the initiation of HAART.
Preventability: Prescriber and patient awareness through labeling. According to the professional labeling, any inflammatory symptoms should be evaluated and treatment instituted when necessary.
Impact on the Risk-Benefit Balance of the Product: Lopinavir/ritonavir significantly lowers HIV-1 viral load, reducing mortality and morbidities in HIV-infected patients; inflammatory reaction can occur in a setting of severe immune deficiency and is usually self-limited, especially if the pre-existing infection is effectively treated.
Public Health Impact: Public health impact is minimal, given the high virologic response from lopinavir/ritonavir-treated individuals and subsequent potential reduction of morbidities and mortalities; this inflammatory response is self-limiting and is treated effectively with standard protocols.

Important Identified Risk 3: Lipid elevations
MedDRA PTs: Dyslipidemia SMQ – narrow search Potential Mechanisms: The etiology of dyslipidemia in HIV patients is multifactorial; it can be associated with the infection itself, opportunistic infections, treatments, stage of the disease, and other cardiovascular risk factors (Fourie 2010; Palacios 2003).
Evidence Source and Strength of Evidence: Elevated lipids have been reported to be associated with the use of PIs as a class effect. • Clinical trials in adult subjects in Phase 2 to 4 clinical trials • Literature • Postmarketing surveillance

Characterization of the Risk:

Frequency:

Searches using the dyslipidemia SMQ – narrow search, MedDRA version 13.1, were performed separately for adult and paediatric subjects in Phase 2 to 4 clinical trials. 445/2612 or 17.04 % (95% CI: 15.61 %, 18.53 %) of adults and 0/100 paediatric subjects had PTs in the search.

Seriousness/outcomes:

Patients with elevated lipids can experience cardiac disorders, pancreatitis, liver disorders, or abnormal liver enzymes that can be life-threatening. In addition, DDIs with certain lipid-lowering agents, such as HMG Co-A reductase Inhibitors (statins, e.g., lovastatin and simvastatin), may result in increased plasma concentrations of the statin drug, increasing the risk of statin adverse events including potentially serious events such as myopathy including rhabdomyolysis.

In Phase 2 to 4 clinical trials, 760 PTs (events) in the SMQ search described above were reported by 445 adults; 1 of 760 events was serious; the event required intervention but did not lead to hospitalization. No adult subjects died due to such an event.

There were no events in paediatric subjects.

Severity and nature of risk:

The patient can experience life-threatening events, such as cardiac disorders, pancreatitis, liver disorders, or abnormal liver enzymes.

In Phase 2 to 4 clinical trials 760 PTs (events) were reported by 445 subjects; 1 of 760 events was serious; the event was hypertriglyceridemia experienced by a [redacted] year-old [redacted] on study Day 22 that required intervention by treatment with lipanthyl (fenofibrate) but did not lead to hospitalization or discontinuation of study drug. No adult subjects died due to such an event. Out of 760 events of dyslipidemia in adults, 102 events were severe.

There were no events in paediatric subjects.

Risk Factors and Risk Groups:

As noted in the label for lopinavir/ritonavir, patients with advanced HIV disease may be at risk of elevated triglycerides. Other risk factors for hyperlipidaemia include obesity, diabetes mellitus, certain medications (ex., other HIV antiretrovirals that increase lipids, certain beta blockers, glucocorticoids, estrogen, and cyclosporine), hypothyroidism, nephrotic syndrome, and hereditary disorders.

Particular caution should be paid to patients with high values at Baseline and with a history of lipid disorders.

Preventability:

Triglyceride and cholesterol testing should be performed prior to initiating lopinavir/ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. In addition, prescribers should be very careful when prescribing PIs with other statins. Caution should be exercised if HIV PIs including lopinavir/ritonavir are used concurrently with rosuvastatin, or with other HMG-CoA reductase inhibitors that are metabolised by the CYP3A pathway (i.e., atorvastatin) and are contraindicated with simvastatin and lovastatin.

Impact on the Risk-Benefit Balance of the Product: Treatment with lopinavir/ritonavir has resulted in increases in the concentration of total cholesterol and triglycerides. Changes in lipid profiles in HIV-infected individuals have been observed, including increased levels of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The impact is that increased lipids can increase the patient's risk for cardiovascular outcome events or cardiovascular related death.
Public Health Impact: Public health impact minimal.

Important Potential Risk 1: QT prolongation with supratherapeutic doses MedDRA Terms: Torsade de pointes/QT prolongation SMQ – broad search
Potential Mechanisms: PIs have been shown to block human ether à-go-go–related gene (hERG) potassium channels in vitro. Lopinavir, nelfinavir, ritonavir, and saquinavir caused dose-dependent block of hERG channels (Anson 2005). Lopinavir has also been observed to block repolarization of potassium current (I[Kr]) channels in neonatal mouse cardiac myocytes.
Evidence Source and Strength of Evidence: Clinical trial data (including Study M06-809, a Phase 1, randomized, open-label, placebo- and active-controlled, multiple-dose study designed to assess the potential for QTc prolongation of lopinavir/ritonavir and ritonavir in healthy volunteers) and literature (Anson 2005; Sani 2005; Reinsch 2009; Qaqa 2010).
Characterization of the Risk:
Frequency: Searches in the torsade de pointes/QT prolongation SMQ – broad search, MedDRA version 15.0, were performed separately for adult and paediatric subjects in Phase 2 to 4 clinical trials. 25/2612 or 0.96% (95 % CI: 0.62%, 1.41%) of adult subjects and 0/100 paediatric subjects had PTs in the search. There were no events with a PT of torsade de pointes. In AbbVie Study M06-809, a Phase 1, randomized, open-label, placebo- and active-control, multiple-dose crossover study in healthy volunteers, the upper bound of the 95% CI for the drug effect of lopinavir/ritonavir 400/100 mg BID, when compared with placebo, was 6.3 ms (mean values of −2.3 to 3.6 ms). When lopinavir/ritonavir was administered at the supratherapeutic dose of 800/200 mg BID (resulting in exposures 3-fold higher than those achieved by the recommended dose of lopinavir/ritonavir at steady state), the 10 ms threshold was exceeded for the upper bound of the 95% CI around the mean QT interval effect. The upper bound of the 95% CI for lopinavir/ritonavir 800/200 mg BID, when compared with placebo, ranged from 11.1 ms to 15.8 ms (mean point estimates of 8.4 ms to 13.1 ms). Seriousness/outcomes: In AbbVie Study M06-809, evaluation of lopinavir/ritonavir PK exposures at labelled doses was conducted in 45 subjects using a crossover study design — 400/100 mg BID or 800/200 mg QD (which is approved in some areas) — including peak plasma drug exposures prior to onset of CYP induction, did not reveal potentially significant increases in QTcF (QT interval corrected for heart rate using Fridericia's

method). In Phase 2 to 4 clinical trials, 26 PTs (events) in the SMQ search described above were reported by 25 adults; 5 of 26 events were serious; 4 events led to hospitalization. Three of the 4 hospitalized patients experienced syncope and the fourth experienced loss of consciousness, with all events assessed as not related or probably not related by the investigator. No adult subjects died due to an event of QT prolongation. There were no events with a PT of torsade de pointes. Severity and nature of risk: Potential risk is low at standard doses of lopinavir/ritonavir. Four of 26 events of torsade de pointes/QT prolongation in adults in clinical trials were severe. There were no events in paediatric subjects.
Risk Factors and Risk Groups: Individuals with congenital long QT syndrome, hypokalemia, or who may be taking concomitant drugs, for any reason, that have associated QTc prolongation as an adverse event.
Preventability: Prescriber and patient awareness through labeling. The labeling provides a summary of the study that detected QT interval prolongation. In addition, it provides guidance to prescribers in noting that particular caution must be used when prescribing lopinavir/ritonavir and medicinal products known to induce QT interval prolongation, and that lopinavir/ritonavir could increase concentrations of the co-administered medicinal products and this may result in an increase of their associated cardiac adverse reactions. Health care professionals to collect information on pre-existing heart conditions that might increase the risk of cardiac toxicity in subjects exposed to PIs and to evaluate the use of concomitant drugs that are associated with the adverse event of QT prolongation.
Impact on the Risk-Benefit Balance of the Product: Drug-induced QT interval prolongation has been associated with the occurrence of life-threatening or fatal ventricular arrhythmias leading to sudden death.
Public Health Impact: Increased morbidity in HIV-infected subjects with a predisposing risk for QT interval prolongation who are exposed to supratherapeutic doses of lopinavir/ritonavir. Otherwise, limited for the general population, as the use lopinavir/ritonavir is indicated for the HIV population.

Important Potential Risk 2: PR prolongation at therapeutic dosing

MedDRA terms:

Conduction defects SMQ – narrow search

Potential Mechanisms:

No studies are available on the molecular and genetic basis of drug-induced prolongation of PR for lopinavir/ritonavir as well as the prognostic significance and clinical relevance specifically in HIV infection.

Clinical significance of PR prolongation (first degree AV block) was studied in a 2016 meta-analysis that included 14 studies and over 400,000 patients, first degree AV block was associated with a higher risk of mortality (RR 1.2; 95% CI 1.0 - 1.5) as well as heart failure or left ventricular dysfunction (RR 1.4; 95% CI 1.2 - 1.7) and atrial fibrillation (RR 1.5; 95% CI 1.2 - 1.7) but was not associated with a higher risk of cardiovascular mortality, coronary heart disease, myocardial infarction, or stroke (Kwok 2016).

Evidence Source and Strength of Evidence:

Clinical trial data (including Study M06-809, a Phase 1, randomized, open-label, placebo- and active-controlled, multiple-dose study designed to assess the potential for QTc prolongation of lopinavir/ritonavir and ritonavir in healthy volunteers) and literature (Bexton 1984; Sani 2005; Charbit 2011).

Characterization of the Risk:

Frequency:

Searches using the conduction defects SMQ – narrow search, MedDRA version 13.1, were performed separately for adult and paediatric subjects in Phase 2 to 4 clinical trials. 8/2612 or 0.31% (95 % CI: 0.1 3%, 0.6%) of adult subjects and 0/100 paediatric subjects had a PT in the search. No events of complete block were identified.

Severity

In AbbVie Study M06-809, a Phase 1, randomized, open-label, placebo- and active-control, multiple-dose crossover study in healthy volunteers, there was an increase in PR interval at 400/100 mg BID of lopinavir/ritonavir on Day 3, when lopinavir concentrations were approximately 30% to 50% higher than those observed at steady state. The mean changes from Baseline in PR interval ranged from 11.6 ms to 24.4 ms over the 12-hour dosing interval.

At lopinavir exposures following 3 days of dosing with supratherapeutic doses of lopinavir/ritonavir (lopinavir/ritonavir 800/200 mg BID producing concentrations approximately 2 to 3 times higher than those observed at steady state in HIV-infected individuals receiving either lopinavir/ritonavir 800/200 mg QD or lopinavir/ritonavir 400/100 mg BID), the mean changes from Baseline in PR interval ranged from 22.0 ms to 31.2 ms over the 12-hour dosing interval. However, maximum PR interval was 286 ms and no second or third degree heart block was observed in this study.

Seriousness/outcomes:

In Phase 2 to 4 clinical trials, 8 PTs (events) in the SMQ search described above were reported by 8 adults; 1 of 8 events was serious, and the subject was hospitalized. Subject [redacted] of Study M05-730 was a [redacted] year-old [redacted] [redacted] who was hospitalized for atrioventricular block on Day 264, which was assessed as serious and possibly related. ECG revealed "auriculo-ventricular block II/I, with some complete passages auricle-ventricular block, the frequency decrease to less than 30, with very significant pauses; the ventriculograms appeared very widened, morphology of right delay, with an axis hyper right." Isoprenaline was initiated and quickly discontinued, as it was poorly tolerated. Study

drug was interrupted. By Day 265 the event was considered to be resolved, however on Day 267 a pacemaker was implanted. On Day 270 study drug was restarted, and the event did not reoccur. On Day 274 the subject was discharged. No subjects died. No events of complete block were identified. There were no events in paediatric subjects. Severity and nature of risk: In Phase 2 to 4 clinical trials, 1 adult subject experienced a severe event, which was also serious; the subject was hospitalized. No subject died from a PR prolongation-related event. There were no events in paediatric subjects. Modest prolongation of the PR interval was also noted in subjects receiving lopinavir/ritonavir in the same AbbVie Study M06-809 described above for the QTcF interval evaluation on Day 3. The mean changes from baseline in PR interval ranged from 11.6 ms to 24.4 ms in the 12 hour interval post dose. Maximum PR interval was 286 ms and no second- or third-degree heart block was observed.
Risk Factors and Risk Groups: Lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of second- or third-degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. Lopinavir/ritonavir should be used with caution in such patients. Long-term follow-up studies asymptomatic young individuals with prolonged PR interval (prevalences of from 0.65% to 1.1% in the general population) have indicated that although the risk of subsequent coronary artery disease (CAD) may be slightly increased, the risk of sudden death, syncope, or advanced AV block is not (Bexton 1984).
Preventability: Prescriber and patient awareness through labeling, section 4.4 of the SmPC – Special warnings and precautions for use which describes that lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Product labelling states rare reports of 2nd or 3rd degree AV block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval have been reported in patients receiving Lopinavir/ritonavir. Lopinavir/ritonavir should be used with caution in such patients. Health care professionals to obtain information on pre-existing heart or heart conduction conditions that might increase the risk for PR interval prolongation in subjects exposed to ARVs.
Impact on the Risk-Benefit Balance of the Product: Lopinavir/ritonavir use significantly lowers viral load in HIV-1-infected individuals; however, lopinavir/ritonavir in supratherapeutic levels and underlying structural heart disease and pre-existing conduction system abnormalities; patients can develop PR prolongation that may result in heart block. Coadministration with drugs known to prolong the PR interval should be with caution.
Public Health Impact: Increased morbidity in HIV-infected subjects with a predisposing risk for arrhythmias such as AV block. Otherwise, limited for the general population, as the use lopinavir/ritonavir is indicated for the HIV population.

Important Potential Risk 3: Risk of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg
Potential Mechanisms: Lopinavir/ritonavir oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations of propylene glycol.
Evidence Source and Strength of Evidence: 2-mL syringe/device risk assessment
Characterization of the Risk: Based on the results of the 2 mL syringe/device risk assessment, infants from 2 to 9 weeks of age and weighing less than 3.8 kg may be at risk of exceeding the blood alcohol concentration (BAC) limit in the context of overdose using a 2 mL syringe (in view of the residual capacity of the 2 mL syringe).
In the worst-case scenario, if a 2-week-old infant weighing 2.7 kg (weight-for-age: birth to 13 weeks growth table [WHO 2016]) is administered the entire volume of the 2-mL syringe, the estimated BAC will be 35.19 mg/dL. At this BAC, reversible, non-specific symptoms may be experienced including poor feeding, mild decrease in activity, and a mild decrease in sensorium. Management would be supportive care, and the risk is considered to be manageable. Correspondingly, the estimated blood propylene glycol concentration will be 21.75 mg/dL. Since the time of the above risk assessment, on 26 July 2017, the European Commission (EC) adopted the decision to expand approval of use of lopinavir/ritonavir Oral Solution in paediatric patients to ages 14 days and older (previously 2 years and older). The EC decision also included a Type IB variation to add a new pack size of 120 ml (2 × 60 ml bottles) and a Type IA variation to add a new 2 ml oral dose syringe for the 120 ml pack size. The RMP was also updated then with this Important Potential Risk, "Risk of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg." Since this risk was added the MAH has monitored for such errors through weekly surveillance including literature, and quarterly case series of the following: AE reports in children < 2 years of age with the oral solution dosage form; medication error reports (in all ages including paediatric patients); and overdose reports (in all ages including pediatric patients). Since the 26 July 2017 approval of the 2 ml syringe, the MAH has not detected new safety signals pertaining to dosing with the 2 ml syringe with such surveillance. Risk of overdose resulting from medication errors with lopinavir/ritonavir oral solution oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg will continue to be monitored as a potential risk. If the MAH identifies a new safety trend, it will be presented in future safety reports in accordance with current regulations and guidelines.
Risk Factors and Risk Groups: Infants from 2 to 9 weeks of age and weighing less than 3.8 kg
Preventability: The label includes information to reflect the risk of medication error and ethanol/propylene glycol toxicity in neonates, especially in premature infants. No reports of medication error resulting in overdose have been reported since the labeling revisions were implemented.

Impact on the Risk-Benefit Balance of the Product: Reversible, mild to moderate symptoms, including poor feeding, mild decrease in activity, and a mild decrease in sensorium
Public Health Impact: Minimal public health concern

SVII.3.2 Presentation of the Missing Information

Not applicable.

Module SVIII Summary of the Safety Concerns

Table 9. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Toxicity in preterm neonates of lopinavir/ritonavir oral solution • Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease) • Lipid elevations
Important potential risks	• QT prolongation with supratherapeutic doses • PR prolongation at therapeutic dosing • Risks of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg
Missing Information	• Not applicable

IRIS = immune reconstitution inflammatory syndrome

Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine PV activities beyond adverse reactions reporting and signal detection include:

Specific adverse reaction follow-up questionnaire for risks of overdose from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg.

The questionnaire for overdose resulting from medication errors is part of routine pharmacovigilance follow-up processes, which includes use of pharmacovigilance questionnaires for follow-up of missing information. The questionnaire includes essentially

routine follow-up questions as well as tables for ease of data entry. Through routine pharmacovigilance follow-up processes, two attempts will be made to gather additional information using the questionnaire for spontaneous reports of overdose resulting from medication errors.

Other forms of routine PV activities for lopinavir/ritonavir – special surveillance

Not applicable.

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

Study Name 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					
Not applicable					

Part IV: Plans for Post-Authorization Efficacy Studies

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

No additional risk minimization measures are planned; routine risk minimization measures for the safety concerns are presented in the following table.

Table 10. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Toxicity in preterm neonates of lopinavir/ritonavir oral solution	Routine risk communication: SmPC Section 4.2 - Posology and method of administration, including dosing instruction for oral solution based on infant's body surface area (BSA) and body weight for accurate dosing to avoid toxicity from excipients SmPC Section 4.4 - Special warnings and precautions for use, regarding particular risk of toxicity in relation to the amount of alcohol and propylene glycol contained in lopinavir/ritonavir oral solution SmPC Section 4.4 – Monitoring instructions for infants for toxicity Patient information leaflet (PIL) Section 2 - What you need to know before you or your child takes lopinavir/ritonavir including important information about some of the ingredients of lopinavir/ritonavir. PIL Section 3 - How to take lopinavir/ritonavir, including important instruction to accurately dose infants and children. Routine risk minimization activities recommending specific clinical measures to address toxicity in preterm neonates of lopinavir/ritonavir oral solution: Close monitoring instruction for infants for toxicity related to lopinavir/ritonavir oral solution is provided in Section 4.4 <u>Other routine risk minimization measures:</u> • Prescription only medicine • Use of treatment should be initiated and supervised by specialists

Safety Concern	Routine Risk Minimization Activities
Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)	Routine risk communication: SmPC Section 4.4 - Special warnings and precautions for use, regarding patients at risk of immune reconstitution informatory syndrome (IRIS) PIL Section 2 - What you need to know before you or your child takes lopinavir/ritonavir, included information on symptoms of inflammation or autoimmune disorders after anti-HIV treatment is started Routine risk minimization activities recommending specific clinical measures to address Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease): • Information on inflammatory reaction to asymptomatic or residual opportunistic infections with relevant examples of these conditions is included in Section 4.4. • The evaluation of inflammatory conditions and treatment as necessary has been provided are included in Section 4.4. <u>Other routine risk minimization measures:</u> • Prescription only medicine • Use of treatment should be initiated and supervised by specialist
Lipid elevations	Routine risk communication: SmPC Section 4.4 - Special warnings and precautions for use, regarding increase blood levels of lipids during antiretroviral therapy. PIL- Section 4.0 - Informs patients that there may be an increase in levels of blood lipids and glucose and that their doctor will test for these changes. Routine risk minimization activities recommending specific clinical measures to address Lipid elevations: • Information to monitor blood lipids during treatment using HIV guideline is provided in Section 4.4. Lipid disorders should be managed as clinically appropriate. • Information on the appropriate lipid-lowering agents and lopinavir/ritonavir and important DDIs - lipid-lowering agents interactions are provided in Section 4.5 • Information on testing of the blood to check for lipid changes is included in PIL Section 4 <u>Other routine risk minimization measures:</u> • Prescription only medicine • Use of treatment should be initiated and supervised by specialists

Safety Concern	Routine Risk Minimization Activities
QT prolongation with supratherapeutic doses	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address QT prolongation with supratherapeutic doses: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists
PR prolongation at therapeutic dosing	Routine risk communication: SmPC Section 4.4 - Special warnings and precautions for use, regarding patients' pre-existing conditions for PR prolongation while taking lopinavir/ritonavir Routine risk minimization activities recommending specific clinical measures to address PR prolongation at therapeutic dosing: Information regarding conditions including the use of certain medications or patient's medical conditions which increase the risk of PR prolongation is provided in SmPC Section 4.4 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists

Safety Concern	Routine Risk Minimization Activities
Risks of overdose from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg	Routine risk communication: SmPC Section 4.2 - Posology and method of administration, including dosing instruction for oral solution based on infant's BSA and body weight for accurate dosing SmPC Section 4.9 – overdose including general information on unintended overdoses in preterm neonates and treatment of overdose PIL Section 2 - What you need to know before you or your child takes lopinavir/ritonavir, including important information about some of the ingredients of lopinavir/ritonavir PIL Section 3 - How to take lopinavir/ritonavir, including important instruction to accurately dose the infants and children. Routine risk minimization activities recommending specific clinical measures to address risks of overdose from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg: • Instruction on accurate dosing based on BSA and body weight for infants and children is provided in Section 4.2 • Instructions to minimize medication errors and overdose leading to potential propylene glycol and ethanol toxicity during dosing and dispensing for infants and children are provided in Section 4.4 • Close monitoring instruction for infants for toxicity related to lopinavir/ritonavir oral solution is provided in Section 4.4 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Since overdosing is a potential risk when small volumes of lopinavir/ritonavir oral solution are administered to young children with a 5-mL syringe, to mitigate this risk, a smaller volume (2 mL/2.5 mL) oral dosing syringe is available to measure lower doses.

BSA = body surface area; PIL = patient information leaflet; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimization Measures

Routine risk minimization activities as describe in Part V.1 are sufficient to manage the safety concerns of lopinavir/ritonavir.

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table 11. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Toxicity in preterm neonates of lopinavir/ritonavir oral solution	Routine risk minimization measures: SmPC Section 4.2 - Posology and method of administration, including dosing instruction for oral solution based on infant's BSA and body weight for accurate dosing to avoid toxicity from excipients SmPC Section 4.4 - Special warnings and precautions for use, regarding particular risk of toxicity in relation to the amount of alcohol and propylene glycol contained in lopinavir/ritonavir oral solution SmPC Section 4.4 – Monitoring instructions for infants for toxicity PIL Section 2 - What you need to know before you or your child takes lopinavir/ritonavir including important information about some of the ingredients of lopinavir/ritonavir. PIL Section 3 - How to take lopinavir/ritonavir, including important instruction to accurately dose infants and children. Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activity: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease)	Routine risk communication: SmPC Section 4.4 - Special warnings and precautions for use, regarding patients at risk of immune reconstitution informatory syndrome (IRIS) PIL Section 2 - What you need to know before you or your child takes lopinavir/ritonavir, included information on symptoms of inflammation or autoimmune disorders after anti-HIV treatment is started Routine risk minimization activities recommending specific clinical measures to address Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease): • Information on inflammatory reaction to asymptomatic or residual opportunistic infections with relevant examples of these conditions is included in Section 4.4. • The evaluation of inflammatory conditions and treatment as necessary has been provided are included in Section 4.4. Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activity: None
Lipid elevations	Routine risk communication: SmPC Section 4.4 - Special warnings and precautions for use, regarding increase blood levels of lipids during antiretroviral therapy. PIL- Section 4.0 - Informs patients that there may be an increase in levels of blood lipids and glucose and that their doctor will test for these changes. Routine risk minimization activities recommending specific clinical measures to address Lipid elevations: • Information to monitor blood lipids during treatment using HIV guideline is provided in Section 4.4. Lipid disorders should be managed as clinically appropriate. • Information on the appropriate lipid-lowering agents and lopinavir/ritonavir and important DDIs - lipid-lowering agents interactions are provided in Section 4.5	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activity: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Information on testing of the blood to check for lipid changes is included in PIL Section 4 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists	
QT prolongation with supratherapeutic doses	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address QT prolongation with supratherapeutic doses: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activity: None
PR prolongation at therapeutic dosing	Routine risk communication: SmPC Section 4.4 - Special warnings and precautions for use, regarding patients' pre-existing conditions for PR prolongation while taking lopinavir/ritonavir Routine risk minimization activities recommending specific clinical measures to address PR prolongation at therapeutic dosing: Information regarding conditions including the use of certain medications or patient's medical conditions which increase the risk of PR prolongation is provided in SmPC Section 4.4 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activity: None
Risk of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg	Routine risk communication: SmPC Section 4.2 - Posology and method of administration, including dosing instruction for oral solution based on infant's BSA and body weight for accurate dosing SmPC Section 4.9 – overdose including general information on unintended overdoses in preterm neonates and treatment of overdose	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: AE Follow-up questionnaire

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	PIL Section 2 - What you need to know before you or your child takes lopinavir/ritonavir, including important information about some of the ingredients of lopinavir/ritonavir PIL Section 3 - How to take lopinavir/ritonavir, including important instruction to accurately dose the infants and children. <u>Routine risk minimization activities recommending specific clinical measures to minimize risk of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg:</u> • Instruction on accurate dosing based on BSA and body weight for infants and children is provided in Section 4.2 • Instructions to minimize medication errors and overdose leading to potential propylene glycol and ethanol toxicity during dosing and dispensing for infants and children are provided in Section 4.4 • Close monitoring instruction for infants for toxicity related to lopinavir/ritonavir oral solution is provided in Section 4.4 <u>Other routine risk minimization measures:</u> • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Since overdosing is a potential risk when small volumes of lopinavir/ritonavir oral solution are administered to young children with a 5-mL syringe, to mitigate this risk, a smaller volume (2 mL/2.5 mL) oral dosing syringe is available to measure lower doses.	Additional PV activity: None

AE = adverse event; BSA = body surface area; DDI = Drug-drug interaction; HIV = human immunodeficiency virus; IRIS = Immune reconstitution inflammatory syndrome; PIL = patient information leaflet; PV = pharmacovigilance; SmPC = Summary of Product Characteristics

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Kaletra/Aluvia (lopinavir/ritonavir)

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

lopinavir/ritonavir's summary of product characteristics (SmPCs) and its package leaflets (PLs) give essential information to health care professionals and patients on how lopinavir/ritonavir should be used.

This summary of the RMP for lopinavir/ritonavir should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

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

I The Medicine and What it Is Used For

Lopinavir/ritonavir oral solution is indicated for treatment of HIV-1 infected adults, adolescents and children 14 days of age and older (see SmPC for the full indication). Lopinavir/ritonavir 200 mg/100 mg film-coated tablets and Lopinavir/ritonavir 100 mg/25 mg film-coated tablets are indicated for treatment of HIV-1 infected adults, adolescents, and children above the age of 2 years (see SmPC for the full indication). Lopinavir/ritonavir contains lopinavir/ritonavir as the active substance and it is given by mouth.

Further information about the evaluation of lopinavir/ritonavir benefits can be found in lopinavir/ritonavir's EPAR, including in its plain-language summary, available on the EMA website.

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

Important risks of lopinavir/ritonavir, together with measures to minimize such risks and the proposed studies for learning more about lopinavir/ritonavir'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 health care 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 (e.g., 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 PV activities.

If important information that may affect the safe use of lopinavir/ritonavir is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of lopinavir/ritonavir are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. 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 lopinavir/ritonavir. 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 (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Toxicity in preterm neonates of lopinavir/ritonavir oral solution. • Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves' disease). • Lipid elevations.
Important potential risks	• QT prolongation with supratherapeutic doses. • PR prolongation at therapeutic dosing. • Risks of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg
Missing information	• Not applicable

II.B Summary of Important Risks

Important identified risk: Harm from the alcohol and propylene glycol contained in lopinavir/ritonavir oral solution in pre-mature newborn babies. **(Toxicity in preterm neonates of lopinavir/ritonavir oral solution)**	
Evidence for linking the risk to the medicine	Lopinavir/ritonavir oral solution contains: • alcohol – 42%, which is 356.3 mg per mL. • propylene glycol – 15%, which is 152.7 mg per mL. These can cause serious and life threatening side effects in premature newborn babies.
Risk factors and risk groups	Preterm neonates (neonates before a postmenstrual age [first day of the mother's last menstrual period to birth plus the time elapsed after birth] of 42 weeks and before a postnatal age of at least 14 days).
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 - Posology and method of administration, including dosing instruction for oral solution based on infant's BSA and body weight for accurate dosing to avoid toxicity from excipients SmPC Section 4.4 - Special warnings and precautions for use, regarding particular risk of toxicity in relation to the amount of alcohol and propylene glycol contained in lopinavir/ritonavir oral solution Close monitoring instruction for infants for toxicity related to lopinavir/ritonavir oral solution is provided in Section 4.4 of SmPC Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists

Important identified risk: Immune Reconstitution Inflammatory Syndrome (IRIS) manifesting as autoimmune disorders – such as Graves' disease	
Evidence for linking the risk to the medicine	HIV treatment usually improves the ability of the immune system to fight infections. This improvement can make the body over-respond to infections in the body which have previously been hidden infections. • This is called IRIS or 'Immune Reconstitution Inflammatory Syndrome.' • Patients with IRIS could be at a higher risk of getting some illnesses called 'auto-immune disorders:' • This is where your immune system attacks healthy parts of your body • This includes hyperthyroidism (Graves' disease).
Risk factors and risk groups	Patients with pre-existing infections and low baseline CD4 cell counts.
Risk minimization measures	Routine risk minimization: SmPC Section 4.4 - Special warnings and precautions for use, regarding patients at risk of immune reconstitution informatory syndrome (IRIS), inflammatory reaction to asymptomatic or residual opportunistic infections with relevant examples of these conditions. Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist

Important identified risk: Increase in fat (lipid) levels in the blood (Lipid elevations)	
Evidence for linking the risk to the medicine	Increased fats (lipids) in the blood have been linked with 'PI' HIV medicines like lopinavir/ritonavir. There are several causes of this: • the HIV infection itself • infections because of the body's immune system being less able to fight infections • treatments for HIV • the stage of the HIV • any heart problems
Risk factors and risk groups	Particular caution should be paid to patients with high values at baseline and with history of lipid disorders.

Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 - Special warnings and precautions for use, regarding: • increase blood levels of lipids during antiretroviral therapy. • Information to monitor blood lipids during treatment using HIV guideline. Lipid disorders should be managed as clinically appropriate. Information on the appropriate lipid-lowering agents and lopinavir/ritonavir and important DDIs - lipid-lowering agents interactions are provided in Section 4.5 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists
Important potential risk: QT prolongations with supratherapeutic doses	
Evidence for linking the risk to the medicine	QTcF interval was evaluated in a study in 39 healthy adults taking either 400/100 mg lopinavir/ritonavir twice daily or 800/200 mg lopinavir/ritonavir twice daily. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec. As noted in the prescribing information, through drug-drug interactions lopinavir/ritonavir can increase concentrations of certain co-administered medicinal products, come of which are known to cause QT prolongation, and this may result in an increase of their associated cardiac adverse reactions. Health care professionals should take care when prescribing lopinavir/ritonavir and medicines that can cause QT prolongation. These include: • chlorpheniramine – for allergies • quinidine – for heart beat problems • antibiotics such as erythromycin and clarithromycin • antibacterials called 'fluoroquinolones' such as moxifloxacin and ciprofloxacin
Risk factors and risk groups	Individuals with congenital long QT syndrome, hypokalemia, or who may be taking concomitant drugs that have associated QTc prolongation as an adverse event.
Risk minimization measures	Routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists

Important potential risk: PR prolongation at therapeutic dosing	
Evidence for linking the risk to the medicine	Lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some patients (text in CCDS). Rare reports of second- or third-degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. Lopinavir/ritonavir should be used with caution in such patients.
Risk factors and risk groups	Individuals with pre-existing structural heart disease and pre-existing conduction system abnormalities or who are taking concomitant drugs that have PR prolongation as an associated adverse event. First-degree AV block, defined as prolongation of the PR interval on the surface electrocardiogram, is not an uncommon finding on electrocardiographic screening of asymptomatic young individuals. Prevalences of 0.65% to 1.1% have been reported. In the majority of cases the PR prolongation may be rendered normal by autonomic intervention. Long-term follow-up studies have indicated that although the risk of subsequent coronary artery disease (CAD) may be slightly increased, the risk of sudden death, syncope, or advanced AV block is not (Bexton 1984).
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 - Special warnings and precautions for use, regarding patients' pre-existing conditions for PR prolongation while taking lopinavir/ritonavir <u>Other routine risk minimization measures:</u> • Prescription only medicine • Use of treatment should be initiated and supervised by specialists
Important potential risk: Errors with dosing that cause too much lopinavir/ritonavir oral solution to be swallowed by infants. **(Risk of overdose resulting from medication errors with lopinavir/ritonavir oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg)**	
Evidence for linking the risk to the medicine	As with all liquid medicines administered with a syringe, it is possible to draw up too much medicine into the syringe and administer an overdose of medicine. Lopinavir/ritonavir oral solution contains ingredients called ethanol and propylene glycol, which may be harmful when given in excessive amounts to young children. It is extremely important that the correct dose of lopinavir/ritonavir oral solution is given to young children. Children should attend all of their HIV clinic appointments so that the dose of HIV medication can be adjusted as they grow and gain weight.

Risk factors and risk groups	Infants from 2 to 9 weeks of age and weighing less than 3.8 kg
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 - Posology and method of administration, including dosing instruction for oral solution based on infant's BSA and body weight for accurate dosing SmPC Section 4.9 – overdose including general information on unintended overdoses in preterm neonates and treatment of overdose Instruction on accurate dosing based on BSA and body weight for infants and children is provided in Section 4.2 Instructions to minimize medication errors and overdose leading to potential propylene glycol and ethanol toxicity during dosing and dispensing for infants and children are provided in Section 4.4 Close monitoring instruction for infants for toxicity related to lopinavir/ritonavir oral solution is provided in Section 4.4 Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • A smaller volume (2 mL/2.5 mL) oral dosing syringe is available to measure lower doses.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorization

Not applicable.

II.C.2 Other studies in post-authorisation development plan

Not applicable.

Part VII: Annexes

Annex 1. EudraVigilance Interface

Annex 2. Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Table 12. Completed and Ongoing Studies

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Link to Report
Da Silva B, Tschampa J, Beron J, et al. Evaluation of myocardial infarction and coronary artery disease in subjects taking lopinavir/ritonavir: a study using clinical trial and pharmacovigilance databases. Int J Clin Pharmacol Ther. 2012;50:391-402. Epub 2012 May 22. Category 3	Address safety concerns of Cardiovascular risk (MI) with cART	Publish MI and CAD data from lopinavir/ritonavir clinical trials and PV database	Submitted to EMA as appendix 38 in lopinavir/ritonavir RMP Edition 6 dated August 2012 (eCTD sequence 0088). The EMA outcome fax (EMA/CHMP/797370/2012) following review of lopinavir/ritonavir RMP Edition 6 was received on 18Dec2012.

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Link to Report
UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC) 2004 – 2014 (Tookey 2016) Category 3	Primary objective: To compare the overall preterm delivery rates between the lopinavir/ritonavir exposed and non lopinavir/ritonavir exposed pregnant women reported in the NSHPC with a delivery between 2004 and 2014 Secondary objectives: To compare preterm delivery rates according to cART type (lopinavir/ritonavir based; other PI-based; NNRTI-based; triple NRTI-based; other cART); To describe and compare severity of preterm delivery across treatment groups (classified as extreme/severe vs. moderate/late preterm); To compare baseline characteristics of the lopinavir/ritonavir exposed and the lopinavir/ritonavir unexposed groups	Conduct an analysis of preterm delivery rates of lopinavir/ritonavir exposed pregnant women compared with lopinavir/ritonavir unexposed pregnant women in NSHPC database	Study report dated 10Dec2015 provided in Appendix 9 of lopinavir/ritonavir RMP Edition 7.1 dated Apr2016. Following assessment of PSUR 16, lopinavir/ritonavir RMP Version 7.1 was submitted to the EMA with the responses to questions in Apr2016 (eCTD sequence 0156).

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Link to Report
Pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in HIV 1- infected children Category 3	To investigate the PKs, safety, and efficacy of BID versus QD dosing of lopinavir/ritonavir tablets dosed by weight as part of cART in HIV-1–infected children.	Safety of the lopinavir/ritonavir 100/25 mg tablet in the paediatric population	The 24-week interim study report was submitted to the EMA on 05Sept2014 (Type II variation EMEA/H/C/000368/II/0148). The date of the European Commission Decision is 30 March 2015. A final study report for the 48-week study is not available. AbbVie has access to the published study results only (Bastiaans 2014, PENTA 2015). EMA was informed in variation VII-0148 that AbbVie would submit the published 48-week PENTA 18 study results when they are available in fulfilment of the post-authorisation measure EMEA (Additional PV activity in the Risk Management Plan). The results were submitted in Sept2016 (variation EMEA/H/C/000368/II/0160; eCTD sequence 0160).

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Link to Report
P19-106: EPPICC study assessing the safety and efficacy of Kaletra oral solution in children aged 14 days to 2 years with HIV-1 infection in Europe PASS Category 3	Study objectives, in children aged under 2 years, are to: i. describe the characteristics of all children treated with Kaletra (including off-label use) in the EPPICC network in the EMA countries within Europe at or after the approval date 26 July 2017 ii. assess the appropriateness of Kaletra dose for weight or body surface area iii. evaluate the safety and tolerability of Kaletra by the following: • describe clinical adverse events including propylene glycol or ethanol toxicity (see Annex 3 for further details)	Safety of chronic exposure to propylene glycol and ethanol in patients 14 days to 2 years of age	Completed with submission of final P19-106 study report, which was appended to PAM-LEG 121.4 response of 25 September 2021 (EMA procedure number EMA/H/C/000368/LEG 121.4; Assessment report dated 27 January 2022; EMA reference: EMA/PRAC/CHMP/23418/2022). The P19-106 study report will also be submitted to EMA as a type 2 variation together with RMP version 10.0 in May 2022. The final study report concluded, "The safety outcomes analysed in this report are consistent with the known safety profile of LPV/r as specified in the LPV/r product information. No new safety concerns related to LPV/r oral solution were identified. The study is limited by the small sample size with limited follow-up data included up to 2 years of age among children on LPV/r."

BID = twice daily; C = Concomitant; CAD = coronary artery disease; cART = combination antiretroviral therapy; CHMP = Committee for Medicinal Products for Human Use; eCTD = electronic common technical document; EMA = European Medicines Agency; HIV-1 = human immunodeficiency virus type 1; EPPICC = European Pregnancy and Paediatric HIV Cohort Collaboration; MI= myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NSHPC = National Study of HIV in Pregnancy and Childhood; PASS = post-authorization safety study; PENTA = Paediatric European Network for Treatment of AIDS; PI = protease inhibitor; PK = pharmacokinetic(s); PSUR = periodic safety update report; PV = pharmacovigilance; QD = once daily; RMP = risk management plan; UK = United Kingdom; vs. = versus

Title	A European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) study assessing the safety and effectiveness of Kaletra® oral solution in children aged 14 days to 2 years with HIV-1 infection in Europe.
Version identifier of the final study report	Year 3 report V2.0 (25th September 2021)
Date of last version of the final study report	15 September 2020
EU PAS register number	EUPAS32607
Active substance	Lopinavir and ritonavir (LPV/r)
Medicinal product	Kaletra® oral solution
Product reference	EMEA/H/C/000368
Procedure number	Post Authorisation Measure LEG 121.3
Marketing authorisation holder(s)	AbbVie Deutschland GmbH & Co. KG
Joint PASS	No
Research question and objectives	Study objectives (in children aged <2 years): 1. Describe characteristics of children treated with LPV/r oral solution (including off-label use) in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) network in European countries regulated by the European Medicines Agency (EMA) at or after EMA approval date (26 July 2017). 2. Assess appropriateness of LPV/r oral solution dose for weight (or body surface area) at LPV/r initiation using AbbVie Kaletra® oral solution Summary of Product Characteristics (SmPC) as reference. 3. Evaluate safety and tolerability of LPV/r oral solution: a. Describe timing and reasons for discontinuation (especially for toxicity). b. Describe clinical adverse events (AEs) whilst on LPV/r and up to 3 months after discontinuation, especially relating to toxicity due to LPV/r (active ingredient), propylene glycol or ethanol. c. Assess incidence of Division of AIDS (DAIDS) grade 1-4 laboratory results. 4. Assess immunological and virological responses to LPV/r.
Country(-ies) of study	**Current report**: Belgium, Denmark, Greece, Italy, Poland, Spain, UK and Ireland.
AbbVie reference number	P19-106
Authors	[redacted]; on behalf

	of the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) Medical Research Council Clinical Trials Unit at UCL, 90 High Holborn, London WC1V 6LJ Main switchboard: +44 (0)20 7670-4700

Market authorisation holder(s)

Market authorisation holder(s)	AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany Email: regulatory_affairs.de@abbvie.com
MAH contact persons	[redacted] Western Europe Regulatory Affairs AbbVie Ltd. AbbVie House, Vanwall Business Park, Maidenhead SL6 4UB, United Kingdom Tel: [redacted] Email: [redacted] [redacted] AbbVie Pharmacovigilance and Patient Safety [redacted] [redacted] AbbVie Pharmacovigilance and Patient Safety [redacted] [redacted] AbbVie Pharmacovigilance and Patient Safety [redacted] For matters pertaining to the contract: [redacted] For matters pertaining to payments: [redacted], cc [redacted]

Table of Contents

1. Abstract

Title:	A European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) study assessing the safety and effectiveness of Kaletra® oral solution in children aged 14 days to 2 years with HIV-1 infection in Europe
Keywords:	Lopinavir/ritonavir, safety, HIV, cohort study, paediatrics
Rationale and Background:	Kaletra (LPV/r) was licensed for use in children living with HIV aged ≥14 days in Europe on 26 July 2017. It has high content of ethanol and propylene glycol which can cause toxicity in very young children. Use and safety of LPV/r in children aged <2 years was assessed using data from EPPICC.
Research Question and Objectives:	What is the short and medium term safety profile of LPV/r in children aged <2 years with HIV-1 infection? The study objectives are to: 1. Describe characteristics of children treated with LPV/r oral solution (including off-label use) in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) network in European countries regulated by the European Medicines Agency (EMA) at or after EMA approval date (26 July 2017). 2. Assess appropriateness of LPV/r oral solution dose for weight (or body surface area) at LPV/r initiation using AbbVie Kaletra® oral solution Summary of Product Characteristics (SmPC) as reference. 3. Evaluate safety and tolerability of LPV/r oral solution: a. Describe timing and reasons for discontinuation (especially for toxicity). b. Describe clinical adverse events (AEs) whilst on LPV/r and up to 3 months after discontinuation, especially relating to toxicity due to LPV/r (active ingredient), propylene glycol or ethanol. c. Assess incidence of Division of AIDS (DAIDS) grade 1-4 laboratory results. 4. Assess immunological and virological responses to LPV/r.
Study Design:	Analysis of pseudo-anonymised longitudinal patient data for children initiating LPV/r oral solution aged <2 years at/after the EMA approval date
Setting:	Children with HIV-1 infection in Europe

Subjects and study size, including dropouts:	All children initiating LPV/r aged <2 years at/after the EMA approval date and followed in participating centres.
Variables and Data Sources	Data from 8 cohorts across 7 European countries: demographic factors, HIV medical history, ART history, AIDS events, death, weight, CD4 cell counts, HIV viral loads, laboratory test results, clinical AEs, discontinuations of LPV/r. Children were followed from LPV/r initiation with data censored at earliest of: last visit, death, 3 months after discontinuation of LPV/r oral solution or 2nd birthday.
Results:	42 patients received LPV/r oral solution while aged <2 years at/after EMA approval date, including 9 newly reported this year. Thirteen were on a licensed dose, 13 an unlicensed dose, 1 was off-label use (age <14 days) and 15 were missing weight/dose at LPV/r start. At LPV/r start, median [IQR] age was 6.9 [2.3-14.4] months and 39/42(93%) were treatment naïve. Overall, 12 patients (33% of 36 with laboratory data) experienced ≥1 grade 3/4 events across 10 laboratory markers. Six clinical AEs in three patients (1 in licensed dose group, 2 in unlicensed) were considered causally related to LPV/r (all previously reported). Three of these were serious; none led to discontinuation of LPV/r. At 6(n=20) and 12(n=16) months after start of LPV/r, ≥80% were virally suppressed (≤1000 copies/mL). 5 (12%) patients discontinued LPV/r while aged<2 years, including one due to lack of effectiveness and 1 due to toxicity.
Discussion:	In general, LPV/r, both licensed and unlicensed doses, appears well-tolerated in this population. While some laboratory AEs occurred relatively frequently, safety outcomes reported are consistent with the safety profile specified in the LPV/r SmPC.
Marketing authorisation holder:	AbbVie
Names and affiliation of principal investigators:	Edith Milanzi, PhD; Charlotte Jackson, PhD; Ali Judd, PhD; Carlo Giaquinto, MD; Intira Jeannie Collins, PhD; on behalf of the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)

2. List of abbreviations

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
AMY	Pancreatic amylase
ANC	Absolute neutrophil count
APT	Alkaline phosphatase
ART	Antiretroviral Therapy
AST	Aspartate aminotransferase
ATV	Atazanavir
cART	Combination ART
CDC	Centers for Disease Control and Prevention
CD4	CD4 T-cell count
CHOL	Total cholesterol
CI	Confidence Interval
DAIDS	Division of AIDS
DRV	Darunavir
EFV	Efavirenz
EMA	European Medicines Agency
EPPICC	European Pregnancy and Paediatric Infections Cohort Collaboration
FBG	Fasting plasma glucose
FTC	Emtricitabine
GI	Gastro-intestinal
GGT	Gamma-glutamyl transferase
HICDEP	HIV Cohorts Data Exchange Protocol
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HIV	Human Immunodeficiency Virus
IRIS	Immune Reconstitution Inflammatory Syndrome
LDL	Low density lipoprotein
LIP	Lipase
LPV/r	Lopinavir/ritonavir

MAH	Marketing Authorisation Holder
NIH	National Institutes of Health
NRTI	Nucleoside Reverse Transcriptase Inhibitor
Non-FBG	Non-fasting plasma glucose
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PHOS	Serum phosphate
PI	Protease Inhibitor
RAL	Raltegravir
SAE	Serious Adverse Event
S-Ca	Serum calcium
S-CREAT	Serum creatinine
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TBIL	Total bilirubin
TDF	Tenofovir Disoproxil Fumarate
TRIG	Triglycerides
VL	HIV-1 RNA Viral Load
ZDV	Zidovudine

3. Contributing Cohort Investigators

[redacted] **and** [redacted] (Collaborative HIV Paediatric Study (CHIPS) and National Study of HIV in Pregnancy and Childhood (NSHPC), UK/Ireland)

[redacted] (CoRISPE-Cat, Spain)

[redacted] **and** [redacted] (CoRISPE-S, Spain)

[redacted] (Denmark Copenhagen cohort)

[redacted] (Greece cohort)

[redacted] **and** [redacted] (Italian Register for HIV infection in children)

[redacted] (Paediatric cohort, Poland)

[redacted] (Hospital St Pierre Cohort, Belgium)

4. Other responsible parties

[redacted]**:** [redacted]

5. Milestones

Milestone	Planned date	Actual date	Comments
Preliminary report draft sent to AbbVie	Mid December 2018	20 December 2018	Sent following completion of contracts
Year 1 interim report submission to the EMA (as Appendix A of the AbbVie LEG report)	25 January 2019	24 January 2019	
Year 1 report to EMA	25 September 2019	27 September 2019	
Year 2 report to EMA	25 September 2020	22 September 2020	
Year 3 report to EMA	25 September 2021		

6. Rationale and background

On 26 July 2017, the European Commission extended the indication for LPV/r (Kaletra®) (80mg + 20mg)/ml oral solution to include children aged 14 days or older for the treatment of HIV-1 infection. This medication has a high content of ethanol and propylene glycol. The SmPC includes a warning regarding its use in very young children, because chronic exposure to propylene glycol and/or ethanol can lead to toxicity (1). The EMA has also highlighted concerns regarding the potential for medication errors since they could lead to overdose of these excipients. Dosing errors could also lead to lack of effectiveness and/or viral resistance, which also is of concern due to potentially suboptimal pharmacokinetics of the active drug in young children receiving LPV/r oral solution. Research suggests that viral resistance occurs less frequently in children on protease inhibitor (PI)-based regimens than non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (2, 3).

In Europe, several established, prospective observational cohort studies of children and adolescents with HIV-1 participate in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) (formerly known as the European Pregnancy and Paediatric HIV Cohort Collaboration). The EPPICC network currently includes 18 cohorts from 16 countries (15 European countries and Thailand) and undertakes studies which assess the safety and effectiveness of antiretroviral therapy in children and adolescents living with HIV in routine care in Europe (4-6).

7. Research question and objectives

The overall aim of this study is to use EPPICC data to answer the following question:

What is the safety and effectiveness of LPV/r (Kaletra®) oral solution in children <2 years of age with HIV-1 infection in routine care in Europe?

The study objectives are to:

1. Describe characteristics of children treated with LPV/r oral solution (including off-label use) in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) network in European countries regulated by the European Medicines Agency (EMA) at or after EMA approval date (26 July 2017).
2. Assess appropriateness of LPV/r oral solution dose for weight (or body surface area) at LPV/r initiation using the AbbVie Kaletra® oral solution Summary of Product Characteristics (SmPC) as reference.
3. Evaluate safety and tolerability of LPV/r oral solution:
    a. Describe timing and reasons for discontinuation (especially for toxicity).

b. Describe clinical adverse events (AEs) whilst on LPV/r and up to 3 months after discontinuation, especially relating to toxicity due to LPV/r (active ingredient), propylene glycol or ethanol.
c. Assess incidence of Division of AIDS (DAIDS) grade 1-4 laboratory results.

4. Assess immunological and virological responses to LPV/r.

8. Amendments and updates

The previous report (Year 2 Report, submitted in September 2020) contained data on 33 patients from 7 countries. This current Year 3 final report includes data on these 33 children and 9 new patients, providing a total of 42 children from 7 countries within EPPICC.
Cohorts have also been able to correct previously submitted data where necessary and, where relevant, updated data showing changes from previous year's reports have been noted in the text.

9. Research methods

9.1. Study design

This study pooled individual patient data from longitudinal observational cohorts participating in EPPICC. EPPICC conducts epidemiological research on the characteristics, treatment and outcomes of pregnant women living with HIV and their infants, and children living with HIV, as well as HIV negative children exposed to HIV in utero. The participating cohorts record the treatment and care of children living with HIV in routine clinical practice. This study therefore provides data on the effect of LPV/r in "real world" settings.

9.2. Setting

The following 8 EPPICC paediatric cohorts (who participate in EPPICC) contributed data to this report:

- Copenhagen Cohort, Denmark
- CoRISPE-Cat, Catalonia, Spain
- CoRISPE-S, Spain
- Collaborative HIV Paediatric Study (CHIPS) and National Surveillance of HIV in Pregnancy and Childhood (NSHPC), UK/Ireland
- Italian Register for HIV infection in children, Italy
- Paediatric Cohort, Greece
- Polish Paediatric Cohort, Poland
- St Pierre Cohort, Belgium

It should be noted that individual patient adverse events/reactions attributed to LPV/r oral solution (and other drugs) are reported by treating physicians in accordance with country specific and European law.

Each contributing cohort has local ethics approval or exemption for participation in this study and has complied with local regulatory requirements (where needed). All data have been processed in accordance with the General Data Protection Regulation (GDPR).

9.3 Subjects

To be eligible for inclusion in this study, patients had to be:

1. Enrolled in an EPPICC cohort.
2. Under 2 years of age and taking LPV/r oral solution on or after 26 July 2017 (the EMA approval date for use of LPV/r (Kaletra®) oral solution in children aged 14 days to <2 years).

9.4. Variables

Data collected on patients receiving LPV/r oral solution included (where available) demographic data (date of birth, sex, ethnicity and mode of infection), Centers for Disease Control and Prevention (CDC) HIV Disease stage, CDC events (7) during follow-up, death during follow up, ART use (including start and stop dates, dosing and reasons for stopping), weight, height, HIV-1 viral load (RNA) and CD4 measurements (absolute cell count and %), hepatitis B (antigen) and C (antibody) co-infection status, reasons for off-label use (of LPV/r oral solution), laboratory test results (biochemistry and haematology), details of all clinical adverse events (AEs) and both reasons for and timing of discontinuations.

9.5. Data sources and measurement

Each participating cohort provided data according to a predefined data specification. The data specification for the study follows the HIV Cohorts Data Exchange Protocol (HICDEP) (http://www.hicdep.org). The HICDEP format is based on a relational structure and data are collected in a series of tables. A Standard Operating Procedure (SOP) was developed specifically for this study (Annex 1). HICDEP tables were included in the SOP together with the relevant look-up tables for the codes used.

Data were subjected to a battery of logical and consistency checks in order to assess accuracy and completeness. Any data queries arising were then discussed and resolved with the relevant cohort data managers, before data were pooled into a joint study database.

The database for this final Year 3 report was locked on 31 July 2021.

9.6. Bias

EPPICC cohorts vary widely with respect to national coverage. Some have complete coverage of all children diagnosed with HIV (e.g. CHIPS UK and Ireland cohort) whilst others are single large tertiary clinic cohorts, which include all children attending that clinic.

EPPICC cohorts include both children born in the country of care and those born abroad (commonly sub-Saharan Africa). In the past those born abroad (particularly those born outside Europe) tended to be older at first presentation to care in the reporting cohort and had survived the high mortality period of early infancy, perhaps without ART in their country of origin. However, more recently, children presenting from abroad are more likely to already be on ART than in the past.

Notwithstanding these issues, given that this report focuses on those aged <2 years of age, it is unlikely to introduce a major selection bias into this analysis.

9.7. Study size

This study aimed to include all children who meet the inclusion criteria within the participating cohorts in EPPICC. In this report, a total of 42 patients from 8 cohorts in 7 countries were included.

9.8. Data transformation

The definitions and coding of variables included in the EPPICC database are described in the SOP (Annex 1). Variables were categorized as follows: age at LPV/r start in months (<2, 2-<6, 6-<12, ≥12), HIV-1 RNA viral load (≤50, >50-400, >400-1000, >1000 c/mL) and time on LPV/r in months (<6, 6-<12, 12-<18 and 18-<24).

9.9 Statistical methods

9.9.1 Main summary measures

Counts, percentages, and medians (with interquartile ranges), person years of follow-up and rate of events (with 95% confidence intervals) are presented.

9.9.2 Main statistical methods

Classification of patients

Patients were categorised to a group based on their age, weight (or body surface area where height data were available), dose and dosing frequency on the day of first reported LPV/r oral solution exposure. The four groups are as follows:

- Group 1: Licensed: patients aged 14 days to <2 years initiating on a licensed dose
- Group 2: Unlicensed: patients aged 14 days to <2 years initiating on an unlicensed dose

- Group 3: Off-label, patients aged <14 days
- Group 4: Missing, patients aged 14 days to <2 years with missing weight and/or dose data at LPV/r initiation

Data on demographic characteristics, ART history, and adverse events occurring whilst on LPV/r oral solution were summarised for all patients combined and also separately for each of four groups, described below, where possible. Weight and height data were considered missing if there was no value recorded within one week prior to or following the LPV/r start date for patients <6 months old at initiation. For children ≥6 months old at LPV/r initiation this window was extended to +/- 4 weeks. Body surface area was used for dosage calculations where recent height data were available. If height data were missing, weight was used for calculating dosage received.

The dosage of LPV/r was calculated as per the Kaletra® oral solution SmPC recommendations:

Prescribed lopinavir dosage (mg/m^2) = Administered lopinavir dose (mg)/ Patient BSA (m^2)
Prescribed lopinavir dosage (mg/kg) = Administered lopinavir dose (mg)/ Patient Weight (kg)

Body surface area (BSA) was calculated as:

$$BSA(m^2) = \sqrt{\frac{height(cm) \times weight\ (kg)}{3600}}$$

The recommended LPV/r dosage (as defined in the Kaletra® SmPC) was used to determine whether patients were receiving a licensed dose at initiation. The SmPC recommended dosage varies with age as follows:

Patients aged 14 days to 6 months (twice daily dosing)

- Using weight: 16/4 mg/kg or
- Using BSA: 300/75 mg/m^2

Patients aged >6 months (twice daily dosing)

- Using weight: <15kg – 12/3 mg/kg
  : 15kg-40kg – 10/2.5 mg/kg or
- Using BSA: 230/75 mg/m^2

Patients were classified as on a licensed dose (Group 1) if the dose they received at LPV/r initiation was within +/- 20% of the recommended dose (as per the AbbVie Kaletra® oral solution SmPC).

LPV/r is not recommended in patients receiving rifampicin. In the event that patients were taking both drugs simultaneously they were classified as on an unlicensed dose (Group 2). Similarly, LPV/r administered in combination with nevirapine (NVP) or efavirenz (EFV) in patients <6 months of age is not recommended, and patients on these drugs in this age group were also classified as being on an unlicensed dose (Group 2).

Patients aged >6 months and taking concomitant EFV or NVP require an increased LPV/r dose of 300/75 mg/m^2 twice daily (which was used as the licensed dosage in these patients). Patients aged >6 months on concomitant EFV or NVP who did not receive the recommended dose increase were categorised as on an unlicensed dose (Group 2).

Patients initiating LPV/r oral solution aged <14 days were categorised as using LPV/r off-label (Group 3). The Kaletra® SmPC states this age recommendation is based on full-term births, defined as being born at 42 weeks gestation. Therefore, among children who started LPV/r aged under 4 months of age, their gestational age at birth (where data are available) plus age at start of LPV/r was taken into account when assigning them to a group. Infants initiating LPV/r oral solution when <44 weeks (gestational age at delivery + age at start of LPV/r) were categorised in the off-label group (Group 3). Patients were categorized to the missing weight/dose group (Group 4) if they were missing data on weight, dose or gestational age at delivery (if aged under 4 months at start of LPV/r) as lack of this data made it impossible to determine the compatibility of their dose with the SmPC recommendations.

Censoring

Patients were followed up from first LPV/r oral solution initiation until they were censored. Follow-up time was censored at the earliest of the following: date of last visit, death, 3 months after discontinuation of LPV/r oral solution or when the patient reached their 2nd birthday. Among children who experienced a clinical adverse event or a laboratory DAIDS grade ≥3 event while on LPV/r (or up to 3 months after discontinuation of LPV/r) and aged <2 years, further information on the outcome/resolution of that event (e.g. resolution date) was included until the patient reached 3 years of age.

Immunological and virological treatment response

CD4 and HIV viral load metrics are presented in Appendix 1, Table 3 for three time points relative to the date of LPV/r initiation: baseline, 6 months and 12 months. With the exception of viral load at baseline all values were the closest result within a window of +/- 3 months. Viral load and CD4

response at 6 and 12 months after start of LPV/r were reported among patients who remained on LPV/r and reached those timepoints and had a CD4 and viral load measurement available. For viral load at baseline only values prior to LPV/r initiation were reported (within 6 months for those ART naïve and 3 months otherwise). WHO immunosuppression for age at baseline was also reported and was categorized as follows (8):

- non-significant immunosuppression: CD4% >35% for children aged <1 year and >25% for children aged between ≥1 and <3 years,
- mild immunosuppression: CD4% 25−34% for children aged <1 year and 20−24% for children aged between ≥1 and <3 years,
- advanced immunosuppression: CD4% 20−24% for children aged <1 year and 15−19% for children aged between ≥1 and <3 years,
- severe immunosuppression: CD4% <20% for children aged <1 year and <15% for children aged between ≥1 and <3 years.

Laboratory adverse events

Data on the following laboratory tests were collected and analysed (Appendix 1, Table 4a-b): absolute neutrophil counts (ANC), total cholesterol (CHOL), triglycerides (TRIG), alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin (T-BIL), gamma-glutamyl transferase (GGT), fasting plasma glucose (FPG), non-fasting plasma glucose (non-FPG), pancreatic amylase (AMY), lipase (LIP), serum low-density lipoprotein (LDL), serum high-density lipoprotein (HDL), serum phosphate (PHOS), serum calcium (S-Ca) and serum creatinine (S-CREAT).

All laboratory values (with the exception of HDL and GGT) were classified according to the Division of AIDS (DAIDS) 2017 grading system for laboratory events (9). No DAIDS grading cut-offs have been developed for HDL and GGT. GGT was graded using the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.03) (10) as follows:

- Grade 1 (mild): > ULN-2.5 x ULN
- Grade 2 (moderate): >2.5 ULN-5.0 x ULN
- Grade 3 (severe): >5.0-20.0 x ULN
- Grade 4 (life-threatening): > 20.0 x ULN

HDL values were categorised using the US National Institutes of Health (NIH) National Heart, Lung and Blood Institute guidelines (11):

- ‘Acceptable’ (>45 mg/dL)
- ‘Borderline’ (40-45 mg/dL)

- ‘Low’ (<40 mg/dL)

For each test type, results by severity (DAIDS grade 1, 2, and grades 3 and 4 combined) were presented. All patients with any laboratory data recorded from start of LPV/r to 30 days after discontinuation of LPV/r or censoring date (as described above) were included in the laboratory analysis of DAIDS events while on LPV/r (from Appendix 1, Table 4a-b). If a patient stopped LPV/r for <30 days then subsequently restarted while age <2 years, this was considered to be part of the same episode on the drug. If a patient stopped LPV/r for >30 days, then any subsequent LPV/r exposure while aged <2 years was considered as a new eligible episode and included in the analysis.

Information provided for each laboratory test (Appendix 1, Table 4a) included the total number of: tests, patients, episodes and DAIDS events, reported separately for grades 1, 2 and ≥3 and Group. A patient with progressively more severe results reported for the same laboratory test during each episode on LPV/r would have their most severe grade reported. For patients with multiple episodes on LPV/r, each episode was considered independently for the purposes of counting DAIDS graded laboratory events.

Where available, laboratory data were captured in the 12 months prior to LPV/r initiation. Where DAIDS graded laboratory values were recorded in the 3 months after LPV/r initiation, prior laboratory tests were assessed to examine whether laboratory abnormalities preceded the onset of LPV/r exposure. Pre-existing laboratory abnormalities which continued during the LPV/r exposure period are described in the text of the results section.

Rates of DAIDS events per 100 person-years were calculated if there were sufficient numbers of patients in follow-up (n≥20) to provide a meaningful estimate. If there were <20 patients then the number and proportion of abnormal test of that grade were reported (with the denominator being the total number of tests of that type conducted) instead of a rate. These are presented in Tables 4a-b.

Further details of all grade ≥3 laboratory test results are provided in Appendix 1, Table 5. This information includes: age at first grade ≥3 laboratory result, timing of the abnormal result relative to LPV/r initiation, number of grade 3 and 4 results and whether subsequent normal values were recorded (including tests undertaken up to 3 years of age).

Clinical adverse events

Clinical adverse events (AEs) which were considered potentially causally associated with LPV/r exposure and all serious AEs (SAEs) irrespective of causal association with LPV/r were reported for all patients whilst on LPV/r oral solution or up to three months after LPV/r discontinuation.

Clinical adverse events were coded using an in-house coding system used by the Medical Research Council Clinical Trials Unit (MRC CTU) at University College London (UCL). This coding system has been validated in international trials and codes AEs according to the body system affected (similar to the Medical Dictionary for Regulatory Activities (MedDRA) coding system).

An adverse event was classified as serious if it met the standard Medicine for Human Use (Clinical Trials) Regulations (2004) definition.

A SAE is defined using this definition if it meets any of the following criteria:

- results in death
- is life-threatening (defined as any event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event that may not be immediately life threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or required intervention (e.g. medical, surgical) to prevent one of the other serious outcomes listed in the definition above).

Clinical AEs were classified and presented according to whether they were considered causally related to LPV/r oral solution by the treating physician. All AEs (serious and non-serious) reported during follow-up by the clinician as definitely, probably or possibly related to LPV/r are reported in Appendix 1, Table 6. AEs and SAEs for which the clinician reported a causal association with LPV/r was remote/unlikely/not related are shown in Appendix 1, Table 7. AEs for which information on the possible causal association with LPV/r was unknown are shown in Appendix 1, Table 8a and those for which information on the seriousness of the adverse event was not available are reported in Table 8b. AEs for which have missing data on both causality and seriousness may therefore appear in both tables.

Discontinuations

The frequency of and reasons for treatment discontinuations are presented in Appendix 1, Table 9. This includes patients who permanently discontinued LPV/r oral solution during follow-up time within this study (i.e. it excludes patients who discontinued and then re-started LPV/r while aged <2 years), irrespective of duration on the study drug. For patients with multiple episodes on LPV/r while aged <2 years, the reason for and duration of discontinuation is based on their final episode on LPV/r oral solution. Reasons for discontinuation of LPV/r are categorised as follows: lack of effectiveness, safety, other reasons (e.g. patient's wish or treatment simplification) and unknown reasons.

9.9.3 Missing values

During the data cleaning process individual cohorts were contacted by the data manager and asked to provide values for missing data where available. No imputation of missing values was undertaken.

9.9.4 Sensitivity analyses

Not applicable (this is a descriptive study).

9.9.5 Amendments to the statistical analysis plan

None.

9.10 Quality control

Data were subjected to a battery of logical and consistency checks in order to assess accuracy and completeness. Where possible, data queries arising were discussed and resolved with the relevant cohort data manager before data were pooled. Further data checks were also conducted by the study statistician prior to data analysis.

10. Results

10.1 Participants

Table 1 presents the 42 patients who met the inclusion criteria for this study summarised by country. Of these patients, 33 were previously reported last year and nine patients were newly reported this year. The largest number of patients on LPV/r were in the Spanish, Italian and UK/Ireland cohorts. The earliest date of LPV/r initiation was 23 March 2016 and the most recent LPV/r initiation date was 2nd March 2021. The last patient last visit date was 21 April 2021.

Table 1. Number of patients included by country

Country	Total number of patients included in Year 2 report	New patients added in this Year3 report	Total number of patients included in Year 3 report
Belgium	2	0	2 (5%)
Denmark	1	0	1 (2%)
Greece	4	0	4 (10%)
Italy	11	0	11 (26%)
Poland	2	0	2 (5%)
Spain	9	5	14 (33%)
UK/Ireland	4	4	8 (19%)
Total	**33**	**9**	**42 (100%)**

10.2 Descriptive data

All tables and figures referred to in this section can be found in Appendix 1.

The 42 patients included were categorized to the following groups (Appendix 1, Figure 1):

On-Label

Group 1: Licensed (n= 13)
(Patients aged 14 days-<2 years taking a licensed dose of LPV/r oral solution)

Off-label

Group 2: Unlicensed (n=13)
(Patients aged 14 days-<2 years taking an unlicensed dose)

Group 3: <14 days of age (n=1)
(Patients <44 weeks of combined gestational age and age after birth at LPV/r initiation)

Missing

Group 4: Missing weight and/or dose at LPV/r start (n=15)
(Patients for whom information was insufficiently complete to permit accurate assignment)

Figure 1 provides information on the number of patients in each group and whether clinical and laboratory data were available for them. Overall, 42 patients experienced 44 episodes on LPV/r while aged <2 years, 36 children (86%) had laboratory data and clinical data were available for 41 (98%) patients.

Baseline characteristics of the 42 patients are presented in Appendix 1 Table 1. Of the 13 children on a licensed dose (Group 1), one was from Denmark, two from Greece, one from Poland, six from Spain, and three from UK/Ireland. Of the 13 children on an unlicensed dose (Group 2), one was from Belgium, one from Greece, six from Italy, one from Poland and four from Spain. One child from Greece was in Group 3 (off-label, age <14 days) as they initiated LPV/r at 13 days of age. Of the 15 children with missing weight or dose (Group 4), one was from Belgium with missing weight, five from Italy were missing weight and height and one was missing dose at LPV/r initiation, four from Spain were missing dose and weight, and five from UK/Ireland were either missing LPV/r initiation date, weight and/or dose data. All of these missing data were confirmed to be unavailable when queried with clinics.

Overall, 45% (19/42) of patients were male. Almost all patients (95%, 40/42) were reported to have acquired HIV through vertical transmission. In the licensed dose group (Group 1), the route of HIV acquisition was reported as transfusion for one patient and unknown for one patient. Ethnicity was reported as white in 21% (9/42), black African in 24% (10/42), other in 19% (8/42) and unknown in 36% (15/42) . The majority of the patients (69%, 29/42) were reported as not having received infant prophylaxis to prevent vertical transmission, 21% (9/42) had received infant prophylaxis and 10% (4/42) of patients had unknown history of infant prophylaxis.

Of these 42 patients, 11 (26%) started LPV/r oral solution prior to the EMA paediatric approval date for children <2 years of age (26 July 2017), while 31 (74%) started in the post-approval period. One patient from the UK cohort was aged <2 years and already on LPV/r at time of entry to the country and cohort (after the EMA paediatric approval date), but the date of LPV/r initiation was unknown. For this patient, date of entry into the cohort was used as a proxy for LPV/r start date.

The median [IQR] age at LPV/r start was 6.9 [2.3-14.4] months, with 21% (9/42) initiating LPV/r before 2 months of age, 29% (12/42) between 2-<6 months, 12% (5/42) between 6-<12 months, and 38% (16/42) after 12 months of age. The great majority of the patients were ART naïve at LPV/r initiation (93%, 39/42). The CDC disease stage at LPV/r initiation was missing or reported as unknown for 43% (18/42) of patients and 40% (17/42), 5% (2/42) and 12% (5/42) were in CDC

disease stages N/A, B, and C respectively. Among the patients with data on immune status at LPV/r start (n=20), half (10/20) had advanced or severe immunosuppression for age at LPV/r start.

Further details on the 14 patients with off-label and unlicensed dose use of LPV/r (Groups 2 and 3) are described in Table 1b. Of the 13 patients in Group 2 (unlicensed dose), 12 were categorised in this group because they initiated LPV/r on doses higher than recommended in the AbbVie Kaletra® SmPC. In addition, one of these 12 patients received one dose per day which contrasts with the SmPC recommendation of twice-daily dosing. The final patient in Group 2 was an infant aged [redacted] from [redacted] (Table 1b, patient number [redacted]) who was on NVP at LPV/r initiation (LPV/r is not recommended for patients <6 months of age and on NVP). For 6 of the 13 patients in Group 2, the responsible clinics in Poland, Italy and Spain reported following the USA National Institutes of Health dosing recommendations (12). One patient in group 2 received a higher dose than recommended.

Group 3 (off-label use) comprised one infant who was aged [redacted] at initiation of LPV/r (Table 1b).

10.3 Outcome data

10.3.1 Patient characteristics during follow-up

Table 2 presents patient characteristics during follow-up on LPV/r and while under 2 years of age. The median [IQR] time spent on LPV/r while aged <2 years was 9.7 [4.1 - 16.3] months overall, with a total follow-up time of 441.9 person-months across all groups. Overall 38% (16/42) had over 12 months of follow-up time on LPV/r. HCV and HBV coinfection status were available for 38 (91%) and 39 (93%) patients respectively. No patients ever had a positive test result for HBV or HCV. One patient from [redacted] (in the unlicensed dose group, Group 2) was diagnosed with AIDS during follow up (*Pneumocystis jirovecii*), as reported in last year's report.

In terms of follow-up status at last visit, one patient from [redacted] died while on LPV/r in an unrelated event (car accident), this was previously reported in last year's report. Two patients (5%) dropped out of the study prior to censoring (both patients lost to follow-up), 5 (12%) were in follow-up having discontinued LPV/r and the remaining 34 (81%) were in follow-up and on LPV/r at censoring.

10.3.2 Immunological and virological treatment response

Both immunological and virological responses following LPV/r initiation (baseline) and 6 and 12 months after LPV/r start are presented in Table 3.

HIV viral load at baseline was recorded for 52% (22/42) of patients, for whom the median [IQR] viral load was 6.5 [5.1-6.6] $\log_{10}$ c/mL, with two patients (one in group 4 and one in group 2) having a viral load ≤1000 c/mL. Sixty per cent of patients (25/42) had at least 6 months follow-up after LPV/r

initiation, of whom 20 (76%) patients had viral load data available at 6 months; the median [IQR] viral load was 2.1 [1.8-2.8] log_{10} c/mL. There were 4 (20%) patients with undetectable viral load ≤50 c/mL at 6 months. When using a higher threshold of viral load ≤1000 c/mL, 80% (16/20) were virally suppressed at 6 months. Of the 16 (38%) patients with at least 12 months on LPV/r, all had viral load data available at 12 months, with a median [IQR] value of 2.0 [1.6 – 2.8] log_{10} c/mL. Six (38%) patients had undetectable viral load ≤50 c/mL, and 13 (81%) had viral load suppressed ≤1000 c/mL.

Values for baseline absolute CD4 cell count and CD4% at LPV/r start were available for 45% (19/42) and 43% (18/42) of patients respectively; for these, the median [IQR] CD4 cell count was 1604 [568 – 2800] cells/µL and the median [IQR] CD4% was 25% [17 -35]. Of the 25 patients on LPV/r at 6 months, CD4 count and CD4% data at 6 months was available for 17 (68%) and 18 (72%) patients respectively. The median [IQR] CD4 cell count at 6 months was 1897 [1203-2490] cells/µL and the median [IQR] CD4% was 33% [27 - 44]. Among patients with CD4 measurements both at baseline and 6 months, the median [IQR] change in CD4 cell count at 6 months (n=10) was 590 [-360 - 1046] cells/ µL and change in CD4% (n=11) was 8% [5 – 11]. Of 16 patients with ≥12 months of follow up on LPV/r, 14/16 (88%) patients had CD4 count and 12/16 (75%) had CD4% data at 12 months after LPV/r initiation. The median [IQR] CD4 cell count at 12 months was 1835 [1339-2160] and median CD4% was 32 [30 – 42]. CD4 count change betweem baseline and 12 months (n=14) was 1245 [-744 – 1657] cells/ µL and 3% [-3 – 4] for CD4% (n=5).

10.4 Main results

The main results are described in sections 10.1-10.3, 10.6 and 10.7.

10.5 Other analyses

Not applicable.

10.6 Adverse events / reactions

10.6.1 Laboratory adverse events

Laboratory data while on LPV/r were available for 86% (36/42) of patients (Figure 1), therefore all further proportions are described in relation to n=36. Table 4a provides information on laboratory test results conducted after LPV/r initiation. The table includes (for each laboratory test) the total number of: test results recorded, patients, episodes, and first Division of AIDS 2014 graded event of each severity (1, 2, ≥3), or alternative grading system where required as described above.

The most frequently recorded laboratory tests were ALT (174), ANC (172), S-CREAT (158), AST (133), TBIL (131) and GGT (122). Overall across the dosing groups, there were 10 laboratory markers for which grade ≥3 test results were reported, with a total of 19 events. The number and percentage of

patients who experienced grade ≥3 tests for each of these markers, amongst those tested, were as follows: 5/36 (14%) for ALT tests; 3/35 (9%) ANC; 1/30 (3%) AST; 1/24 (4%) APT; 1/30 (3%) CHOL; 1/28 (4%) GGT; 3/31 (10%) TBIL; 1/21 (5%) LDL, 2/30 (7%) TRIG and 1/19 (5%) FPG. No test results were reported for non-fasting plasma glucose (non-FPG). Among patients for whom grade ≥3 test results while on LPV/r were reported, and those with data 12 months prior to LPV/r initiation (53%, 23/42), none had laboratory abnormalities preceding start of LPV/r.

Twelve markers (ALT, ANC, APT, AST, CHOL, HDL, GGT, LDL, SCa, S-CREAT, TBIL and TRIG) had test results available for at least 20 patients each. Rates (per 100 person-years) of each DAIDS grade (1, 2, ≥3) with 95% CI for these laboratory markers are presented in Table 4b. Rates of grade ≥3 events were generally low across the markers. For ALT, across 174 tests in 36 patients, 5 (14%) experienced a grade ≥3 event, with a rate of 2.5 per 100 PY (95% CI 0.8 – 5.8). For TBIL, across 131 tests in 31 patients, 3 patients (10%) experienced a grade ≥3 event, giving a rate of 2.0 per 100 PY (95% CI 0.4 – 5.7). Rates for grade ≥3 events for APT [0.7 per 100 PY (95% CI 0.0 – 4.1)] , AST [0.6 per 100 PY (95% CI 0.0 – 3.5)], CHOL [0.7 per 100 PY (95% CI 0.0 – 4.1)], GGT [0.7 per 100 PY (95% CI 0.0 – 3.7)] and LDL [1.0 per 100 PY (95% CI 0.0 - 5.7) were similar and generally very low.

Table 5 provides further information on the 19 grade ≥3 (severe) laboratory events in 12 patients. Seven of these events were previously reported in Year 2 (one patient reported last year from [redacted] with a grade 3 GGT lab result has updated corrected data confirming no grade 3 event and has therefore been removed from this table). Of the five newly reported patients, 1 patient ([redacted]) from [redacted] had a reported grade 3 ANC event at age [redacted], and 1 patient from [redacted] ([redacted]) had grade 4 events for ALT, AST and FPG, all of which resolved. Another [redacted] patient ([redacted]) had a grade 3 LDL test result for which no resolution was reported. Patient [redacted] had a grade 3 ALT event which resolved. Patient [redacted] had grade 3 ALT and TRIG test results which also normalized while in follow up. All of these five patients remained on LPV/r.

Of the seven patients with grade ≥3 laboratory events that were previously reported, one patient from [redacted] ([redacted]) had grade 3 GGT and ALT events which subsequently resolved. Patient [redacted] from [redacted] who was also taking NVP stopped LPV/r due to toxicity and their APT grade 3 event did not resolve by age 3. For five patients from Italy and Spain with at least one grade ≥3 result for ALT ([redacted]), TBIL ([redacted], [redacted]), LDL ([redacted]) CHOL ([redacted]), or TRIG ([redacted]), the severe events were not reported as resolved when queried with clinics.

10.6.2 Clinical adverse events

Three patients had a total of six clinical AEs and serious AEs (SAEs) considered by the treating physician to be definitely or probably causally related to LPV/r (Table 6), in conjunction with other ART. All events were previously reported last year with no new events. One patient ([redacted]) was diagnosed with immune reconstitution inflammatory syndrome (IRIS), one had raised triglycerides ([redacted]), and one had episodes of vomiting, raised triglycerides and raised cholesterol ([redacted]). The latter patient, who was on an unlicensed dose (dose too high) experienced four AE episodes in total, all of which were considered definitely related to LPV/r and two of which were severe and reported as SAEs. Both events (vomiting) subsequently resolved. LPV/r and 3TC were discontinued after the first vomiting event but LPV/r was restarted 2 months later. This patient also had two moderate events of raised triglycerides and raised cholesterol at 9 and 15 months of age while on an ABC+LPV/r+RAL+ZDV regimen, which was not reported to have been resolved by age 3 years when data was censored. The patient remained on LPV/r at last visit prior to censoring. The patient was also taking amoxicillin, amoxicillin-clavulanate, nystatin and oseltamivir at the time of these events.

The patient with raised triglycerides at 15 months of age was considered to have had a mild AE probably related to their 3TC+ABC+LPV regimen. This event was not reported to have been resolved when data was censored, and ART was not stopped due to the event.

The episode of IRIS was a SAE considered probably related to the patient's ABC+FTC+LPV regimen. This event resolved within several weeks and the patient remained on LPV/r.

Details of all AEs and SAEs considered not causally related to LPV/r oral solution (5 patients with 7 events) are reported in Table 7. All events were included in the previous report last year with no new events this year. One [redacted] infant ([redacted]) aged [redacted] died in a car accident, and this event was not related to ART. One patient from [redacted] had two severe AEs (patient [redacted], seriousness unknown for both events), a recurrent bacterial pneumonia and chronic lymphoid interstitial pneumonitis, both events were considered not related to ART and the patient remained on LPV/r.

One patient had an event of diarrhoea which resolved; a second had mucocutaneous candidiasis which also resolved. One patient had a lower respiratory infection and breathlessness / dyspnoea, which overlapped in time and were reported as separate SAEs; both were life-threatening and both were resolved, with the patient remaining on LPV/r. In 5 of the 7 events, the patients were taking concomitant non-ART medications at the time of their event.

There were two clinical AEs, both with unknown seriousness, for which a causal association to LPV/r was reported as unknown (Table 8a). As shown in Table 8b, there were 12 clinical AEs in six patients where the SAE status was not reported (this includes the two events also shown in Table 8a). While six of these AEs are reported as mild or moderate in severity, for the remaining six both severity and seriousness are unknown; all of these events are reported here for completeness. Two events were previously reported last year: recurrent or persistent oral candida (patient [redacted]) and extrapulmonary cryptococcal infection ([redacted]), both of which were reported as not related to LPV/r. The rest of the events are presented here for the first time. The [redacted] patient [redacted] also experienced *Pneumocystis jirovecii* pneumonia, CMV hepatitis, neutropenia and anemia, all of which were mild to moderate and were resolved. Other events where seriousness was unknown were: persistent generalised lymphadenopathy (patient [redacted] CMV hepatitis (patient [redacted]), rash/lesions (patient [redacted]) and [redacted] fistula with colostomy (patient [redacted]). The rash/lesions resolved, but the patient discontinued LPV/r approximately 4 months after recovery, for unknown reasons. Resolution status was unknown for the other three events. The patient with [redacted] fistula discontinued LPV/r approximately 6 months after the event, for reasons other than safety or effectiveness. Four of the six patients remained in follow up by time of censoring.

10.7 Discontinuations

Of the 42 patients included in this report, 5 (12%) discontinued LPV/r oral solution whilst aged <2 years (Table 9). One patient discontinued at <1 month after initiation (Group 1), two between 1 and <6 months (Groups 1 and 4), and two patients (Group 2 and 4) between six and 12 months. One patient in Group 4 was reported to have discontinued due to lack of effectiveness. One patient in Group 2 discontinued due to safety, specifically GI tract toxicity, after 11.4 months on LPV/r. At the time of discontinuation, this patient was also taking lamivudine, nevirapine and zidovudine. Three had “other” reasons for discontinuation where two were specified as simplified treatment and one moving abroad.

11. Discussion

11.1 Key findings

This report describes a small cohort of 42 young children aged <2 years at the time of LPV/r initiation, treated in routine care in countries across Europe. This is an increase from 33 children reported last year. Most of the included children acquired HIV perinatally and the majority initiated LPV/r as part of their first ART regimen in their first year of life.

Of the 42 patients included in this report, 13 were categorised into the unlicensed dose group. Twelve of these patients were receiving a higher dose compared to the recommended dose in the AbbVie Kaletra® SmPC, and one was receiving NVP concomitantly with LPV/r while aged <6 months. Six of these patients were from Italy, one from Belgium, four from Spain, one from Greece and one from Poland. An additional patient from [redacted] initiated LPV/r at the age of [redacted] which is [redacted] short of the 14 days recommended minimum age for initiating LPV/r (off-label use).

The clinicians who treated some of the patients taking an unlicensed dose reported following the USA NIH guidelines, which recommend a higher dose than in Europe (12); this may also account for the higher doses used in other children on unlicensed doses in this report, although this could not be confirmed for all the cases. Fifteen patients were missing data on doses and/ or weight and so it was not possible to fully determine whether they were taking licensed or unlicensed doses. One patient in this group was known to have initiated LPV/r at <2 years of age, but their exact age/weight and dose at initiation was not known as they had initiated treatment abroad.

At 6 months post LPV/r initiation, among the 20 infants with viral load measurements available, 4 (20%) patients had undetectable viral load at ≤50 c/mL and 80% (n=16/20) achieved viral suppression ≤1000 c/mL. A similar trend was observed at 12 months on LPV/r, where 38% (6/16) children with viral load measurement available had undetectable viral load<50c/mL and 81% (13/16) had viral suppression ≤1000 c/mL. This is consistent with findings from literature which suggest a slower time to achiving undetectable viral load ≤50 c/mL in infants compared to older children but demonstrates that a high proportion of children with data available were suppressed at the ≤1000 c/mL threshold (13). Overall immune response appeared good, with the median CD4% amongst the small subset of patients with data available increasing after LPV/r initiation. One death was reported (car accident), which was not related to HIV or LPV/r, and one patient was diagnosed with AIDS during follow-up, both events were previously reported last year. Six clinical adverse events in 3 patients were considered causally related to LPV/r (or concomitant ART), all events were previously reported last year. None of these events led to discontinuation of LPV/r, although three of them were not reported as resolved by the end of follow-up.

Overall, 19 grade ≥3 (severe) laboratory results were reported in 12 patients: five tests for ALT, three tests each for ANC and T-BIL two for TRIG and one each for APT, AST, CHOL, GGT, FPG, and LDL. One of these patients stopped LPV/r due to GI tract toxicity. All these events are labelled in the SmPC for LPV/r, although the SmPC does not stratify by age: GGT and ALT elevation, raised triglycerides, raised cholesterol and neutropenia are all classified as “common” undesirable effects (occurring in ≥1/100 to <1/10 of patients) and hyperbilirubinemia is classified as “uncommon” (≥1/1000 to <1/100). The

frequency of TBIL grade 3/4 AEs in our study is perhaps higher than implied by the SmPC: 3/36 patients with any laboratory data (8.3%) experienced these events, or 3/31 with TBIL tests carried out (10%), with a rate of 2.0 (0.4 – 5.7) per 100 person-years. However, we note that these numbers are small and the confidence intervals wide, and that a physician decision to order a test may introduce selection bias.

Overall, 12 of 36 patients with laboratory data experienced a grade 3 or 4 event (33%). This is similar to that reported from a phase II/III trial of LPV/r in HIV-infected children with dosing based on WHO weight bands, in which 32/96 (33%) children had a grade ≥3 event (19). A randomised trial aiming to compare malaria incidence between children with HIV on LPV/r versus NNRTI therapy reported that neutropenia was the most common laboratory AE in the LPV/r arm, with a rate of 24.0 per 100 person years, which is higher than observed in our study (1.5 per 100 person years (95% CI 0.3 – 4.5)) (20).

One clinical AE of IRIS in a [redacted] patient was determined by the physician to be probably causally associated with the ART regimen, which included abacavir, emtricitabine, and LPV/r; this event was described in previous reports. IRIS is precipitated by rapid immune recovery after the initiation of effective ART in patients with underlying infection or inflammation (14, 15) and may be related to all 3 drugs in the patient's combination antiretroviral regimen.

One patient on abacavir, emtricitabine, and LPV/r regimen experienced two events of vomiting both of which were classified as severe and considered definitely associated with ART. Vomiting is noted as one of the most common adverse reactions related to Kaletra in the SmPC. The patient later switched to raltegravir, zidovudine and LPV/r and also experienced hyperlipidemia, which was also considered definitely causally associated with this regimen. In addition, five patients experienced SAEs (including one death in a car accident) whilst on LPV/r which were not considered causally related to the drug.

In summary, this three-year study did not suggest any new safety signals causally related to LPV/r in the licensed or unlicensed dose groups, although this was based on a small sample size and as noted above the incidence of TBIL abnormalities is perhaps higher than expected. Data on the seriousness of AEs was unknown for some events and for two children, the clinicians' assessment of causality was not available.

The laboratory abnormalities and AEs described in this report which were considered to be related to the LPV/r oral solution are recognised adverse reactions already specified in the LPV/r product

specification. Among the AEs reported, none were reported to be related to ethanol or propylene glycol toxicity. Overall, 12% of patients (5/42) discontinued LPV/r, one was due to lack of effectiveness, one due to safety reasons (GI tract toxicity) and the other three were for other reasons. All discontinuations were permanent.

11.2 Limitations

Firstly, interpretation of the results is limited by the small sample size, although this has increased year on year. The study's relatively small size is largely due to the continued success in preventing vertical HIV transmission in Europe and globally (16). However, there remain insufficient numbers for meaningful calculation of rates of events for a number of safety markers and several of the calculated rates have wide confidence intervals.

Secondly, patients were categorized according to their initial dosing group (licensed, unlicensed, <14 days of age, missing weight and/or dose) at LPV/r initiation (baseline). The analysis did not account for changes in LPV/r dosage over time (although dose immediately prior to any AE was reported in the relevant clinical events table (Appendix 1, Tables 5-8) where available).

Thirdly, the study censors data once children reached 2 years of age or three months after LPV/r discontinuation. Among children who experienced an AE on LPV/r while <2 years, we included follow up data until age 3 years to inform on the resolution of these events only and therefore longer term safety and effectiveness outcomes are not assessed.

Fourthly, this is a descriptive study. The assessment of the likely causal relationship between LPV/r exposure and clinical AEs was based solely on the attending clinician's opinion. There is no comparison group from which to draw conclusions on the role of LPV/r in the observed laboratory and clinical events.

Finally, this study uses observational data collected in routine care and pooled from 8 cohorts. There may be differences in data collection methods as well as clinical practices across countries, cohorts and sites. All EPPICC cohorts, however, follow the same standard operating procedure when providing data. This minimizes the risk of differences and biases arising from heterogeneity of reporting. Data collection was impacted by the COVID-19 pandemic; this study used data from routine care and data were missing for some variables in some patients, although cohorts have worked hard to ensure the data are as complete as possible. However, some patients did not have VL or CD4 measurements within the specified time frames (e.g. at LPV/r initiation and at 6 and 12 months after LPV/r start), and assessment of resolution of AEs is dependent on information on resolution being captured in clinic records. Some of the missing data may have been partly due to reduced clinical visits during the pandemic and it should be noted that lack of evidence that an AE

resolved does not necessarily mean that it never resolved. There were 12 clinical adverse events in six patients for which the seriousness was not reported; most of these were considered not related to LPV/r and / or were of mild or moderate severity. No imputation of missing values was undertaken.

11.3 Generalisability

The data in this study represent 'real world' prescribing of LPV/r oral solution in very young children. It is not possible to reliably estimate the coverage of the EPPICC paediatric cohorts, in terms of the number of children <2 years of age included in these cohorts compared with the number living with HIV as a whole in the countries represented. This is due to a wide variation in the quality and coverage of the surveillance systems used in these countries, making national estimates, and comparison of estimates between countries, unreliable. The UK and Ireland cohort (CHIPS) and the Italian cohort, which contributed 19% and 26% of patients respectively, are both national cohorts including all children receiving HIV-related care in their respective countries. The two Spanish cohorts (33% of patients in this study) account for most children living with HIV in Spain (17). The Polish cohort (5%) includes data from all children attending the largest paediatric HIV clinic in the country (18) and the Greek, Belgian and Danish cohorts each represent the main centre for paediatric HIV care in the respective countries.

12. Other information

Not applicable.

13. Conclusion

We present in this Year 3 (final) report cumulative data on the safety and effectiveness of LPV/r oral solution in children <2 years of age in EPPICC. Among the children with viral load data available at 6 and 12 months of LPV/r, the large majority (≥80%) were virally suppressed under 1000 copies/mL. The safety outcomes analysed in this report are consistent with the known safety profile of LPV/r as specified in the LPV/r product information. No new safety concerns related to LPV/r oral solution were identified. The study is limited by the small sample size with limited follow-up data included up to 2 years of age among children on LPV/r.

14. References

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APPENDIX 1: Figures and Tables

Figure 1: Flowchart of patients <2 years of age at first exposure to LPV/r oral solution (n=42)

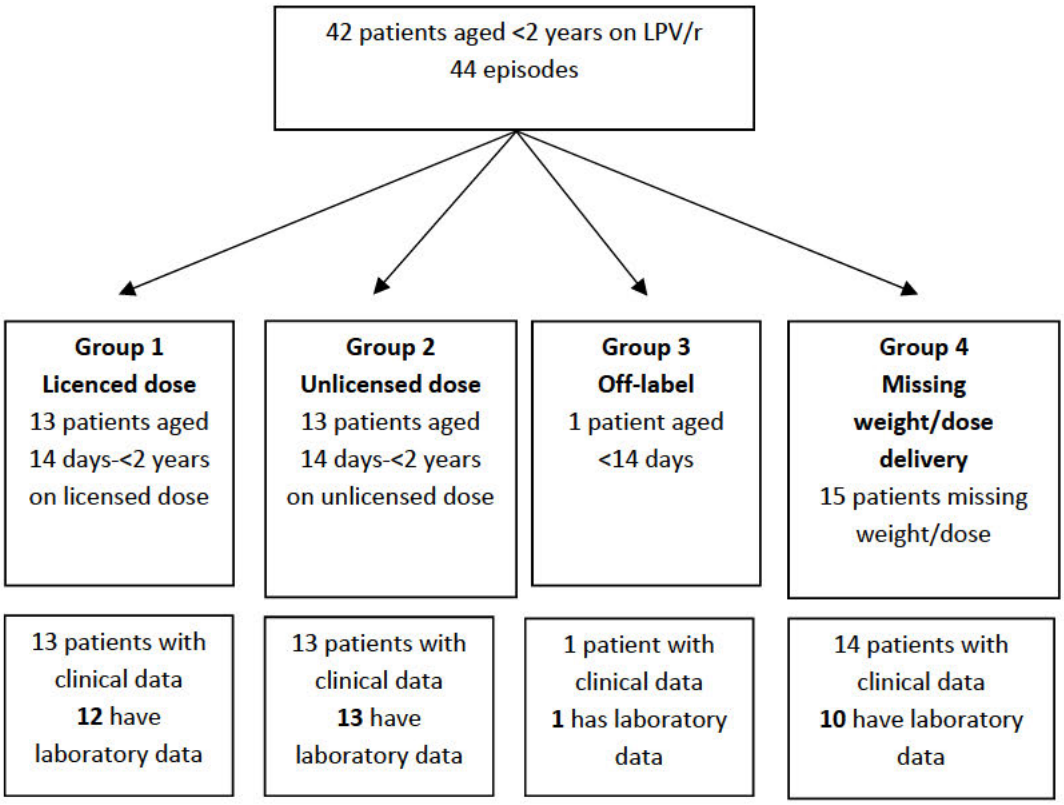

Table 1: Characteristics of patients at LPV/r initiation (n=42)

	Group 1 Licensed dose (n = 13)		Group 2 Unlicensed dose (n = 13)		Group 3 Off-label: age <14 days (n = 1)		Group 4 Missing weight/dose (n = 15)		Total (n = 42)	
	N (%)/ Median [IQR]									
Country	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Belgium	0	(0)	1	(8)	0	(0)	1	(7)	2	(5)
Denmark	1	(8)	0	(0)	0	(0)	0	(0)	1	(2)
Greece	2	(15)	1	(8)	1	(100)	0	(0)	4	(10)
Italy	0	(0)	6	(46)	0	(0)	5	(33)	11	(26)
Poland	1	(8)	1	(8)	0	(0)	0	(0)	2	(5)
Spain	6	(46)	4	(31)	0	(0)	4	(27)	14	(33)
UK/Ireland	3	(23)	0	(0)	0	(0)	5	(33)	8	(19)
Sex										
Male	7	(54)	7	(54)	0	(0)	5	(33)	19	(45)
Female	6	(46)	6	(46)	1	(100)	10	(67)	23	(55)
Mode of HIV acquisition										
Transfusion	1	(8)	0	(0)	0	(0)	0	(0)	1	(2)
Vertical transmission	11	(85)	13	(100)	1	(100)	15	(100)	40	(95)
Unknown	1	(8)	0	(0)	0	(0)	0	(0)	1	(2)
Ethnicity										
White	5	(38)	3	(23)	0	(0)	1	(7)	9	(21)
Black African	5	(38)	2	(15)	1	(100)	2	(13)	10	(24)
Other	1	(8)	2	(15)	0	(0)	5	(33)	8	(19)
Unknown	2	(15)	6	(46)	0	(0)	7	(47)	15	(36)
Infant prevention of vertical transmission prophylaxis exposure										
None	13	(100)	8	(62)	1	(100)	7	(47)	29	(69)
Yes	0	(0)	4	(31)	0	(0)	5	(33)	9	(21)
Unknown	0	(0)	1	(8)	0	(0)	3	(20)	4	(10)
Started LPV/r before the approval date*										
No	9	(69)	9	(69)	1	(100)	12	(80)	31	(74)
Yes	4	(31)	4	(31)	0	(0)	3	(20)	11	(26)
Age at ART start (months)*										
Median	4.3 [2.2- 12.8]		6.9 [1.1-11.7]		0.4 [0.4-0.4]		10.6 [1.7-14.7]		5.5 [1.4-12.8]	
Age at LPV/r start (months)*										
Median	4.3 [2.3 -12.8]		10.3 [1.1-12.6]		0.4 [0.4-0.4]		12.4 [4.0 – 15.1]		6.9 [2.3 – 14.4]	
Age at LPV/r start*										
<2 months	1	(8)	5	(38)	1	(100)	2	(13)	9	(21)
2-<6 months	8	(62)	1	(8)	0	(0)	3	(20)	12	(29)
6-<12 months	0	(0)	3	(23)	0	(0)	2	(13)	5	(12)
12+ months	4	(31)	4	(31)	0	(0)	8	(53)	16	(38)
ART history prior to LPV start										
Naive	12	(92)	12	(92)	1	(100)	14	(93)	39	(93)
1-5 ART drugs	1	(8)	1	(8)	0	(0)	1	(7)	3	(7)
CDC stage at ART start										
N or A	5	(38)	5	(38)	1	(100)	6	(40)	17	(40)
B	0	(0)	1	(8)	0	(0)	1	(7)	2	(5)

C	1	(8)	3	(23)	0	(0)	1	(7)	5	(12)
Missing/Unknown	7	(54)	4	(31)	0	(0)	7	(47)	18	(43)
CDC stage at LPV/r start										
N or A	5	(38)	5	(38)	1	(100)	6	(40)	17	(40)
B	0	(0)	1	(8)	0	(0)	1	(7)	2	(5)
C	1	(8)	3	(23)	0	(0)	1	(7)	5	(12)
Missing/Unknown	7	(54)	4	(31)	0	(0)	7	(47)	18	(43)
WHO immune status at LPV/r start (n=20)**										
None	2	(33)	1	(17)	1	(100)	5	(71)	9	(45)
Mild	0	(0)	0	(0)	0	(0)	1	(14)	1	(5)
Advanced	0	(0)	1	(17)	0	(0)	0	(0)	1	(5)
Severe	4	(67)	4	(67)	0	(0)	1	(14)	9	(45)

***** One child from group 4 is missing date of LPV/r start as they initiated treatment abroad but remained on LPV/r while aged<2 years at time of entry to the cohort in EPPICC. Date at entry to the cohort was used as proxy for LPV/r start date.

**Percentages only include patients with data on CD4 cell count or CD4% at baseline.

Table 1b: Description of unlicensed/off-label use at start of LPV/r (n=14)

Number	Country/ Patient number	Group	Age at LPV/r initiation (months)	LPV/r dose (mg)	Dose frequency (doses per day)	BSA (m^2)	Reason for unlicensed/off-label classification	Reason for unlicensed/off-label use[α]
1	[redacted]	Unlicensed dose	[redacted]	80	2	0.26	Initiated LPV/r at <6 months of age whilst on NVP	Initiated LPV/r at <6 months of age whilst on NVP
2	[redacted]	Unlicensed dose	[redacted]	120	2	0.41	Dose too high	Site rounded BSA to 0.5 which would mean dose is correct
3	[redacted]	Off-label: age <14 days	[redacted]	58	2	0.23	Initiated LPV/r before age 14 days	-
4	[redacted]	Unlicensed dose	[redacted]	120	2	0.41	Dose too high	-
5	[redacted]	Unlicensed dose	[redacted]	120	2	0.34	Dose too high	Following NIH paediatric ART guidelines which recommend a higher dose
6	[redacted]	Unlicensed dose	[redacted]	100	2	0.27	Dose too high	-
7	[redacted]	Unlicensed dose	[redacted]	180	2	0.48	Dose too high	-
8	[redacted]	Unlicensed dose	[redacted]	250	1	0.40	Dose too high	-
9	[redacted]	Unlicensed dose	[redacted]	100	2	-	Dose too high	-
10	[redacted]	Unlicensed dose	[redacted]	160	2	0.56	Dose too high	Following NIH paediatric ART guidelines which recommend a higher dose
11	[redacted]	Unlicensed dose	[redacted]	60	2	0.21	Dose too high	Following NIH paediatric ART guidelines which recommend a higher dose
12	[redacted]	Unlicensed dose	[redacted]	96	2	0.23	Dose too high	Following NIH paediatric ART guidelines which recommend a higher dose
13	[redacted]	Unlicensed dose	[redacted]	152	2	0.19	Dose too high	Following NIH paediatric ART guidelines which recommend a higher dose
14	[redacted] *	Unlicensed dose	[redacted]	128	2	0.44	Dose too high	Following NIH paediatric ART guidelines which recommend a higher dose

*Newly reported

α:Unable to obtain reasons for high doses where indicated by a dash

Table 2: Characteristics during follow-up on LPV/r (n=42)

	Group 1 Licensed dose (n = 13)		Group 2 Unlicensed dose (n = 13)		Group 3 Off-label: age <14 days (n = 1)		Group 4 Missing weight/dose (n = 15)		Total (n = 42)	
	N (%) /Median [IQR]									
Time on LPV/r aged <2 yrs (months)										
Median	6 [4.6-19.7]		11.3 [5.7-13.6]		1.7 [1.7-1.7]		9.5 [2.6-16.3]		9.7 [4.1-16.3]	
<6	7	(54)	4	(31)	1	(100)	4	(27)	16	(38)
6-<12	1	(8)	4	(31)	0	(0)	5	(33)	10	(24)
12-18	1	(8)	2	(15)	0	(0)	4	(27)	7	(17)
>18	4	(31)	3	(23)	0	(0)	2	(13)	9	(21)
HCV positive*										
Value present	13	(100)	11	(85)	1	(100)	13	(87)	38	(91)
Yes	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
HBV positive										
Value present	13	(100)	11	(85)	1	(100)	14	(93)	39	(93)
Yes	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
AIDS diagnosis during follow up										
No	13	(100)	12	(92)	1	(100)	15	(100)	41	(98)
Yes	0	(0)	1	(8)	0	(0)	0	(0)	1	(2)
Follow-up status†										
Death	0	(0)	1	(8)	0	(0)	0	(0)	1	(2)
Dropped out	0	(0)	1	(8)	1	100	0	(0)	2	(5)
In FU but not on LPV/r	0	(0)	1	(8)	0	(0)	4	(27)	5	(12)
In follow-up and on LPV/r at last visit	13	(100)	10	(77)	0	(0)	11	(73)	34	(81)
Reasons for drop out										
Patient LTFU/ not known to be dead	0	(0)	1	(8)	1	(100)	0	(0)	2	(100)

Notes: *HCV was an antibody test (results from children <18 months of age were excluded).

† Follow-up status at time of data censor as per Methods (at earliest of the following: date of last visit, death, 3 months after discontinuation of LPV/r or 2nd birthday).

Table 3: Immunological and virological status at initiation of LPV/r and at 6 and 12 months (n=42)

	Group 1 Licensed dose (n = 13)	Group 2 Unlicensed dose (n =13)	Group 3 Off-label: age <14 days (n = 1)	Group 4 Missing weight/dose (n = 15)	Total (n = 42)
	N (%) /Median [IQR]				
VL (c/mL) at LPV/r start					
Value present	9 (69)	8 (62)	0 (0)	5 (33)	22 (52)
Median VL (log_{10} c/mL)	6.6 [6.5-6.7]	5.6 [4.3-6.5]	-	5.3 [3.6-5.7]	6.5 [5.1-6.6]
≤50	0 (0)	0 (0)	-	0 (0)	0 (0)
>50-≤400	0 (0)	1 (13)	-	0 (0)	1 (5)
>400- ≤1000	0	0	-	1 (20)	1 (5)
>1000	9 (100)	7 (88)	-	4 (80)	20 (91)
VL at 6 months					
≥6m in FU & on LPV/r	6 (46)	8 (62)	0 (0)	11 (73)	25 (60)
Value present	6 (100)	7 (88)	0 (0)	7 (64)	20 (76)
Median VL (log_{10} c/mL)	2.0 [1.8-4.6]*	2.1 [1.8-2.7]	-	2.4 [1.7-2.8]	2.1 [1.8-2.8]*
≤50	2 (33)	0 (0)	-	2 (29)	4 (20)
>50-≤400	2 (33)	5 (71)	-	2 (29)	9 (45)
>400- ≤1000	0 (0)	1 (14)	-	2 (29)	3 (15)
>1000	2 (33)	1(14)	-	1 (14)	4 (20)
VL at 12 months					
≥12m in FU & on LPV/r	5 (38)	5 (38)	0 (0)	6 (40)	16 (38)
Value present	5 (100)	5 (100)	0 (0)	6 (100)	16 (100)
Median VL (log_{10} c/mL)	2.7 [1.6-3.4]	2.0 [2.0-2.2]	-	1.8 [1.4-2.5]	2.0 [1.6-2.8]
≤50	2 (40)	1 (20)	-	3 (50)	6 (38)
>50-≤400	0 (0)	3 (60)	-	2 (33)	5 (31)
>400-≤1000	1 (20)	1 (20)	-	0 (0)	2 (13)
>1000	2 (40)	0 (0)	-	1 (17)	3 (19)
CD4 count at LPV/r start					
Value present	5 (38)	6 (46)	1 (100)	7 (47)	19 (45)
Median (cells/µl)	1668 [653-1900]	926 [333-1487]	3667 [3667-3667]	2469 [1584-3432]	1604 [568-2800]
CD4 count at 6m					
≥6m in FU & on LPV/r	6 (46)	8 (62)	0 (0)	11 (73)	25 (60)
Value present	4 (67)	7 (88)	0 (0)	6 (55)	17 (68)
Median CD4 count (cells/µl)	1916 [1406-2212]	1396 [1203-3133]	-	1686 [704-3072]	1897 [1203-2490]
CD4 count change at 6m					
≥6m in FU & on LPV/r	6 (46)	8 (62)	0 (0)	11 (73)	25 (60)
Value present	2 (33)	4 (50)	0 (0)	4 (36)	10 (40)
Median change in CD4 count (cells/µl)	590 [-797-702]	901 [332-1928]	-	-112 [-612-2087]	590 [-360-1046]
CD4 count at 12m					
≥12m in FU & on LPV/r	5 (38)	5 (38)	0 (0)	6 (40)	16 (38)
Value present	5 (100)	4 (80)	0 (0)	5 (83)	14 (88)
Median (cells/µl)	1784 [1734-1870]	1570 [1327-2107]	-	2054 [1892-2160]	1835 [1339-2160]
CD4 count change at 12m					
≥12m in FU & on LPV/r	5 (38)	5 (38)	0 (0)	6 (40)	16 (38)
Value present	5 (100)	4 (80)	0 (0)	5 (83)	14 (88)

Median change in CD4 count (cells/µl)	457 [-744-1657]	1245 [1012-1477]	-	1031 [-746-2808]	1245 [-744-1657]
CD4 % at LPV/r start					
Value present	5 (38)	6 (46)	0 (0)	7 (47)	18 (43)
Median CD4%	19 [17-23]	20 [9-27]	-	32 [29-39]	25 [17-35]
CD4 % at 6m					
≥6m in FU & on LPV/r	6 (46)	8 (62)	0 (0)	11 (73)	25 (60)
Value present	5 (83)	7 (88)	0 (0)	6 (55)	18 (72)
Median %	34 [28-38]	32 [27-53]	-	36 [16-44]	33 [27-44]
CD4 % change at 6m					
≥6m in FU & on LPV/r	6 (46)	8 (62)	0 (0)	11 (73)	25 (60)
Value present	3 (50)	4 (50)	0 (0)	4 (36)	11 (44)
Median change in CD4%	9 [-3-11]	16 [6.5-28]	-	5.3 [1-7]	8 [5-11]
CD4 % at 12m					
≥12m in FU & on LPV/r	5 (38)	5 (38)	0 (0)	6 (40)	16 (38)
Value present	4 (80)	3 (60)	0	5 (83)	12 (75)
Median CD4 %	30 [28-45]	32 [30-39]	-	34 [31-48]	32 [30-44]
CD4% change at 12m					
≥12m in FU & on LPV/r	5 (38)	5 (38)	0 (0)	6 (40)	16 (38)
Value present	2 (40)	2 (40)	0 (0)	1 (17)	5 (31)
Median change in CD4%	-1 [-6-4]	13 [3-23]	-	-3 [-3 to -3]	3 [-3-4]

* One child had VL recorded as below the lower limit of detection of the assay; however the limit of detection was not reported. This child is therefore not included in the calculation of the median as the precise VL was unknown, however they were considered to be virologically suppressed and so included in the ≤50 $\log_{10}$ c/mL category. Median VL is therefore based on n=5 for Group 1 and n=19 overall.

Table 4a: Laboratory data for patients on LPV/r (n=36 with lab data)

	ALT	AMY	ANC	AST	APT	CHOL	GGT	HDL	LDL	LIP	PHOS	SCa	S_CREAT	TBIL	TRIG	FPG	NonFPG
Group 1																	
Total tests	58	20	68	37	33	33	36	30	21	3	19	19	67	41	29	19	0
Total episodes	12	5	12	10	9	10	8	9	5	2	7	8	11	10	10	4	0
Total patients	12	5	12	10	9	10	8	9	5	2	7	8	11	10	10	4	0
N (%) grade 1	1 (8)	0 (0)	1 (8)	5 (50)	2 (22)	4 (40)	2 (25)	3 (33)	2 (40)	0 (0)	1 (14)	0 (0)	1 (9)	1 (10)	9 (90)	0 (0)	0 (0)
N (%) grade 2	4 (33)	0 (0)	2 (17)	3 (30)	0 (0)	4 (40)	1 (13)	6 (67)	4 (80)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
N (%) grade 3/4	3 (25)	0 (0)	1 (8)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	1 (10)	0 (0)	0 (0)
Group 2																	
Total tests	72	37	73	69	54	60	67	49	41	13	37	47	60	58	56	60	0
Total episodes	14	5	14	13	10	12	13	10	10	4	6	8	11	13	12	10	0
Total patients	13	5	13	12	9	11	12	9	9	4	6	7	10	12	11	9	0
N (%) grade 1	2 (15)	1(20)	3 (23)	4 (33)	3 (33)	6 (55)	6 (50)	3 (33)	3 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (64)	2 (22)	0 (0)
N (%) grade 2	2 (15)	0 (0)	4 (31)	2 (17)	1 (11)	5 (45)	1 (8)	5 (56)	4 (44)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (36)	1 (11)	0 (0)
N (%) grade 3/4	2 (15)	0 (0)	2 (15)	1 (8)	1 (11)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)	2 (17)	0 (0)	1 (11)	0 (0)
Group 3																	
Total tests	2	0	2	2	0	2	2	1	1	0	0	2	1	0	2	0	0
Total episodes	1	0	1	1	0	1	1	1	1	0	0	1	1	0	1	0	0
Total patients	1	0	1	1	0	1	1	1	1	0	0	1	1	0	1	0	0
N (%) grade 1	0 (0)	-	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)
N (%) grade 2	0 (0)	-	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)
N (%) grade 3/4	0 (0)	-	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)
Group 4																	
Total tests	42	4	29	25	22	19	17	13	13	9	7	14	30	32	19	17	0
Total episodes	11	1	10	7	7	8	7	6	6	3	4	5	8	10	8	6	0
Total patients	10	1	9	7	6	8	7	6	6	3	4	5	7	9	8	6	0
N (%) grade 1	1 (10)	0 (0)	1 (11)	1 (14)	1 (17)	1 (13)	4 (57)	2 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14)	1 (11)	2 (25)	0 (0)	0 (0)
N (%) grade 2	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)	3 (38)	0 (0)	3 (50)	4 (67)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	0 (0)
N (%) grade 3/4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	0 (0)
Total																	
Total no. tests	**174**	**61**	**172**	**133**	**109**	**114**	**122**	**93**	**76**	**25**	**63**	**82**	**158**	**131**	**106**	**96**	**0**
Total episodes	**38**	**11**	**37**	**31**	**26**	**31**	**29**	**26**	**22**	**9**	**17**	**22**	**31**	**33**	**31**	**20**	**0**
Total patients	**36**	**11**	**35**	**30**	**24**	**30**	**28**	**25**	**21**	**9**	**17**	**21**	**29**	**31**	**30**	**19**	**0**

	ALT	AMY	ANC	AST	APT	CHOL	GGT	HDL	LDL	LIP	PHOS	SCa	S_CREAT	TBIL	TRIG	FPG	NonFPG
N (%) grade 1	**4 (11)**	**1 (9)**	**5 (14)**	**10 (33)**	**6 (25)**	**11 (37)**	**12 (43)**	**8 (32)**	**5 (24)**	**0 (0)**	**1 (6)**	**0 (0)**	**2 (7)**	**2 (6)**	**18 (60)**	**2 (11)**	**0 (0)**
N (%) grade 2	**6 (17)**	**0 (0)**	**6 (17)**	**6 (20)**	**1 (4)**	**12 (40)**	**2 (7)**	**14 (56)**	**12 (57)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (3)**	**5 (17)**	**1 (5)**	**0 (0)**
N (%) grade 3/4	**5 (14)**	**0 (0)**	**3 (9)**	**1 (3)**	**1 (4)**	**1 (3)**	**1 (4)**	**0 (0)**	**1 (5)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**3 (10)**	**2 (7)**	**1 (5)**	**0 (0)**

Notes:

Column percentages of number of patients with a grade 1-4 event within each group.

All grading for laboratory results for n (%) patients with ≥1 test result in each grade

No non-FPG tests reported

T-BIL is not reported for those <28 days of age.

All laboratory values (with the exception of HDL and GGT) were classified according to the Division of AIDS (DAIDS 2014) grading system for laboratory events.

GGT was classified according to the CTCAE-National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events.

HDL was classified according to the US NIH-National Institute of Health, National Heart, Lung and Blood Institute guidelines.

Table 4b: Event rates for laboratory tests with ≥20 patients

Test	No of tests	No of patients/episodes	Patients with ≥1 test result in each grade (/100 person-years)								
			Grade 1 (Mild)			Grade 2 (Moderate)			Grade 3 / 4 (Severe)		
			N (%)	PY	Rate/ 100 PY (95% CI)	N (%)	PY	Rate/ 100 PY (95% CI)	N (%)	PY	Rate/ 100 PY (95% CI)
ALT	174	36/38	4 (11)	200.5	2.0 (0.5 - 5.1)	6 (17)	200.5	3.0 (1.1 - 6.5)	5 (14)	200.5	2.5 (0.8 - 5.8)
ANC	172	35/37	5 (14)	196.8	2.5 (0.8 - 5.9)	6 (17)	196.8	3.0 (1.1 - 6.6)	3 (9)	196.8	1.5 (0.3 - 4.5)
APT	109	24/26	6 (25)	137.6	5.1 (2.0 - 10.5)	1 (4)	137.6	0.7 (0.0 - 4.1)	1 (4)	137.6	0.7 (0.0 - 4.1)
AST	133	30/31	10 (33)	157.5	6.3 (3.0 - 11.7)	6 (20)	157.5	3.8 (1.4 - 8.3)	1 (3)	157.5	0.6 (0.0 - 3.5)
CHOL	114	30/31	11 (37)	136.7	8.0 (4.0 - 14.4)	12 (40)	136.7	9.5 (5.1 - 16.3)	1 (3)	136.7	0.7 (0.0 - 4.1)
GGT	122	28/29	12 (43)	148.8	8.1 (4.2 - 14.1)	2 (7)	148.8	1.3 (0.2 - 4.9)	1 (4)	148.8	0.7 (0.0 - 3.7)
HDL	93	25/26	8 (32)	116.5	6.9 (3.0 - 13.5)	14 (56)	116.5	12.8 (7.2 - 21.2)	0 (0)	116.5	0.0 (0.0 - 3.2)*
LDL	76	21/22	5 (24)	97.7	5.1 (1.7 - 11.9)	12 (57)	97.7	13.3 (7.1 - 22.7)	1 (5)	97.7	1.0 (0.0 - 5.7)
S_CREAT	158	29/31	2 (7)	201.1	1.0 (0.5 - 3.6)	0 (0)	201.1	0.0 (0.0 - 1.8)	0 (0)	201.1	0.0 (0.0 - 1.8)*
SCa	82	21/22	0 (0)	109.4	0 .0(0.0 - 3.4)*	0 (0)	109.4	0.0 (0.0 - 3.4)*	0 (0)	109.4	0.0 (0.0 - 3.4)*
TBIL	131	31/33	2 (6)	153.1	1.3 (0.2 - 4.7)	1 (3)	153.1	0.7 (0.0 - 3.6)	3 (10)	153.1	2.0 (0.4 - 5.7)
TRIG	106	30/31	18 (60)	127.4	14.1 (8.4 - 22.3)	5 (17)	127.4	3.9 (1.3 - 9.2)	2 (7)	127.4	1.6 (0.2 - 5.7)

*One sided confidence interval for tests where no grade 3 or 4 events were observed

Table 5: Test results for patients with grade ≥3 laboratory test results whilst on LPV/r (n=12 with 19 events)[α]

Patient # Country Sex	LPV/r start date Group	LPV/r end date (reason for LPV/r stopping)	Test	No of grade ≥3 tests	Test date range (for grade ≥3 tests	No. of grade 3 tests	No. of grade 4 tests	Other ART drugs at test(s)	LPV/r dose (mg)	Age at first grade ≥3 test(months)	"Normal" value after last grade ≥3 result (date of next normal test)	Last any test on LPV/r†
[redacted]	[redacted]-18 Group 2	Toxicity - GI tract [redacted]-19	APT	1	[redacted]-19	0	1	3TC+NVP+ZDV		[redacted]	No	[redacted]-19
[redacted]	[redacted]-16 Group 2	Still on LPV/r	ANC	1	[redacted]-16	1	0	3TC+ZDV	100	[redacted]	Yes [redacted] 16)	[redacted]-17
			TBIL	10	[redacted]-16 [redacted]-17	8	2		100	[redacted]	Yes	[redacted]-17
[redacted]	[redacted]-17 Group 2	Still on LPV/r	TBIL	1	[redacted]18	1	0	-	100	[redacted]	No	[redacted]-18
[redacted]	[redacted]17 Group 4	Still on LPV/r	CHOL	1	[redacted]18	1	0	3TC+ABC	170	[redacted]	No	[redacted]-19
			TRIG	1	[redacted]-18	1	0	3TC+ABC	170	[redacted]	No	[redacted]-19
[redacted]	[redacted]-19 Group 2	Still on LPV/r	ANC	1	[redacted]-19	0	1		-	[redacted]	Yes [redacted]-19)	[redacted]-19
			ALT	1	[redacted]-19	1	0	3TC+ABC +RAL	150	[redacted]	No	[redacted]-19
[redacted]	[redacted]-18 Group 2	Still on LPV/r	ALT	1	[redacted]-18	0	1		120	[redacted]	Yes [redacted]-20	[redacted]-20
			AST	1	[redacted]-18	0	1		120	[redacted]	Yes [redacted]-20	[redacted]-20
			FPG	1	[redacted]-18	0	1	3TC+ABC		[redacted]	Yes [redacted]-20	[redacted]-20
[redacted]	[redacted]-16 Group 2	Still on LPV/r	LDL	1	[redacted]-17	1	0	ABC+RAL+ZDV	136	[redacted]	No	[redacted]-18
[redacted]	[redacted]-18 Group 1	Still on LPV/r	GGT	1	[redacted]-18	1	0		96	[redacted]	Yes [redacted]-19	[redacted]-19
			ALT	2	[redacted]-19 [redacted]-19	2	0	3TC+ZDV	136	[redacted]	Yes [redacted]-19	[redacted]-19
[redacted]	[redacted]-17 Group 1	Still on LPV/r	T-BIL	10	[redacted]-17 [redacted]-18	9	1	ABC+FTC	160	[redacted]	No	[redacted]-18
[redacted]	[redacted]-19 Group 1	Still on LPV/r	ALT	1	[redacted]-20	1	0		112	[redacted]	Yes [redacted]-20)	[redacted]-21
			TRIG	1	[redacted]-20	1	0	3TC+ABC	128	[redacted]	Yes [redacted]-20)	[redacted]-21
[redacted]	[redacted]-21 Group 1	Still on LPV/r	ALT	1	[redacted]-21	1	0	3TC+ZDV	80	[redacted]	Yes [redacted]-21)	[redacted]-21

[redacted]	[redacted]-19 Group 1	Still on LPV/r	ANC	1	[redacted]-19	1	0	3TC+ABC+ZDV	120	[redacted]	Yes [redacted]-19)	[redacted]-19

†Last reported test of the same marker as reported grade ≥3 test (for example, last reported BIL test if reported grade ≥3 BIL test). Data were censored in the main analysis on patients' second birthday although data on outcomes of lab events were included through to age 3 years for those who had a grade 3/4 event before the age of 2.

α: Year 2 report included patient [redacted] with GGT grade 3 event, updated data this year were corrected to show that the tests were not grade 3/ 4 and therefore this patient does not appear in this table in the Year 3 report

*Newly reported for this report

Table 6: Clinical adverse events (AE) and serious AEs (SAE) considered causally related to LPV/r (n=3 with 6 events)

Patient # Country Sex	LPV/r start date/ Group	LPV/r stop date (reason)	AE type/Date	AE Resolution status/Date	Grade	Serious AE	ART at AE date/ Causality	Age at AE (months)	LPV/r dose* (mg)	Concomitant medication
[redacted]	[redacted]-17 Group 1	Still on LPV/r	Immune reconstitution inflammatory syndrome (IRIS) [redacted]-17	Recovered [redacted]-17	Severe	Yes	ABC+FTC+LPV Probable	[redacted]	112	Antibiotics+Antibiotics+Benzodiazepine derivatives+Corticosteroids+Cotrimoxazole - Comb. of sulfonamides and trimethoprim (BACTRIM, EUSAPRIM, NOPIL)+Fluconazole (DIFLUCAN)+Folinate of calcium (LEUCOVORINE)+hydroxycarbamide +vitamin D+vitamin D
[redacted]	[redacted]-16 Group 2	Still on LPV/r	Vomiting [redacted]-16	Recovered [redacted]-17	Severe	Yes	3TC+ABC+LPV Definitive	[redacted]	80	Septrin + Amoxicillin +Amoxicillin-clavulanate + Ferrous sulfate + Nistatine + Oseltamivir Amoxicillin
			Vomiting [redacted]-17	Recovered [redacted]-18	Severe	Yes	3TC+ABC+NVP Definitive	[redacted]		Septrin + Amoxicillin +Amoxicillin-clavulanate + Ferrous sulfate + Nistatine + Oseltamivir Amoxicillin
			Raised triglycerides [redacted]-17	-**	Moderate	No	ABC+LPV+RAL+ZDV Definitive	[redacted]	120	Septrin + Amoxicillin +Amoxicillin-clavulanate + Ferrous sulfate + Nistatine + Oseltamivir Amoxicillin
			Raised cholesterol [redacted]-17	-**	Moderate	No	ABC+LPV+RAL+ZDV Definitive	[redacted]	120	Septrin + Amoxicillin +Amoxicillin-clavulanate + Ferrous sulfate + Nistatine + Oseltamivir Amoxicillin
[redacted]	[redacted]-19 Group 2	Still on LPV/r	Raised triglycerides [redacted]-19	-**	Mild	Unknown	3TC+ABC+LPV Probable	[redacted]	160	None reported

*Dose prescribed at the time of the event (per dosing event (BD dosing)).

**No data on resolution of AE at time of data censor.

Table 7: Clinical AEs and SAEs considered not causally related to LPV/r (n=5 with 7 events)

Patient/ Country/ Sex	LPV/r start date Group	LPV/r stop date (reason)	AE type/Date	AE resolution status/Date	Grade	Serious AE	ART at AE/ Causality	Age at AE (months)	LPV/r dose* (mg)	Concomitant medication
[redacted]	[redacted]-19 Group 2		Death in car accident [redacted]	Not applicable	Life-threatening	Yes	3TC+ABC+LPV. Not related	[redacted]	128	None reported
[redacted]	[redacted]-19 Group 2	Still on LPV/r	Recurrent bacterial pneumonia* [redacted]-19	Unknown	Severe	Unknown	Not related	[redacted]	-	None reported
			Chronic lymphoid interst. pneumonitis - mild* [redacted]-19	Unknown	Severe	Unknown	3TC+LPV+RAL Not related	[redacted]	250	Corticosteroids+Cotrimoxazole - Comb. of sulfonamides and trimethoprim (BACTRIM, EUSAPRIM, NOPIL)+Valganciclovir
[redacted]	[redacted]17 Group 1	Still on LPV/r	Diarrhoea, loose stool, unspecified or <30 days [redacted]-17	Recovered [redacted]-17	Severe	Yes	ABC+FTC+LPV Not related	[redacted]	160	Phenoxymethylpenicillin+ (Penilevel 250mg) Folic Acid + Ranitidine + Vitamin D+ Prednisone Praziquantel + Deltius +Sicklos
[redacted]	[redacted]-19 Group 1	Still on LPV/r	Mucocutaneous Candidiasis [redacted]-19	Recovered [redacted]-19	Moderate	Yes	Not related	[redacted]		Sulfamethoxazole and trimethoprim (Bactrim)
[redacted]	[redacted]-18 Group 1	Still on LPV/r	Lower respiratory infection [redacted]-18	Recovered [redacted]-18	Life-threatening	Yes	3TC+ABC+LPV Not related	[redacted]	92	Azithomycine (ZITHROMAX)+Cotrimoxazole - Comb. of sulfonamides and trimethoprim (BACTRIM, EUSAPRIM, NOPIL)+Fluconazole (DIFLUCAN)+Methadone+vitamin D
			Breathlessness, dyspnoea [redacted]-18	Recovered [redacted]-18	Life-threatening	Yes	3TC+ABC+LPV Not related	[redacted]	92	Azithomycine (ZITHROMAX)+Cotrimoxazole - Comb. of sulfonamides and trimethoprim (BACTRIM, EUSAPRIM, NOPIL)+Fluconazole (DIFLUCAN)+vitamin D

Table 8a: Clinical AEs and SAEs with unknown causal association to LPV/r (n=2)

Patient/ Country/ Sex	LPV/r start date Group	LPV/r stop date (reason)	AE type/Date	AE resolution status/Date	Grade	Serious AE	ART at AE/ Causality	LPV/r dose* (mg)	Age at AE (months)	Concomitant medication
[redacted]	[redacted]-17 Group 2	Still on LPV/r	Persistent generalised lymphadenopathy*	Unknown	Unknown	Unknown	Unknown	-	-	None reported
[redacted]	[redacted]-19 Group 2	Still on LPV/r	CMV hepatitis*	[redacted]-19 Unknown	-	Unknown	3TC+ABC+LPV+RAL Unknown	150	[redacted]	Cotrimoxazole - Comb. of sulfonamides and trimethoprim (BACTRIM, EUSAPRIM, NOPIL)+Fluconazole (DIFLUCAN)+Other anti-hypertensive agents [C02, C03, C04, C07, C08]+Valganciclovir

*Event newly reported this year

Table 8b: Clinical adverse events with unknown seriousness (n=6 with 12 events)

Patient/ Country/ Sex	LPV/r start date/Group	LPV/r stop date (reason)	AE type/date	Resolution status/ date	AE Grade	Serious AE	ART at AE/ Causality	LPV/r Dose (mg)	Age at AE (months)	Medication
[redacted]	[redacted]-16 Group 2	Still on LPV/r	Recurrent or persistent oral candida [redacted]-16	Recovered [redacted]-16	Unknown	Unknown	3TC+LPV+ZDV Not related	100	[redacted]	None reported
			Pneumocystis jirovecii pneumonia* [redacted]-16	Recovered [redacted]-16	Moderate	Unknown	Not related	-	[redacted]	None reported
			Acute otitis media* [redacted]-17	Recovered [redacted]-17	Mild	Unknown	3TC+ABC+LPV Not related	200	[redacted]	None reported
			CMV hepatitis* [redacted]-16	Recovered [redacted]-16	Moderate	Unknown	3TC+LPV+ZDV Not related	100	[redacted]	Azithomycine (ZITHROMAX)+Cotrimoxazole - Comb. of sulfonamides and trimethoprim (BACTRIM, EUSAPRIM, NOPIL)+Ganciclovir (CYMEVENE)
			Neutropenia* [redacted]-16	Recovered [redacted]-16	Mild	Unknown	3TC+LPV+ZDV Related (probable) to ZDV	-	[redacted]	Azithomycine (ZITHROMAX)+Cotrimoxazole - Comb. of sulfonamides and trimethoprim (BACTRIM, EUSAPRIM, NOPIL)+Ganciclovir (CYMEVENE)
			Anaemia* [redacted]-16	Recovered [redacted]16	Mild	Unknown	3TC+LPV+ZDV Related (probable) to ZDV	-	[redacted]	Azithomycine (ZITHROMAX)+Cotrimoxazole - Comb. of sulfonamides and trimethoprim (BACTRIM, EUSAPRIM, NOPIL)+Ganciclovir (CYMEVENE)
[redacted]	[redacted]-17 Group 2	Still on LPV/r	Persistent generalised lymphadenopathy*β Unknown	Unknown	-	Unknown	Unknown	-	-	None reported
[redacted]	[redacted]-19 Group 2	Still on LPV/r	Raised triglycerides† [redacted]-19	Not recovered	Mild	Unknown	3TC+ABC+LPV Probable	160	[redacted]	None reported
[redacted]	[redacted]-19 Group 2	Still on LPV/r	Extrapulmonary cryptococcal infection [redacted]-19	Unknown	Unknown	Unknown	Not related	-	[redacted]	None reported
			CMV hepatitis*β [redacted]-19	Unknown	Unknown	Unknown	3TC+ABC+LPV+RAL Unknown	150	[redacted]	Cotrimoxazole - Comb. of sulfonamides and trimethoprim (BACTRIM, EUSAPRIM, NOPIL)+Fluconazole (DIFLUCAN)+Other anti-hypertensive agents [C02, C03, C04, C07, C08]+Valganciclovir
[redacted]	[redacted]-16 Group 4	[redacted]-17 Unknown	Rash / Lesions* [redacted]-17	Recovered [redacted]17	Unknown	Unknown	3TC+ABC+LPV+NVP Related (probable) to NVP	Unknown	[redacted]	None reported

[redacted]	[redacted]-17 Group 4	[redacted]-19 Other causes	[redacted] fistula with colostomy* [redacted]-19	Unknown	Unknown	Unknown	3TC+LPV+ZDV Not related	Unknown	[redacted]	None reported

*Event newly reported this year

† Event also reported in Table 6 as it was considered related to LPV/r.

β Event also reported in Table 8a as LPV/r causality unknown

Table 9: Reasons for LPV/r discontinuations (n=5/42)

	Group 1 Licensed dose	Group 2 Unlicensed dose	Group 3 Off-label	Group 4 Missing weight/dose	Total
Total initiating LPV/r	13	13	1	15	42
Total discontinuations	2 (15)	1 (8)	0 (0)	2 (13)	5 (12)
		N (%)			
Time to discontinuation					
<1 month	1 (50)	0 (0)	0 (0)	0 (0)	1 (20)
1 - <6 months	1 (50)	0 (0)	0 (0)	1 (50)	2 (40)
6 - <12 months	0 (0)	1 (100)	0 (0)	1 (50)	2 (40)
≥12 months	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Reasons for discontinuation					
Lack of effectiveness	0 (0)	0 (0)	0 (0)	1 (50)	1 (20)
Safety	0 (0)	1 (100)	0 (0)	0 (0)	1 (0)
Other	2 (100)	0 (0)	0 (0)	1 (50)	3 (60)

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms included: Targeted Questionnaire: Lopinavir/Ritonavir and Medication errors (including overdose)

Reporter Information: Family Member ☐ HCP ☐ Other (specify)		
Name:		
Street Address		
City:	State:	Zip:
Phone:		
Fax:		
Email:		
Title/Specialty:		
Person completing form:		

Does parent/guardian agree to have MD/HCP contacted? Yes ☐ No ☐		
Physician/HCP Name:		
Street Address:		
City:	State:	Zip:
Phone Number:		

Affiliate Reference#:
AER#
Other Reference#:

Patient Information:

Initials:	Patient ID:	Sex: Male ☐ Female ☐	Date of Birth:	Age at time of event:
Height: cm ☐ inches ☐	Weight: kg ☐ pounds ☐	Birth Weight (if under 4 years):	Race: Black ☐ Caucasian ☐ Hispanic ☐ Asian ☐ Other	
Allergies: Yes ☐ No ☐ (type and manifestation)				
Patient Medical History (include family history, (risk factors), HIV,…):				

Suspect Product:

Name	Prescribed Dose	Dose given	Device used*	Device ml size	Administered by**	Dose Form***	Frequency	Route	How many doses or over what timeframe	Start Date (d/m/y)	End Date (d/m/y)	Indication	If stopped, did event abate? If so, provide date

***** Device could include (Syringe, measuring spoon, medication dose cup, IV, Pump) ** Administered by could include (physician, pharmacist, nurse, healthcare provider, parent, or caregiver)
*** Dose form could include: IV solution, Tablet, Capsule, solution, gel, syrup, granules etc

Please provide Abbvie product Lot number for time of event: _____ Expiration date _____ Lot number and expiration for device (if appropriate) _____

If unable to provide Lot number, provide rationale: discarded ☐ not accessible to physician ☐ not on patient's file ☐ did not receive in original package ☐ not legible on package ☐

If AbbVie product was discontinued, was it restarted? _____ Date _____ Dose _____

Please provide detailed event information including symptoms the patient experienced leading up to the events: _____

_____

If overdose was suspected, please provide reason overdose occurred, if known _____

If resistance is suspected, has this patient been treated with other protease inhibitors prior to KALETRA therapy_____

Adverse Event	Event Onset (d/m/y)	Outcome (d/m/y)	Event Criteria+	Causality++	Outcome Status**

+ Event Criteria codes: Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability, or Non serious

++ Causality Code: Reasonable Possibility, No Reasonable Possibility, Non-Assessable

** Outcome codes: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Concomitant (C), Past (P), Treatment (T) medication information: (Please include herbal, recreational, OTC medication and supplements):

Name	C, P or T	Form	Dose	Frequency	Route	Start date	End Date	Indication

Please provide evidence of loss of virologic response (i.e., HIV viral RNA load, copies/mL) or of development of resistance of lopinavir/ritonavir, if suspected (three or more of the following lopinavir-associated amino acid substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V): _____

Please provide Laboratory and Diagnostic Test results:

Laboratory test	Prior to Event		Test Peak during event		When event improved/resolved		Reference range (including units of measure)
	Test date d/m/y	Test result	Test date (d/m/y)	Test result	Test date (d/m/y)	Test result	
Drug level							
CBC							
BUN							
Creatinine							
Liver panel							
Blood gases							
Sodium							
Potassium							
Chloride							
O2 sat							
Serum osmolality							
Glucose							
Ethanol (blood alcohol) level							
Serum propylene glycol level							
Viral RNA (copies/ml)							
Protease mutations							

Diagnostic test	Date (d/m/y)	Results (key findings) (If desired attach results)
Glasgow coma scale		
X-Ray		
EKG		
BP		
Pulse		
EEG		
MRI		
CT		

Please provide what treatment or interventions the patient underwent for the events: _____

If the patient died, Date of Death: _____/_____/_____ (d/m/y)	Autopsy: Yes ☐ No ☐ Unknown ☐	Autopsy Date: _____/_____/_____ (d/m/y)
Autopsy results:	Cause of Death:	

Annex 6. Details of Proposed Additional Risk Minimization Activities (If Applicable)

Not applicable.