Title Page

Title	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
Protocol Version Identifier	P19-106 – Version 1
Date of Last Version of Protocol	24 March 2020
EU PAS Register Number	EUPAS32607
Active Substance	ATC code: J05AR10; lopinavir and ritonavir
Medicinal Product	Kaletra (80 mg + 20 mg)/mL oral solution
Product Reference	EMEA/H/C/000368
Procedure Number	EMEA/H/C/000368 LEG121
Marketing Authorisation Holder(s)	AbbVie Deutschland GmbH & Co. KG
Joint PASS	No
Research Question and Objectives	The study objectives, in children under 2 years of age, are to: 1. 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 2. assess the appropriateness of Kaletra dose for weight or body surface area using the AbbVie Kaletra SmPC as a reference 3. evaluate the safety and tolerability of Kaletra 4. assess the immune and virologic response to Kaletra-containing therapy
Countries of Study	Belgium, Denmark, Greece, Italy, Poland, and Spain, United Kingdom/Ireland. Future cohorts in the following countries may also be included: Netherlands, Romania, Sweden
Author	[redacted]

Author (continued)	[redacted]

This study will be conducted in compliance with this protocol.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany
MAH Contact Person	[redacted]

1.0 Table of Contents

List of Figures

2.0 Abbreviations

AE	Adverse event
ART	Antiretroviral therapy
CDC	Centers for Disease Control and Prevention
CHIPS	Collaborative HIV Paediatric Study
CTCAE	Common Toxicity Criteria for Adverse Events
DAIDS	Division of AIDS
EMA	European Medicines Agency
EPPICC	European Pregnancy and Paediatric Infections Cohort Collaboration
EU	European Union
GGT	Gamma glutamyl transferase
HDL	High-density lipoprotein cholesterol
HICDEP	HIV Cohorts Data Exchange Protocol
HIV	Human immunodeficiency virus
LPV/r	Lopinavir/ritonavir (Kaletra)
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NSHPV	National Study of HIV in Pregnancy and Childhood
PASS	post-authorization safety study
PENTA	Paediatric European Network for Treatment of AIDS
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VL	Viral load

3.0 Responsible Parties

AbbVie Deutschland GmbH & Co. KG

Paediatric European Network for Treatment of AIDS (PENTA).

4.0 Abstract

Title: 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

Rationale and Background: On 26 July 2017, the European Commission approved the extension of the indication of Kaletra (80 mg + 20 mg)/mL oral solution to include children 14 days of age or older for the treatment of human immunodeficiency virus (HIV)-1.

Kaletra oral solution has a high content of ethanol and propylene glycol. The Summary of Product Characteristics (SmPC) includes a warning regarding its use in very young children, which may lead to chronic exposure to propylene glycol and ethanol and related toxicities in the pediatric population. The European Medicines Agency (EMA) has also highlighted concerns regarding medication errors that could result in overdose, which could also increase exposure to these excipients. In addition, EMA has also highlighted concerns regarding lack of efficacy/viral resistance in relation to potentially suboptimal pharmacokinetic parameters in young children receiving Kaletra.

In January 2018, the CHMP requested that AbbVie set up a pharmacovigilance cohort from existing European paediatric cohorts such as European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) in order to be able to detect any safety issue in relation to propylene glycol or ethanol toxicity.

The EPPICC pharmacovigilance network includes 21 cohorts from 16 European countries and Thailand.

The rationale for this study is multifold. The study shall describe the characteristics of children less than 2 years of age while treated with Kaletra oral solution at or after the approval date of 26 July 2017 in the EMA scope of authority within Europe. The study will also assess the appropriateness of Kaletra oral solution formulation dose for weight or body surface area while under 2 years of age and the safety and tolerability

of Kaletra in children under 2 years of age by describing adverse events (AEs) experienced while on Kaletra, in particular in relation to propylene glycol or ethanol toxicity. In addition, the study will assess the immune and virologic response to Kaletra-containing therapy and the incidence and reasons for discontinuation of Kaletra.

Research Question and Objectives: The study objectives, in children under 2 years of age, are to:

1. 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
2. assess the appropriateness of Kaletra dose for weight or body surface area using the AbbVie Kaletra SmPC as a reference
3. evaluate the safety and tolerability of Kaletra by the following:
    - describe discontinuation of Kaletra and reasons (in particular toxicity-related)
    - describe clinical adverse events while on Kaletra or up to 3 months after discontinuation of Kaletra, in particular in relation to study drug or propylene glycol or ethanol toxicity
    - assess the incidence of clinically significant laboratory abnormalities (Division of AIDS [DAIDS] grade 1 – 4)
    - assess the immune and virologic response to Kaletra-containing therapy

Study Design: This is a descriptive cohort study. In this study, patients will be included based on their exposure to Kaletra while < 2 years of age and they will be followed over time to ascertain the occurrence of key outcomes of interest (e.g., AEs).

Population: All HIV-1–infected patients < 2 years of age within EMA countries of Europe are eligible for inclusion if treated with Kaletra oral solution at or after the approval date (26 July 2017).

Variables: Variables to be collected on all children taking Kaletra will include demographic data, medical history, all antiretroviral prophylaxis and treatments received, other concomitant medications, anthropometric measurements, CD4 and HIV-1 RNA viral load (VL), AEs, discontinuation of study drug, follow-up, and laboratory markers routinely conducted as part of standard of care.

Among patients who experience serious adverse events (SAEs) while on Kaletra or clinical AEs reported by the attending clinician as causally related to Kaletra (possibly, probably or definitely), a detailed questionnaire will be sent to the clinic. The questionnaire seeks further information on the type of event, if it was related to ethanol and/or propylene glycol related toxicities or medication errors, the laboratory tests conducted, interventions the patient underwent for these events and their outcome.

Data Sources: Pooled analysis of pseudonymized individual patient clinical and laboratory data from the following European Union (EU) cohorts participating in the EPPICC pharmacovigilance program (confirmed to have eligible patients, as of August 2019):

- Hospital St Pierre Cohort, Brussels, Belgium
- Copenhagen Cohort, Denmark
- Greece Cohort
- Italian Register for HIV Infection in Children, Italy
- Polish Paediatric Cohort
- CoRISPE-cat, Catalonia, Spain
- CoRISPE-S, Spain (now including the Madrid Paediatric Cohort Study)
- Collaborative HIV Paediatric Study (CHIPS) and National Study of HIV in Pregnancy and Childhood (NSHPC), United Kingdom (UK)/Ireland

Other EU cohorts within EPPICC who may have eligible patients in the future:

- ATHENA national observational HIV cohort, Netherlands

- Centro Hospitalar do Porto, Porto, Portugal
- "Victor Babes" Hospital Cohort, Romania
- Karolinska University Hospital, Stockholm, Sweden

Study Size: As per the Year 1 report with data lock date of 16 May 2019, among EU cohorts in EPPICC, 14 patients were reported to meet the study inclusion criteria by that date amongst cohorts participating in this study. This number is expected to increase over time as newly diagnosed infants receive Kaletra in this post-approval period.

Data Analysis: Data from EPPICC will be summarized using descriptive statistics for the set of all patients and for each of the 4 groups described below. Due to the expected small sample size, graphic summary of individual patient response (e.g., CD4 and HIV-1 RNA viral load over time on Kaletra) may be explored.

Patients will be categorized to a group based on their age, weight (or body surface area where height data are available), dose, and dosing frequency on the day of first reported Kaletra exposure. The 4 groups are as follows:

Group 1: Licensed: patients 14 days to < 2 years of age initiating on a licensed dose
Group 2: Unlicensed: patients 14 days to < 2 years of age initiating on an unlicensed dose
Group 3: Patients < 14 days of age
Group 4: Patients 14 days to < 2 years of age with missing weight and/or dose data at Kaletra initiation

The number of children meeting the inclusion criteria for the study during each reporting interval and cumulatively will be presented. The duration of Kaletra exposure (censored at earliest of 2 years of age or at 3 months after discontinuation of Kaletra or at date of death or last visit) will be summarized in months and patient-months.

To address the first study objective, demographic, medical history including antiretroviral therapy [ART] regimen, concomitant medication, and anthropometric data (including body surface area) will be summarized.

To address the second study objective, patients who received off-label use, licensed dosing, and unlicensed dosing will be summarized.

To address the third study objective, the following will be summarized:

- Patients who discontinued Kaletra, along with a summary of the reasons for discontinuation
- Patients followed up to 2 years of age, along with a summary of the reasons for drop out
- Laboratory abnormalities by grade to reflect the incidence of laboratory abnormalities whilst exposed to Kaletra while < 2 years of age.
    - Division of AIDS (DAIDS 2014) gradings for pediatric laboratory AEs will be used to categorize the severity of results, where available. Gamma glutamyl transferase (GGT) will be graded using Common Toxicity Criteria for Adverse Events (CTCAE) 4.03, and high-density lipoprotein cholesterol (HDL) will be graded using the US National Heart, Lung, and Blood Institute (NHLBI) categories; results by severity will be presented as numbers of events and rates per 100 person-years of follow-up, provided there are sufficient numbers of patients in follow-up ($n \geq 20$) to provide a meaningful estimate. Among patients who experience a DAIDS grade 3 or 4 event, additional details will be collected with follow-up data up to the age of 3 years or the end of the study period.
- AEs; AEs considered related to Kaletra, propylene glycol, and ethanol; SAEs; and SAEs considered related to Kaletra propylene glycol, and ethanol.
    - Among patients who experience a clinical AE causally related to Kaletra and have the additional questionnaire completed, a detailed summary of the event, additional tests conducted, treatment and outcome will be provided on a patient-level basis.

To address the fourth study objective, patients with an HIV-1 RNA value ≥ 50, ≥ 400, and ≥ 1000 copies/mL while receiving Kaletra will be summarized, as well as CD4 counts and percentages.

Milestones: Major study milestones and their planned dates are as follows.

Study duration: 3 years (August 2018 – September 2021)

Preliminary timeline and key milestones are described below:

Year 1 (2018 – 2019) – Completed

- Finalize study protocol and standard operating procedure for data merger: August – September 2018
- Submission to ethics approval and regulatory approval at cohort level, sign data sharing agreement with cohorts: October 2018
- Data merger: October – November 2018
- Data cleaning: November – December 2018
- Preliminary analysis and initial report*: first draft early December
- Final draft of preliminary report to AbbVie: 20 December 2018
- AbbVie submit preliminary report to EMA: 25 January 2019
- Draft/Final study report for Year 1: June 2019
- AbbVie report to EMA: July 2019

  * The preliminary report may be limited to data from a subgroup of cohorts if others are delayed by ethics approval.

Year 2 – 3

Annual milestones (for 2020 and 2021*):

- Data merger: January
- Data cleaning: February – March
- Analysis and write up: April – July

- Draft/final report to AbbVie: August
- AbbVie submission to EMA: 25 September annually

  * Following the reclassification of this study to a PASS, some cohorts will require ethics approval of the updated protocol.

5.0 Amendments and Updates

The study was reclassified as a post-authorization safety study (PASS) on 28 November 2019; the study protocol, therefore, has been updated using a PASS template. Following the reclassification of this study to a PASS, some cohorts will require ethics approval of the updated protocol.

6.0 Milestones

Major study milestones and their planned dates are as follows.

Study duration: 3 years (August 2018 – September 2021)

Preliminary timeline and key milestones are described below:

Year 1 (2018 – 2019) – Completed

- Finalize study protocol and standard operating procedure for data merger: August – September 2018
- Submission to ethics approval and regulatory approval at cohort level, sign data sharing agreement with cohorts: October 2018
- Data merger: October – November 2018
- Data cleaning: November – December 2018
- Preliminary analysis and initial report*: first draft early December
- Final draft of preliminary report to AbbVie: 20 December 2018
- AbbVie submit preliminary report to EMA: 25 January 2019
- Draft/Final study report for Year 1: June 2019
- AbbVie Year 1 report to EMA: July 2019

  * The preliminary report may be limited to data from a subgroup of cohorts if others are delayed by ethics approval.

Year 2 – 3 (2020 – 2021)

Annual milestones:

- Data merger: January
- Data cleaning: February – March
- Analysis and write up: April – July
- Draft/final report to AbbVie: August
- AbbVie submission to EMA: 25 September annually

7.0 Rationale and Background

On 26 July 2017, the European Commission approved the extension of the indication of Kaletra (80 mg + 20 mg)/mL oral solution to include children 14 days of age or older for the treatment of human immunodeficiency virus (HIV)-1.

Kaletra oral solution has a high content of ethanol and propylene glycol. The Summary of Product Characteristics (SmPC) includes a warning regarding its use in very young children, which may lead to chronic exposure to propylene glycol and ethanol and related toxicities in the pediatric population. The European Medicines Agency (EMA) has also highlighted concerns regarding medication errors that could result in overdose, which could also increase exposure to these excipients. In addition, EMA has also highlighted concerns regarding lack of efficacy/viral resistance in relation to potentially suboptimal pharmacokinetic parameters in young children receiving Kaletra.

In Europe, several established, prospective observational cohort studies of HIV-1–infected children and adolescents participate in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC). The EPPICC pharmacovigilance network includes 21 cohorts from 16 European countries and Thailand.

The rationale for this study is multifold. The study shall describe the characteristics of children less than 2 years of age while treated with Kaletra oral solution at or after the approval date of 26 July 2017 in the EMA scope of authority within Europe. The study

will also assess the appropriateness of Kaletra oral formulation dose for weight or body surface area while under 2 years of age and the safety and tolerability of Kaletra in children under 2 years of age by describing adverse events (AEs) experienced while on Kaletra, in particular in relation to propylene glycol or ethanol toxicity. In addition, the study will assess the immune and virologic response to Kaletra-containing therapy and the incidence and reasons for discontinuation of Kaletra.

8.0 Research Question and Objectives

The study objectives, in children under 2 years of age, are to:

1. 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
2. assess the appropriateness of Kaletra dose for weight or body surface area using the AbbVie Kaletra SmPC as a reference
3. evaluate the safety and tolerability of Kaletra by the following:
    - describe discontinuation of Kaletra and reasons (in particular toxicity-related)
    - describe clinical AEs while on Kaletra or up to 3 months after discontinuation of Kaletra, in particular in relation to study drug or propylene glycol or ethanol toxicity
    - assess the incidence of clinically significant laboratory abnormalities (Division of AIDS [DAIDS] grade 1 – 4)
4. assess the immune and virologic response to Kaletra-containing therapy

9.0 Research Methods

9.1 Study Design

This is a descriptive cohort study.

9.2 Setting

Eligible subjects will be HIV-1–infected children < 2 years of age taking Kaletra oral solution in "real-life" routine care settings in EMA countries within Europe.

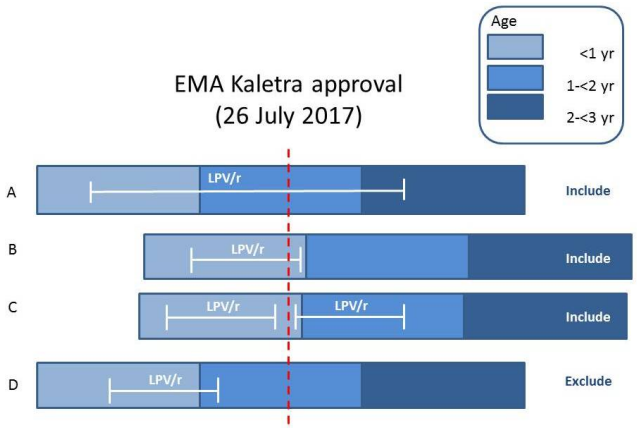
Data will be collected by annual pooling of pseudonymized individual patient data for the time interval during which each patient is included in the study. Patients in the participating cohorts are followed up throughout their time in pediatric HIV care, which may be longer than the time interval of the study.

For this study, children enter at risk of events at start of Kaletra and are censored at the earliest of the following: 2 years of age or at 3 months after discontinuation of Kaletra or at date of death or last visit.

To fully assess the outcomes of AEs including clinically significant laboratory or clinical findings which occur while < 2 years of age (e.g., if resolved or not), follow-up data will be collected for all patients who experience such AEs up to 3 years of age or the end of the study period, whichever is earlier.

Example patients are represented in Figure 1 to illustrate the inclusion criteria. Patients A, B, and C all meet the inclusion criteria for this study with one or more episodes on Kaletra while < 2 years of age at or after the approval date. Patient D had one episode on Kaletra while < 2 years of age, but this episode ended prior to the approval date and, therefore, Patient D would be excluded from the study.

Figure 1. Example of Patients Who Meet Inclusion Criteria for the Study by Age and Timing of Kaletra Exposure Relative to the EMA Approval Date (Indicated by Red Dashed Line)



LPV/r = lopinavir/ritonavir (Kaletra)

The data merger will include all children < 2 years of age who received Kaletra oral formulation at or after the EMA approval date. In the second and third year of this study, follow-up data will be reported on existing patients, as well as data on any new patients commencing Kaletra in the intervening period.

An EPPICC standard operating procedure has been developed and the data merger will follow the HIV Cohorts Data Exchange Protocol (HICDEP).

9.3 Variables

Variables to be collected on all children taking Kaletra will include:

- Demographic data: date of birth, sex, mode of infection, ethnicity, country of HIV care
- Medical history: birth weight, prematurity, United States (US) Centers for Disease Control and Prevention (CDC) events, hepatitis B and C co-infection status
- All antiretroviral prophylaxis and treatments received, start and stop dates, prescribed dose, formulations, reason for stopping

- Other concomitant medications, including start and stop dates
- Anthropometric: weights and heights at every clinic visit
- CD4 and HIV-1 RNA viral load (VL): all CD4%, CD4 cell count, VL measurements and dates, and VL lower limit of detection.
- Adverse events: clinical AEs and serious adverse events (SAEs), onset and end dates, severity of event, causal relationship with Kaletra, all antiretroviral therapy (ART) drugs at time of event, concomitant medication at time of event, outcome of event, and SAE category, if applicable
- Discontinuations of study drug, including the reasons (e.g., AEs, etc.)
- Follow-up: follow-up status, date of death/loss to follow-up/withdrawal from study/transfer to other clinics, or date of last visit.

The following laboratory markers routinely conducted as part of standard of care will be collected, commencing up to 12 months prior to start of Kaletra (where available) and data will be censored when the patient reaches 2 years of age or at 3 months after discontinuation of Kaletra:

Marker	Lab_ID	Marker	Lab_ID
Absolute neutrophil count	ANC	Lipase	LIP
Total cholesterol	CHOL	Serum HDL	HDL
Triglycerides	TRIG	Serum LDL	LDL
Alanine aminotransferase	ALT	Alkaline phosphatase	APT
Total bilirubin	TBIL	Aspartate aminotransferase	AST
Gamma-glutamyl transferase	GGT	Serum phosphate	PHOS
Blood glucose fasting	FPG	Serum calcium	S-Ca
Blood glucose non-fasting	Non-FPG	Serum creatinine	S-CREAT
Pancreatic amylase	P-AMY		

Among patients who experience SAEs while on Kaletra or clinical AEs reported by the attending clinician as causally related to Kaletra, a detailed questionnaire (Annex 3) will be sent to the clinic. The questionnaire seeks further information on the type of event, including questions that help the study team assess the relationship of events to ethanol and/or propylene glycol related toxicities or medication errors (including overdosing), the

laboratory tests conducted, interventions the patient underwent for these events and their outcome. In addition, EPPICC will notify AbbVie of such events within 7 working days of the event being confirmed following data cleaning/management.

9.4 Data Sources

Pooled analysis of pseudonymized individual patient clinical and laboratory data from the following European Union (EU) cohorts participating in the EPPICC pharmacovigilance program (confirmed to have eligible patients, as of August 2019):

- Hospital St Pierre Cohort, Brussels, Belgium
- Copenhagen Cohort, Denmark
- Greece Cohort
- Italian Register for HIV Infection in Children, Italy
- Polish Paediatric Cohort
- CoRISPE-cat, Catalonia, Spain
- CoRISPE-S, Spain (now including the Madrid Paediatric Cohort Study)
- Collaborative HIV Paediatric Study (CHIPS) and National Study of HIV in Pregnancy and Childhood (NSHPC), United Kingdom (UK)/Ireland

Other EU cohorts within EPPICC who may have eligible patients in the future:

- ATHENA national observational HIV cohort, Netherlands
- Centro Hospitalar do Porto, Porto, Portugal
- "Victor Babes" Hospital Cohort, Romania
- Karolinska University Hospital, Stockholm, Sweden

9.5 Study Sample Size

As per the Year 1 report with data lock date of 16 May 2019, among EU cohorts in EPPICC, 14 patients were reported to meet the study inclusion criteria by that date and

were included in the study. This number is expected to increase over time as newly diagnosed infants receive Kaletra in this post-approval period.

9.6 Data Management

Data will be subjected to a battery of logical and consistency checks in order to assess accuracy and completeness. Any data queries arising will be discussed and resolved with the relevant cohort data managers, before data are pooled into a joint study database. The study database corresponding to each study report will be locked prior to data analysis.

All data transfer will take place using a secure encryption process. Data will be stored on secure servers and backed up daily. Access to data will be limited to authorized users only.

9.7 Data Analysis

Data from EPPICC will be summarized using descriptive statistics (proportions, means, medians, interquartile ranges) for the set of all patients and for each of the 4 groups described below. Due to the expected small sample size, graphic summary of individual patient response (e.g., CD4 and HIV-1 RNA VL over time on Kaletra) may be explored. No imputation of missing data will be performed.

Patients will be categorized to a group based on their age, weight (or body surface area where height data are available), dose and dosing frequency on the day of first reported Kaletra exposure. The 4 groups are as follows:

- Group 1: Licensed: patients 14 days to < 2 years of age initiating on a licensed dose
- Group 2: Unlicensed: patients 14 days to < 2 years of age initiating on an unlicensed dose
- Group 3: Patients < 14 days of age
- Group 4: Patients 14 days to < 2 years of age with missing weight and/or dose data at Kaletra initiation

The number of children meeting the inclusion criteria for the study during each reporting interval and cumulatively will be presented. The duration of Kaletra exposure (censored at earliest of 2 years of age or at 3 months after discontinuation of Kaletra or at date of death or last visit) will be summarized in months and patient-months.

To address the first study objective, demographic, medical history including ART regimen, concomitant medication, anthropometric data (including body surface area), will be summarized.

To address the second study objective, the numbers and proportions of patients who received off-label use (< 14 days of age), licensed dosing (as per recommendations in the Kaletra SmPC) and unlicensed dosing will be presented.

To address the third study objective, the following will be presented:

- The number and proportion of patients who discontinued Kaletra, along with a summary of the reasons for discontinuation will be presented.
- The number and proportions of patients followed up through to 2 years of age, along with a summary of the reasons for drop out will be presented.
- Rate of laboratory abnormalities by grade, if numbers are sufficient (if n ≥ 20): All children ever exposed to Kaletra, with laboratory data available are included in the laboratory analysis with follow-up from start of Kaletra and censored at the earliest of the following: 2 years of age or at 3 months after discontinuation of Kaletra or at date of death or last visit, to reflect the incidence of laboratory abnormalities whilst exposed to Kaletra while < 2 years of age.
    - Division of AIDS (DAIDS 2014) gradings for pediatric laboratory AEs will be used to categorize the severity of results,[1] apart from high-density lipoprotein cholesterol (HDL) and gamma glutamyl transferase (GGT), where DAIDS gradings are not available. Therefore, GGT will be graded using Common Toxicity Criteria for Adverse Events (CTCAE) 4.03: Grade 1 is > upper limit of normal (ULN) to 2.5 × ULN, Grade 2 is > 2.5 ULN to 5.0 × ULN, Grade 3 is > 5.0 to 20.0 × ULN, and Grade 4 is

> 20.0 × ULN. For HDL, guidelines from the US National Heart, Lung, and Blood Institute (NHLBI) will be used instead to categorize HDL levels as "acceptable" (> 45 mg/dL), "borderline" (40 – 45 mg/dL), or "low" (< 40 mg/dL).[2] For each test type, results by severity will be presented as numbers of events and rates per 100 person-years of follow-up, provided there are sufficient numbers of patients in follow-up (n ≥ 20) to provide a meaningful estimate. Among patients who experience a DAIDS Grade 3 or 4 event, details will be provided of the duration of the event, other ART drugs received at time of event and if the event resolved, allowing for follow-up data up to the age of 3 years or the end of the study period.

- The numbers and proportions of patients reporting AEs; AEs considered related to Kaletra; SAEs; and SAEs considered related to Kaletra, propylene glycol, and ethanol will be presented.
  - Clinical AEs will be 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).
  - Among patients who experience a clinical AE causally related to Kaletra and have the additional questionnaire completed, a detailed summary of the event, additional tests conducted, treatment and outcome will be provided on a patient-level basis.

To address the fourth study objective, the number and proportion of patients with an HIV-1 RNA value ≥ 50, ≥ 400, and ≥ 1000 copies/mL while receiving Kaletra will be presented, as well as CD4 counts and percentages.

9.8 Quality Control

As stated above, data will be subjected to a battery of logical and consistency checks in order to assess accuracy and completeness. Further data checks will also be conducted by the study statistician prior to data analysis.

9.9 Limitations of the Research Methods

This is a descriptive observational study that will include the reporting of the causal relationship between Kaletra exposure and any clinical AEs based solely on the attending clinicians' opinion. Numbers of eligible children may be small, particularly in the first year of the study, and data may not always be available for some outcomes of interest (e.g., laboratory markers). The retrospective nature of the data collection means that some data may be missing.

There are 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. EPPICC cohorts also 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 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). Those born abroad tend to be older at first presentation to care in Europe and have survived the high mortality period of early infancy without ART in their country of origin. This could potentially lead to the inclusion of patients with less severe disease in early childhood in this study resulting in selection bias.

10.0 Protection of Human Subjects

This is an observational study utilizing data obtained in routine care; no patients will experience any changes to their care as a result of being included in the study.

11.0 Management and Reporting of Complaints (Safety and Quality)

This is a non-interventional database study based on secondary use of data collected for other purposes. No reporting of individual AEs to regulatory agencies is planned for this

database study because there is no access by AbbVie to individual patient/subject records. Pre-specified health outcomes of interest, including any that qualify as AEs, will be summarized as part of each interim analysis and in the final study report, which will be provided to regulatory agencies by AbbVie as required.

In addition, relevant safety information will be summarized in the appropriate Periodic Safety Update Reports, Periodic Benefit Risk Evaluation Reports, and/or Development Safety Update Reports if required.

12.0 Plans for Disseminating and Communicating Study Results

AbbVie shall communicate study results via the annual report to the EMA, which also will include an annual search for case reports in the AbbVie global safety database and a literature search.

13.0 References

1. Division of AIDS National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS table for grading the severity of adult and pediatric adverse events. Version 1.0. December 2004; clarification 2009, Bethesda, MD: 2014 [cited 2020 March 03]. Available at: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.
2. US National Institute of Health Lung and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report [cited 2020 March 03]. Available at: https://www.nhlbi.nih.gov/files/docs/peds_guidelines_sum.pdf.

Annex 1. ENCePP Checklist for Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: 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

EU PAS Register® number: EUPAS32607
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6.0
1.1.2 End of data collection[2]	☒	☐	☐	6.0
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6.0
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Title page
1.1.6 Final report of study results.	☒	☐	☐	6.0

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

End of data collection is 31 December 2020.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8.0
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.0
2.1.2 The objective(s) of the study?	☒	☐	☐	8.0
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.0
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Descriptive study, no hypothesis testing will occur

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2, 9.4, Annex 3
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.0

Comments:

No measures of association will be analyzed.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	6.0
4.2.2 Age and sex	☒	☐	☐	8.0
4.2.3 Country of origin	☒	☐	☐	9.4
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2, 9.7
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3, 9.7
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Descriptive study of LPV/r exposures only.

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.0
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.2, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Regarding 7.1, measures of association are not being analyzed in this descriptive study.

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Measures of association are not being analyzed in this descriptive study.

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.7
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Measures of association are not being analyzed in this descriptive study.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6, 9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

EPPICC will store all data

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5, 9.7

Comments:

Measures of association are not being analyzed in this descriptive study.

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	6

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5.0

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.0
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.0

Comments:

Name of the main author of the protocol: [redacted]

Date: 11 March 2020

Signature: [redacted]

Annex 2. List of Protocol Signatories

AbbVie Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Pharmacovigilance and Patient Safety
		Global Epidemiology
		Data and Statistical Sciences
		Global Medical Affairs
		Global Regulatory Strategy, Western Europe Regulatory Affairs
		QPPV
		Medical Writing

EPPICC Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Epidemiology
		Epidemiology
		Data Management
		Statistics
		Epidemiology
		Clinical

Annex 3. Related Adverse Event Questionnaire

EPPICC Kaletra (LPV/r) Pharmacovigilance Study Related Adverse Event (AE) Questionnaire: Please complete if a child experienced an adverse event considered to be causally related to Kaletra

Reporter Information. Position:	Country:	Date (dd/mm/yy):

Patient Information:

Patient ID:	Sex: Male ☐ Female ☐	Month and year of birth (mm/yy):	Height at time of event: cm ☐ inches ☐	Weight at time of event : kg ☐ pounds ☐
Allergies: Yes ☐ No ☐ (type and manifestation)				
Patient Medical History (include family history, (risk factors), HIV,…):				

Details of adverse event:

Adverse Event	Event Onset(d/m/y)	Outcome (dd/mm/yy)	Event Criteria+	Causality++	Outcome Status**
				Kaletra: Propylene glycol: Ethanol:	
				Kaletra: Propylene glycol: Ethanol:	
				Kaletra: Propylene glycol: Ethanol:	

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

++Please state if the event was causally related to each of the following: Kaletra, propylene glycol, and ethanol: Definitive, Probably related, Possibly related, Unlikely/Remotely related or Not assessable/unknown.

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

Details of antiretroviral use at time of event:

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 dd/mm/yy	End Date dd/mm/yy	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 detailed event information including symptoms the patient experienced leading up to the events: _____

_____

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

_____

35

Please provide Kaletra 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 ☐

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

EPPICC Kaletra (LPV/r) Pharmacovigilance Study Related Adverse Event (AE) Questionnaire: Please complete if a child experienced an adverse event considered to be causally related to Kaletra

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

Details of laboratory and diagnostic test conducted:

Laboratory test	Prior to Event		Test Peak during event		When event improved/resolved		Reference range (including units of measure)
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 Inhibitor resistance mutations							

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

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

_____

If Kaletra was discontinued, was it restarted? Yes ☐ No ☐. If Yes, provide details of restart: Date (dd/mm/yy): _____ Dose _____

If resistance is suspected, has this patient been treated with other protease inhibitors prior to Kaletra therapy? _____

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/R, L24I, V32I, L33F, M46I/L, I47V/A, I50V, F53L, I54L/A/M, L63P, A71V/T, G73S, L76V, V82A/F/T/S, I84V and L90M*):_____

_____

If the patient died, Date of Death: _____/_____/_____ (dd/mm/yy)	Autopsy: Yes ☐ No ☐ Unknown ☐	Autopsy Date: _____/_____/_____ (dd/mm/yy)
Autopsy results:	Cause of Death:	

Please provide any additional relevant information that would provide clarity to the case