

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21906/S-0146, 21251/S-0138, 21226/S-0041
Priority or Standard	Standard
Submit Date(s)	September 17, 2014
Received Date(s)	September 17, 2014
PDUFA Goal Date	July 17, 2014
Division / Office	DAVP
Reviewer Name(s)	Regina Alivisatos, MD
Review Completion Date	April 14, 2015
Established Name	Lopinavir/Ritonavir (LPV/RTV, LRV/r)
(Proposed) Trade Name	Kaletra
Therapeutic Class	Protease Inhibitor Antiviral
Applicant	AbbVie
Formulation(s)	200/50 mg film-coated tablets, 100/25 mg film-coated tablets, and as an 80/20 mg/mL oral solution. 133.3/33.3 mg soft gelatin capsules (SGCs) (b) (4)
Dosing Regimen	Adults: LPV/r 400/100 mg twice daily (BID) or LPV/r

800/200 mg once daily (QD)
Pediatric Patients: BID based
on body weight (10/2.5 to 16/4
mg/kg) or body surface area
(230/57.5 to 300/75 mg/m²),
not to exceed the
recommended adult dosage.

Indication(s)	Treatment of HIV-1 Infection
Intended Population(s)	HIV-1–infected adult and pediatric patients (14 days and older)

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1	Recommendation on Regulatory Action	6
1.2	Risk Benefit Assessment.....	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	7
1.4	Recommendations for Postmarket Requirements and Commitments	7
2	INTRODUCTION AND REGULATORY BACKGROUND	8
2.1	Product Information	8
2.2	Tables of Currently Available Treatments for Proposed Indications	8
2.3	Availability of Proposed Active Ingredient in the United States	9
2.4	Important Safety Issues With Consideration to Related Drugs.....	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission	10
2.6	Other Relevant Background Information	12
3	ETHICS AND GOOD CLINICAL PRACTICES.....	13
3.1	Submission Quality and Integrity	13
3.2	Compliance with Good Clinical Practices	13
3.3	Financial Disclosures.....	13
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	13
4.1	Chemistry Manufacturing and Controls	13
4.2	Clinical Microbiology.....	14
4.3	Preclinical Pharmacology/Toxicology	14
4.4	Clinical Pharmacology	14
4.4.1	Mechanism of Action.....	14
4.4.2	Pharmacodynamics.....	15
4.4.3	Pharmacokinetics.....	15
5	SOURCES OF CLINICAL DATA.....	16
5.1	Tables of Studies/Clinical Trials	16
5.2	Review Strategy	17
5.3	Discussion of Individual Studies/Clinical Trials.....	17
6	REVIEW OF EFFICACY	19
	Efficacy Summary.....	19
6.1	Indication	20
6.1.1	Methods	20
6.1.2	Demographics.....	21
6.1.3	Subject Disposition	24
6.1.4	Analysis of Primary Endpoint(s)	24
6.1.5	Analysis of Secondary Endpoints(s).....	25

6.1.6	Other Endpoints	26
6.1.7	Subpopulations	26
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	27
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	27
6.1.10	Additional Efficacy Issues/Analyses	27
7	REVIEW OF SAFETY.....	27
	Safety Summary	27
7.1	Methods.....	28
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	29
7.1.2	Categorization of Adverse Events.....	29
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	29
7.2	Adequacy of Safety Assessments	30
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	30
7.2.2	Explorations for Dose Response.....	30
7.2.3	Special Animal and/or In Vitro Testing	31
7.2.4	Routine Clinical Testing	31
7.2.5	Metabolic, Clearance, and Interaction Workup	31
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	31
7.3	Major Safety Results	31
7.3.1	Deaths.....	31
7.3.2	Nonfatal Serious Adverse Events	31
7.3.3	Dropouts and/or Discontinuations	32
7.3.4	Significant Adverse Events	33
7.3.5	Submission Specific Primary Safety Concerns	34
7.4	Supportive Safety Results	34
7.4.1	Common Adverse Events	34
7.4.2	Laboratory Findings	36
7.4.3	Vital Signs	37
7.4.4	Electrocardiograms (ECGs)	37
7.4.5	Special Safety Studies/Clinical Trials	37
7.4.6	Immunogenicity	37
7.5	Other Safety Explorations.....	37
7.5.1	Dose Dependency for Adverse Events	37
7.5.2	Time Dependency for Adverse Events.....	37
7.5.3	Drug-Demographic Interactions	37
7.5.4	Drug-Disease Interactions.....	37
7.5.5	Drug-Drug Interactions.....	38
7.6	Additional Safety Evaluations	38
7.6.1	Human Carcinogenicity	38
7.6.2	Human Reproduction and Pregnancy Data.....	38
7.6.3	Pediatrics and Assessment of Effects on Growth	38

7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	39
7.7	Additional Submissions / Safety Issues	39
8	POSTMARKET EXPERIENCE.....	39
9	APPENDICES	40
9.1	Literature Review/References	40
9.2	Labeling Recommendations	40
9.3	Advisory Committee Meeting.....	41

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

An approval action is recommended for sNDAs 21906/S-0146, 21251/S-0138, and 21226/S-0041 to [REDACTED] (b) (4) 24-week results of the clinical PENTA 18/KONCERT study submitted by AbbVie in response to a PREA/PMC evaluating the pharmacokinetic, safety, and activity of twice daily and once daily dosing of Kaletra (LPV/r) tablets in virologically-suppressed, HIV-1 infected pediatric subjects. The safety results were comparable between subjects who switched to once daily LPV/r and those that remained on a twice daily LPV/r regimen with the exception of an increased incidence of gastrointestinal adverse events, most frequently diarrhea with the once daily regimen.

1.2 Risk Benefit Assessment

In this supplemental NDA application submitted in response to a PREA/PMC, the Applicant provided the 24 week results of the PENTA 18/KONCERT trial [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4)

The review of the 24 week safety data submitted with this NDA supplement did not identify any new or unexpected toxicity. The adverse event rates and laboratory findings suggest no clinically significant differences in the safety profile of LPV/r when dosed once or twice daily in pediatric subjects. As expected and consistent with once daily treatment studies in adults, there was a higher incidence of gastrointestinal events in the once daily treatment group. Specifically the most common AE identified by MedDRA System Organ Class (SOC) was "gastrointestinal disorders" occurring in 32.5% (28) of subjects on the once daily treatment arm compared to 16% (14) on the twice daily treatment arm. The most common AE from the gastrointestinal disorders SOC was diarrhea occurring in 18 (21%) once daily versus ten (11.4%) twice daily treated subjects followed by abdominal pain in 14 QD subjects (16%) versus six (7%) BID subjects, vomiting in 9 (10%) QD subjects versus three (3.4%) BID subjects, and nausea in eight (9.3%) QD subjects versus one (1%) BID subject.

Overall the reported adverse events were mild to moderate in severity and there were few SAEs, with similar frequency between the treatment arms. There was no difference between the arms with regards to treatment discontinuations overall or due to adverse events.

(b) (4)

(b) (4) Therefore the label should be revised to reflect that once daily dosing of LPV/r (b) (4) in pediatric subjects is not recommended.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

There are no recommendations for Postmarketing Risk Evaluation and Mitigation Strategies related to this supplemental NDA submission.

1.4 Recommendations for Postmarketing Requirements and Commitments

No further postmarketing requirements and commitments are recommended apart from those previously requested in the initial approval letter.

2 Introduction and Regulatory Background

2.1 Product Information

Lopinavir is a peptidomimetic HIV-1 protease inhibitor (PI) that selectively inhibits the virus-specific processing of viral ^{(b) (4)} Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature infectious virions. The mechanism of action of Kaletra is similar to other protease inhibitors used in the treatment of HIV-1 infection. Currently, the approved dosing regimen for Kaletra is 400/100 mg given orally twice daily or 800/200 mg once daily for the treatment of HIV-1 infection in combination with other antiretroviral agents ^{(b) (4)}. The pediatric dosage is administered BID based on body weight (10/2.5 to 16/4 mg/kg) or body surface area (230/57.5 to 300/75 mg/m²), not to exceed the recommended adult dosage. With this ^{(b) (4)} labeling supplement the Applicant is requesting to update the label with the 24-week results of a clinical (PENTA 18/KONCERT) study evaluating the pharmacokinetic, safety and activity of twice daily and once daily dosing of Kaletra tablets in pediatric subjects. This information is submitted in response to a PREA/PMC issued with the approval of NDA 021906/S-024 and NDA 021251/S-031 on April 27, 2010.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently 28 drugs approved for the treatment of HIV-1 infection (excluding fixed dose combinations). In addition cobicistat is an approved pharmacokinetic enhancer used in combination with other ARVs. Based on the mechanism of action on the life cycle of the human immunodeficiency virus, the drugs are classified into six HIV-1 drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 antagonists, and integrase inhibitors. Table 1 summarizes the approved anti-retroviral drugs.

Table 1: Approved Antiretroviral Drugs

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx®/Videx EC®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir (TDF)	Viread®

	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavirdine	Rescriptor®
	Nevirapine	Viramune®
	Efavirenz (EFV)	Sustiva®
	Etravirine	Intelence®
	Rilpivirine	Edurant®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	fos-amprenavir	Lexiva®
	Atazanavir (ATV)	Reyataz®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Tipranavir (TPV)	Aptivus®
	Darunavir (DRV)	Prezista®
Fusion/Entry Inhibitor	Enfuvirtide (ENF)	Fuzeon®
CCR5 receptor antagonist	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir Dolutegravir Elvitegravir	Isentress® Tivicay® Vitekta®
PK enhancer	Cobicistat	Tyboost®

2.3 Availability of Proposed Active Ingredient in the United States

Kaletra is approved in over (b) (4) countries for the treatment of HIV-1 infection. The package insert has undergone several revisions since the September 15, 2000 approval, including the addition of results from numerous drug-drug interaction studies, dosing information in special populations (hepatic and renal impairment), addition of long-term safety and efficacy (144-204 weeks) results from the phase 1 and 2 trials, an alternative dosing regimen for antiretroviral-naïve and experienced patients (800/200 mg once daily), pediatric dosing recommendations, pregnancy dosing recommendations, QT and PR prolongation labeling, approval and labeling for a new tablet formulation in October, 2005, the results of study M05-730 (48 weeks) including wording from the Dosage and Administration section regarding a higher incidence of

diarrhea associated with the once daily (QD) dosing regimen in April, 2008 and complete revision of the ADVERSE EVENTS section of labeling in 2013.

2.4 Important Safety Issues With Consideration to Related Drugs

Class-related adverse events/laboratory abnormalities and potential for significant drug-drug interactions are common for the approved protease inhibitors. Ritonavir is the hallmark protease inhibitor for drug-drug interactions due to its potent inhibition of CYP3A metabolism. Lopinavir is the active antiretroviral agent and ritonavir serves as a pharmacologic enhancer by inhibiting the metabolism of lopinavir via the CYP3A system. Because lopinavir is co-formulated with ritonavir, the potential exists for numerous drug-drug interactions, some with clinical significance. Various interaction studies between Kaletra and other commonly used medications in HIV-infected patients were conducted. Results from these interaction studies and other potentially significant drug interactions are prominently displayed in the package insert. As with other protease inhibitors, the Kaletra label includes warnings and precautions for new onset diabetes, hyperglycemia, increased bleeding episodes in patients with hemophilia, and fat redistribution. In addition and pertinent to the current submission, the most common adverse reactions associated with Kaletra are from the GI tract including nausea, vomiting and most often, diarrhea. The incidence of diarrhea was greater in adult patients treated with once daily dosing compared to those treated twice daily and this is reflected in the USPI.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The current submission is in response to a PREA/PMC issued with the approval of NDA 021906/S-024 and NDA 021251/S-031 on April 27, 2010.

The April 29, 2005 approval of Kaletra capsules for QD administration (800/200 mg, NDA 021226/S-016) in treatment-naïve adult subjects came with a postmarketing requirement (PMR) under PREA to "submit the results of the ongoing and completed PK, safety, and activity studies evaluating Kaletra QD administration in pediatric HIV-1–infected subjects."

On March 24, 2006, AbbVie submitted results of several investigator-initiated studies as part of a review of the literature regarding QD versus BID dosing of Kaletra in pediatric subjects toward the fulfillment of the PMR (NDA 021226 submission dated March 24, 2006). However the Agency determined that this submission did not fulfill the PMR and requested reviewable data for assessment.

(b) (4)



Clinical Review
Regina Alivisatos, MD
SNDA 21906/S-0146, 21251/S-0138, 21226/S-0041
Kaletra (Lopinavir/Ritonavir, LPV/r)

(b) (4)

On December 07, 2009, FDA held a teleconference with AbbVie to discuss the pediatric commitment. The Agency proposed to release AbbVie from its original April 29, 2005 PMR (NDA 021226/S-016) and issue a new commitment to obtain PK and safety data from 50 pediatric subjects (naïve and early treatment experienced) treated with once-daily Kaletra tablets for 24 weeks.

On February 02, 2010, AbbVie submitted a Pediatric Study Deferral Request (NDA 021906/eCTD Sequence 0053) proposing to submit 24-week results from a study sponsored and conducted by the Paediatric European Network for the Treatment of AIDS (PENTA) titled "KONCERT: Kaletra ONCE daily Randomized Trial of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily LPV/r tablets dosed by weight as part of combination antiretroviral therapy in HIV-1 infected children" (PENTA 18 Study) toward fulfillment of its PMR under PREA. The study protocol was submitted to NDA 021906 on April 08, 2010 (eCTD Sequence 0065).

The approval letter for NDA 021906/S-024 and NDA 021251/S-031 was issued on April 27, 2010. In a May 19, 2010 FDA letter, the Agency released AbbVie from the previous PMR for Kaletra NDA 021226/S-016 because of the new PMC.

The approval letter of April 27, 2010 contained the following PMR 1632-1:

"Please submit the 24-week results of PENTA 18 evaluating the pharmacokinetic, safety and activity of twice daily and once daily dosing of Kaletra tablets in a reviewable format. Submit a final report that includes detailed summaries of pharmacokinetic, safety and activity data as well as electronic datasets. Report Due Date: December 31, 2013."

In September, 2013 the Applicant requested a deferral extension because of a delay in analyzing the study results from the PENTA. This was granted in FDA letter dated October 18, 2013. The new final report due date was September 30, 2014.

2.6 Other Relevant Background Information

Generally, patients seem to prefer once daily dosing over twice dosing as a matter of convenience, and pediatric patients may prefer the smaller tablet size of the LPV/r 100/25 mg tablet, rather than the larger LPV/r 200/50 mg tablet. Therefore it was postulated that the availability of once daily dosing regimens for pediatric patients may improve adherence compared with twice daily dosing regimens. To support a switch from BID dosing to QD dosing in adults or pediatric subjects, it is important to demonstrate that the virologic suppression, positive immunologic effects, and safety profile are maintained with QD dosing.

In treatment experienced adults, in a study that investigated once daily versus twice dosing of LPV/r 200 mg/25 mg tablets, improved adherence was confirmed at 48 weeks. The efficacy and safety of LPV/r dosed QD in adults were demonstrated to be similar to those of LPV/r dosed BID, with the exception of increased nausea reported with BID dosing and increased diarrhea reported with QD dosing.

The question of whether once daily dosing of LPV/r in pediatric subjects is appropriate has not been adequately addressed to date. Several small PK studies in pediatric subjects were previously submitted in the March 24, 2006 submission to NDA 021226; however, these studies did not address safety and efficacy of once daily dosing of LPV/r.

Additionally, a retrospective, observational, single-center study by Foissac¹ et al (2011) compared the safety and efficacy of once daily and twice daily dosing of LPV/r in pediatric subjects who were initially taking LPV/r as twice daily dosing. Five treatment-naïve and 31 treatment-experienced pediatric patients were switched from twice daily to once daily weight based LPV/r dosing, on the basis of a clinical decision to promote convenience and increase adherence to treatment. The investigators reported that among the 34 evaluable subjects, the proportion of subjects with undetectable viral load (< 50 copies/mL) was significantly greater with twice daily dosing than with once daily dosing (74% versus 57% respectively, $P < 0.001$). The investigators further stated that their analysis demonstrates that one explanation for this difference in virologic suppression may be differences in dosing adherence. Subjects receiving once daily dosing who had virologic suppression were reported to have perfect adherence to treatment, compared with two-thirds of non-responders, who reported lapses in adherence. Safety results showed no significant or clinically relevant difference in lipids between pediatric subjects who were administered once or twice daily LPV/r.

1 Foissac F, Urien S, Hirt D, et al. Pharmacokinetics and virological efficacy after switch to once-daily lopinavir-ritonavir in treatment-experienced HIV-1-infected children. *Antimicrob Agents Chemother*. 2011;55(9):4320-25.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI could not independently inspect clinical trial sites because this trial was not conducted by the Applicant. However, all clinical centers were visited at least once during the trial by properly authorized individuals from the MRC (Medical research Council) UK Clinical Trials Units and following data was validated from source documents:

- eligibility and signed consent
- clinical disease progression to new CDC C event or death
- all HIV-1 RNA viral loads ≥ 50 copies/ml
- a random sample of clinical records
- a random sample of CD4 measurements
- a random sample of laboratory results
- a random sample of original records of antiretroviral prescriptions

3.2 Compliance with Good Clinical Practices

The PENTA 18 trial was conducted in accordance with the ICH Good Clinical Practice guidelines. The trial protocol and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) in each country. Written informed consent was obtained from all subjects prior to any trial-related procedures.

3.3 Financial Disclosures

Please see section 9.4 for the Clinical Investigator Financial Disclosure Form.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new Chemistry or Manufacturing information was submitted with this application.

4.2 Clinical Microbiology

No new nonclinical virology data were included in this supplemental NDA. As noted by the Agency Virology Reviewer, there was an imbalance between the treatment arms with regards to HIV baseline viral load, as can be seen in the following table copied from the Clinical Virology review.

Table 2

HIV RNA (copies/mL)	Baseline		Week 24 (Snapshot)	
	QD Kaletra N=86 n (%)	BID Kaletra N=87 n (%)	QD Kaletra N=86 n (%)	BID Kaletra N=87 n (%)
<50	73 (85%)	83 (95%)	73 (85%)	83 (95%)
≥50 to <400	10 (12%)	4 (5%)	6 (7%)	2 (2%)
≥400	3 (3%)	0	3 (3%)	0

* 938, 20639 and 91201 copies/mL

As per the Virology Reviewer, Dr. Narayana Battula,

(b) (4)

. On the once daily treatment arm there were ten subjects with HIV RNA greater of equal to 50 copies/mL to less than 400 copies/mL compared to four such subjects on the twice daily treatment arm. In addition there were three subjects with HIV RNA greater than 400 copies/mL on the once daily treatment arm. However there did not appear to be a direct correlation between virologic failure and baseline HIV RNA levels in this analysis.

4.3 Preclinical Pharmacology/Toxicology

No new Pharmacology/toxicology information was submitted with this application. As noted there was an imbalance between the treatment arms with regards to HIV demographics, as can be seen in the following table copied from the Clinical Virology review:

4.4 Clinical Pharmacology

As part of the 48-week safety and efficacy study, a PK substudy titled "Kaletra ONCE daily Randomized Trial (KONCERT): QD vs. BID PK" was conducted and submitted as part of this application. The results of the Applicant's analyses can be seen in section 4.4.3 of this review. For further details of the substudy and additional analyses, please the FDA Clinical Pharmacology review by Dr. Stanley Au.

4.4.1 Mechanism of Action

Not applicable

4.4.2 Pharmacodynamics

Not applicable

4.4.3 Pharmacokinetics

Fifty-three subjects were assessed for PK in the 48-week safety and efficacy study, 27 were randomized to switch from twice daily to once daily dosing of the LPV/r 100/25 mg tablet(s), based on the body weight bands and are the focus of the QD versus BID PK analysis. Each took LPV/r 100/25 mg tablets twice daily for at least two weeks prior to the Week 0 PK assessment clinic visit. Following the completion of the Week 0 PK assessment clinic visit, the 27 patients began taking their LPV/r once daily in the morning, until their Week 4 PK assessment clinic visit. For twice daily and once daily dosing, it was expected that LPV and ritonavir were at steady state prior to the Week 0 and Week 4 PK assessment clinic visits, respectively.

The PK of LPV and ritonavir were evaluated over 12 hours for LPV/r BID and 24 hours for LPV/r QD dosing following administration of the morning BID or QD dose of LPV/r 100/25 mg tablets.

Subjects: Twenty-seven subjects were included in the QD versus BID PK substudy; 26 of the 27 subjects completed the planned PK sampling at the Week 0 and Week 4 study visits and had evaluable PK samples. One subject (in the ≥ 15 to ≤ 25 kg weight band) did not have Week 4 PK assessments, because the samples were lost in the clinical site laboratory; data for this subject were not included in the PK analysis.

There were seven subjects in the ≥ 15 to ≤ 25 kg weight band, eight in the > 25 to ≤ 35 kg weight band, and 11 in the > 35 kg weight band.

Results: Once daily dosing of LPV/r resulted in a similar LPV $C_{\max}$, lower AUC_{0-24} , and lower C_{last} . The geometric mean LPV AUC_{0-24} and $C_{\max}$ appeared to be lower in patients > 35 kg compared with those observed in patients in the ≥ 15 to ≤ 25 kg or > 25 to ≤ 35 kg weight bands.

Once daily dosing of LPV/r resulted in a similar ritonavir AUC_{0-24} , higher $C_{\max}$, and lower C_{last} compared with BID dosing. The mean ritonavir AUC_{0-24} and $C_{\max}$ appeared to be lower in

patients > 35 kg compared with subjects in the ≥ 15 to ≤ 25 kg and > 25 to ≤ 35 kg weight bands.

Conclusions: The standard for bioequivalence between once and twice daily dosing of LPV/r in pediatric subjects was not met. The GMR of the LPV AUC₀₋₂₄ falls outside the 80% to 125% limits for bioequivalence.

Comment: The lack of bioequivalence between the treatment regimens and specifically for the AUC may explain in part the efficacy results of the KONCERT trial where there were a greater number of failures on the once daily treatment arm as compared to the twice daily.

The Agency Clinical Pharmacology Review Team agreed with the Applicant's conclusions that lower LPV AUC and C_{last} values were observed with once daily dosing compared to twice daily when same total daily dose was administered on both treatment arms. They concluded that based on the available LPV/r pediatric exposure data that alternative once daily dosing regimens do not need to be further evaluated by the Applicant. Further no specific factors were identified that explained the lower LPV exposures on the once daily treatment arm.

5 Sources of Clinical Data

This SE8 supplemental NDA is an electronic submission and contains the interim clinical study reports for the PENTA-18 KONCERT study. The electronic document room location for the submission is: <\\CDSESUB1\evsprod\NDA021906\021906.enx>.

KONCERT was a prospective, multicenter, randomized open label, phase 2/3 study designed to assess to assess pharmacokinetics, safety and efficacy of twice-daily (BID) versus once-daily (QD) LPV/r tablets dosed as part of combination antiretroviral therapy in human immunodeficiency virus type-1 (HIV-1) infected pediatric subjects.

In addition to the KONCERT trial the submission also contains a separate section pertaining to DDIs between LPV/r and etravirine, rilpivirine, and simeprevir. This section of the submission and relevant labeling changes are reviewed in Appendix 5 of this document.

5.1 Tables of Studies/Clinical Trials

Table 3 Clinical studies included in submission

Type of Study		Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy	KONCERT	To evaluate the PK, safety, efficacy and acceptability of QD and BID dosing of LPV/r tablets (Kaletra). Specifically: - To confirm weight-based dosing recommendations by evaluating the PK of BID LPV/r 100/25 mg formulation tablets dosed on body weight and comparing to historical adult and pediatric data of pharmacokinetics of LPV/r soft gel capsules and oral solution respectively. - To compare the PK of BID dosing with QD dosing of LPV/r tablets in the same children. - To evaluate whether QD dosing of LPV/r is comparable to BID dosing in terms of virologic suppression at 48 weeks, including adherence and acceptability.	Phase 2/3 randomized, prospective, open-label, multicenter study	HAART regimen with LPV/r 100/25 mg tablets taken BID or QD dosed per body weight bands	173	HIV-1–infected subjects < 18 years of age with viral suppression (HIV-1 RNA < 50 copies/mL) for at least the prior 24 weeks	48 weeks total

BID = twice daily; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; LPV/r = lopinavir/ritonavir; PK = pharmacokinetics; QD = once daily

5.2 Review Strategy

The clinical review is based on the evaluation of the NDA common technical document sections two and five and includes the 24 week interim study report from the now completed 48 week KONCERT study. A clinical overview of efficacy and safety were provided by the Applicant and were reviewed. Integrated summaries of safety and efficacy were not included as they were not applicable to this submission. The efficacy analyses were confirmed by independent FDA analyses of the data. For this review the efficacy (HIV RNA and CD4) data, adverse event, and laboratory data were reviewed in detail. JMP Statistical Discovery v 9.0.2 and SAS software was used to evaluate the efficacy and safety data.

In addition the Applicant submitted a separate PK/PD study report for the results of a once daily versus twice daily substudy.

Minor differences between AbbVie’s and FDA’s analyses for efficacy and safety were noted. The differences had no impact on the overall conclusions.

5.3 Discussion of Individual Studies/Clinical Trials

The Koncert (PENTA 18) trial was a prospective, open label, multicenter, randomized (1:1) phase 2/3 trial. Pediatric subjects were randomized (1:1) either to continue HAART with LPV/r tablets taken twice-daily or to continue HAART but switch to LPV/r tablets dosed once-daily. Randomization was stratified by body weight band (≥ 15 to ≤ 25 kg, >25 to ≤ 35 kg, >35 kg). Subjects were to be followed for a minimum of 48 weeks. The primary response variable for this PREA/PMC submission is viral failure (HIV-1 RNA ≥ 50 copies/ml) within 24(+6) weeks of randomization. Treatment was to be continued for 48 weeks and the primary measure of outcome was viral failure at 48 weeks.

Subjects were recruited from 49 ex-US sites, with the following number from each country: UK (9), Germany (7), Thailand (8), Spain (6), France (5), Brazil (3), Italy (3), Argentina (2), Netherlands (2), Romania (2), Ireland (1), and Portugal (1).

The primary objective was to demonstrate (b) (4) twice daily dosing in maintaining HIV-1 RNA < 50 copies/mL at Week 48 in virologically suppressed, HIV-1 infected pediatric subjects and assuming a non-inferiority margin of 12%. The primary outcome for the interim 24-week report under review was HIV-1 RNA ≥ 50 copies/ml (confirmed) at any of weeks 4, 8, 12, or 24.

Comment: It should be noted that the trial was not powered to demonstrate (b) (4) of the QD arm at week 24 but at week 48.

Pre-defined secondary endpoints include evaluating the pharmacokinetics, safety and tolerability of the two treatment regimens at 4, 8, 12, 24, 36, and 48 weeks. The number of HIV-1 mutations present at week 4, 8, 12, 24 conferring resistance to drugs in a subject's anti-retroviral treatment regimen at randomization or during the trial, change in CD4 (absolute, z-score and percentage) from baseline to 24 weeks, and new CDC stage C diagnosis or death. Adherence and acceptability of the regimens was also assessed.

Subjects were randomized in a 1:1 fashion to one of the following treatment groups:

Treatment Group 1 (once daily): Switch to LPV/r once a day AM or PM (n = 86)

Treatment Group 2: Stay on LPV/r twice daily (doses 12 hours apart) (n = 87).

Major inclusion criteria specified that subjects enrolled be HIV-1 infected pediatric subjects aged < 18 years, weighing ≥ 15 kg, able to swallow tablets, willing to switch to a once daily regimen, and receiving LPV/r twice daily as part of an antiretroviral (ARV) regimen with documented undetectable plasma HIV-1 RNA levels for 24 weeks preceding the screening visit. They had

to be willing at the screening visit to change to the LPV/r tablet formulation if not currently taking tablets and to change the LPV/r dose.

Subjects were excluded if they were on an antiretroviral regimen that included a non-nucleoside reverse transcriptase inhibitor (NNRTI) or any protease inhibitor (PI) other than LPV/r. They were also not included if they had previously failed virologically on a PI-containing regimen (where virological failure is defined as two successive HIV-1 RNA results >1000 copies/ml (confirmed) more than 24 weeks after starting HAART, i.e. changes for toxicity are not counted as failure). People with acute illness, or with abnormal renal or liver function, were also not included. If subjects were receiving concomitant therapy except for prophylaxis they were not eligible, unless the concomitant therapy was discussed and approved by a trial medical expert. Pregnant females or females at risk of pregnancy were not included.

Evaluations for subject safety (physical examination, safety laboratories) and efficacy (HIV-1 RNA, CD4+ lymphocyte count) were performed at the following scheduled visits: Week 4, 8, 12, 24, 36, and 48.

Subjects were monitored for virologic failure (i.e. suboptimal virologic response or virologic rebound) and were managed according to clearly defined algorithms.

A total of 200 subjects were screened and 173 were randomized (QD 86 subjects, BID 87 subjects). Forty-six children were enrolled in the ≥ 15 to ≤ 25 kg weight band, 50 children in the > 25 to ≤ 35 kg weight band and 77 in the > 35 kg weight band. Of the 173 randomized subjects, all received at least one dose of study medication. Only one subject on the QD arm was lost to follow-up during the first 24 weeks of the trial.

6 Review of Efficacy

Efficacy Summary

Through 24 weeks, Kaletra administered once daily to pediatric subjects was shown (b) (4). Specifically, in the Agency snapshot analysis of subjects with baseline HIV RNA less than 50 copies/mL 73/86 (85%) of once daily subjects had virologic success compared to 83/87 (95%) of twice daily subjects (95% CI: -20% to -2%, Risk difference - 11%, Fisher's Exact p value 0.023), indicating not only that (b) (4).

The difference in the proportion of subjects with virologic failure within the first 24 (+6) weeks of the trial between dosing groups was statistically significant. Further analyses can be seen in the Statistical Review by Dr. Fraser Smith.

By the 24-week assessment, nine of 86 subjects with a baseline HIV RNA of less than 50 copies/mL (10%) with once daily dosing and three of 87 subjects with twice daily dosing (3%) had virologic failure with a confirmed viral load ≥ 50 copies/mL (95% CI -1% to 16%, risk difference 7%, $p = 0.08$). There was one subject with missing data within the assessment window. Failure was generally attributed to poor adherence of treatment although one subject developed a L90M PI mutation, which is a possible reason for their virological failure.

There were no significant differences between arms in the change from baseline to week 24 in CD4, CD4% or CD4 z score

6.1 Indication

KALETRA is a peptidomimetic HIV-1 protease inhibitor (PI) given orally once or twice daily for the treatment of HIV-1 infection in combination with other antiretroviral agents in antiretroviral naïve or experienced adult or pediatric patients. (b) (4)

No changes are proposed for section 1, Indications and Usage. For proposed changes to section 8.4, Use in Specific Populations, Pediatrics, Please see section 7.6.3 of this review.

6.1.1 Methods

All data analysis tables in this section were generated by the statistical reviewer using SAS, a statistical analysis software package.

In general, the Division evaluates the proportion of patients with HIV RNA < 400 or < 50 copies/mL as the primary efficacy endpoint at Weeks 24 and 48 and the Week 48 “snap shot” results are now presented in the package insert. Specific to this submission the primary efficacy analysis compared the percentage of virologic responders and virologic failures at Week 24 in subjects randomized to receive QD and BID dosing regimens using risk differences and their corresponding exact 95% confidence intervals. The FDA snapshot algorithm was used to determine the proportion of subjects responding based on plasma HIV-1 RNA less than 50 copies per mL while 400 copies/mL was used as the cutoff for secondary efficacy analyses. Fisher’s exact test was also used to compare QD and BID regimens. Sensitivity analyses adjusted for different potential confounding covariables in order to examine the robustness of the primary efficacy analysis while interaction tests were performed using Zelen’s exact test.

It should be noted however that the study was not powered to assess efficacy at the 24 week but rather at the 48 week timepoint utilizing a delta of – 12%. Although the Applicant did not

submit a rationale for the proposed NI margin, the same margin was used in support of the once daily dosing regimen in treatment experienced adult subjects.

In addition, during the review it became apparent that there were more once daily treated subjects who had evidence of greater immunosuppression at baseline (as defined as lower CD4 cell counts and higher HIV RNA levels) compared to the twice daily arm. In order to ascertain the effects of the imbalances between the treatment arms the MO requested that the FDA statistician further evaluate these imbalances. The results of these analyses can be found in the Agency Statistical Review by Dr. Frasier Smith.

Overall, all efficacy measurements used in the study are standard and validated. All clinical and laboratory procedures are standard and well accepted.

6.1.2 Demographics

The KONCERT study was conducted in 12 countries (Argentina, Brazil, France, Germany, Ireland, Italy, the Netherlands, Portugal, Romania, Spain, Thailand, and the United Kingdom). There were no US sites. As per the current Kaletra USPI, there are no clinically important differences in LPV PK due to race. Further Kaletra was used in the pediatric subjects as part of HAART regimens consistent with DHHS guidelines. Based on the above the results of the KONCERT study are applicable to the US population. Enrollment by country can be seen in the following table:

Table 4
Subjects by Country/KONCERT

Country (Number of sites)	Number Randomized		Total
	QD	BID	
Argentina (2)	6	1	7
Brazil (3)	10	17	27
France (5)	2	6	8
Germany (7)	13	11	24
Ireland (1)	1	0	1
Italy (3)	2	1	3
Netherlands (2)	1	2	3
Portugal (1)	1	1	2
Romania (2)	2	1	3
Spain (6)	10	6	16
Thailand (8)	29	30	59
UK (9)	9	11	20
Total (49)	86	87	173

Generated by MO dm xpt

Of note, the greatest number of pediatric subjects was enrolled in Thailand. It should also be noted that the population studied was very diverse with regards to race and adequately comparable to the overall US population demographic.

Overall the treatment arms were similar with regards to baseline demographic characteristics. The treated subjects on both arms were predominantly female, Asian with a mean age of 11.3.

Table 5
Baseline Patient Demographics/KONCERT

Characteristic	QD	BID	Total
Patients randomized	86	87	173
Sex, n (%)			
Male	41 (48)	38 (44)	79 (46)
Female	45 (52)	49 (56)	94 (54)
Age, yr			
Mean (SD)	11.2 (3.4)	11.4 (3.5)	11.3 (3.5)
Range	4.3, 17.6	3.8, 17.7	3.8, 17.7
Weight, kg			
Overall			
Mean (SD)	35.5 (13.6)	35.4 (13.4)	35.5 (13.5)
Range	15.0, 72.5	15.6, 68.9	15.0, 72.5
Band 1: ≥ 15 to ≤ 25 kg			
Mean (SD)	20.6 (3.2)	20.6 (2.6)	20.6 (2.9)
Range	15.0, 24.6	15.6, 25.0	15.0, 25.0
Band 2: > 25 to ≤ 35 kg			
Mean (SD)	30.3 (2.8)	30.2 (2.5)	30.2 (2.6)
Range	25.3, 34.5	26.0, 34.5	25.3, 34.5
Band 3: > 35 kg			
Mean (SD)	47.8 (10.4)	47.6 (9.5)	47.7 (9.9)
Range	35.4, 72.5	35.3, 68.9	35.3, 72.5
Race, n (%)			
White	27 (31)	17 (20)	44 (25)
Black	17 (20)	29 (33)	46 (27)
Black/White	5 (6)	6 (7)	11 (6)
Asian	31 (36)	30 (34)	61 (35)
Other	6 (7)	5 (6)	11 (6)

Source csr and dm.xpt

Baseline HIV characteristics can be seen in the following table:

Table 6
Baseline HIV Characteristics

Characteristic	QD	BID	Total
Baseline CD4 + T-cell			
%, Mean (SD)	32.0 (6.5)	33.9 (8.6)	32.9 (7.7)
< 30%, n (%)	34 (40)	28 (33)	62 (36)
30% to < 40%, n (%)	42 (49)	37 (43)	79 (46)
≥ 40%, n (%)	9 (11)	21 (24)	30 (18)
Missing, n	1	1	2
Baseline CD4+ T-cell count			
(cells/ μ L), Mean (SD)	875.6 (303.2)	999.0 (395.4)	937.3 (356.7)
Baseline HIV –1 RNA			
< 50 copies/mL, n (%)	74 (86)	83 (95)	157 (91)
≥ 50 copies/mL, n (%)	12 (14)	4 (5)	16 (9)

Source csr and dm.xpt

BID = twice daily; HIV = human immunodeficiency virus; QD = once daily; SD = standard deviation

Of note at baseline more subjects in the once daily group had a viral load of ≥ 50 copies/mL (14% versus 5%) at the time of randomization, and fewer subjects in the once daily group had CD4+ T-cell % $\geq 40\%$ (11% versus 24%) compared with subjects in the twice daily group. In addition, the mean CD4 count was lower in subjects on the once daily treatment arm.

Comment: The differences in HIV demographics between the treatment arms suggest that the subjects on the BID arm were less immunosuppressed than those on the once daily treatment arm.

6.1.3 Subject Disposition

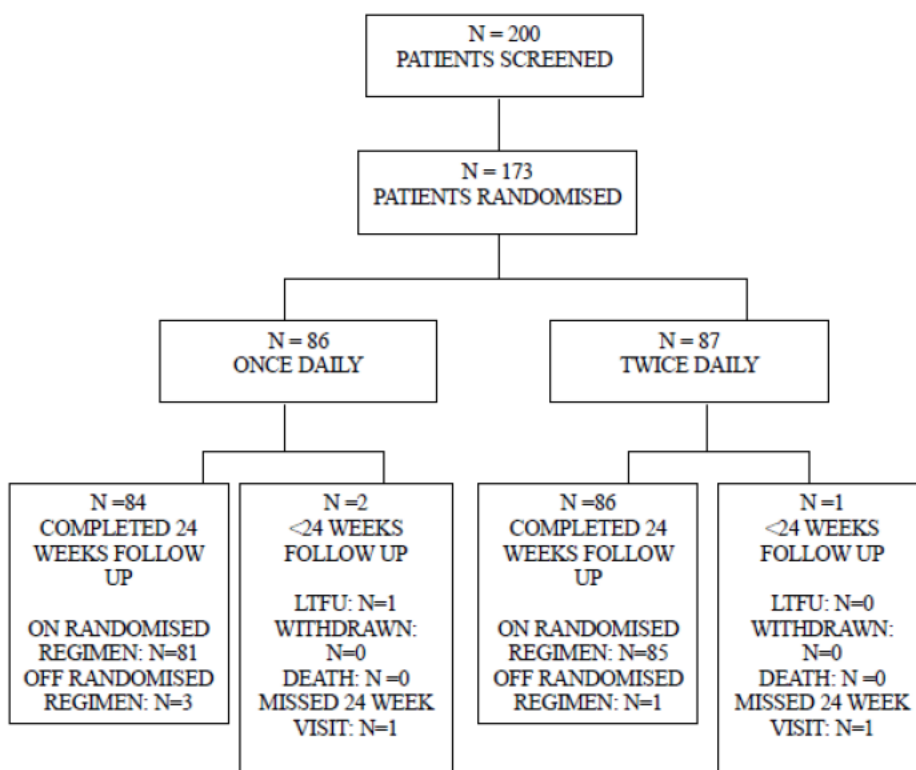


Figure 2. Disposition of patients up to the week 24 (+6 weeks) interim assessment

Source: 24 week Clinical study report section 10.1, page 51, figure 2

6.1.4 Analysis of Primary Endpoint(s)

In the Agency analysis, through 24 weeks, Kaletra administered once daily to pediatric subjects (b) (4) the comparator group of Kaletra twice daily. Specifically, in the Agency snapshot analysis of subjects with baseline HIV RNA less than 50 copies/mL 73/86 (85%) of once daily subjects had virologic success compared to 83/87 (95%) of twice daily subjects (95% CI: -20% to -2%, Risk difference - 11%, Fisher's Exact p value 0.023), indicating not only that the (b) (4)

(b) (4). The difference in the proportion of subjects with virologic failure within the first 24 weeks of the trial between dosing groups was statistically significant. Further analyses can be seen in the Statistical Review by Dr. Fraser Smith.

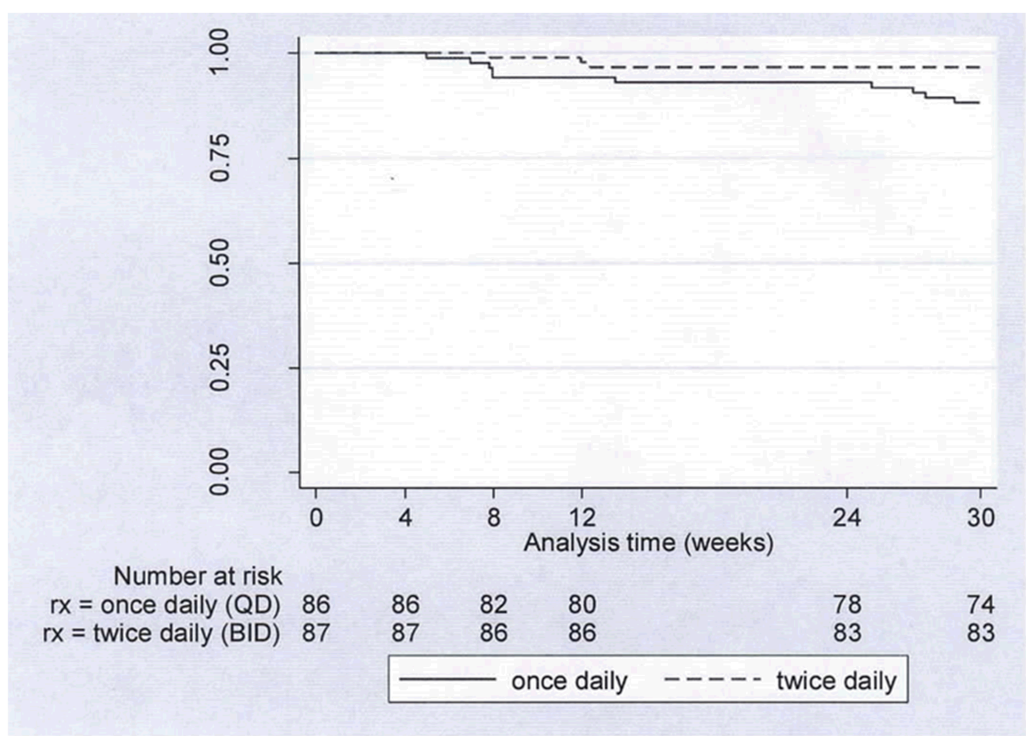
By the 24-week assessment, nine of 86 subjects with a baseline HIV RNA of less than 50 copies/mL (10%) with once daily dosing and three of 87 subjects with twice daily

dosing (3%) had virologic failure with a confirmed viral load ≥ 50 copies/mL (95% CI - 1% to 16%, risk difference 7%, $p = 0.08$). There was one subject with missing data within the assessment window. Failure was generally attributed to poor adherence of treatment although one subject on the once daily treatment arm developed an L90M PI mutation which could have in part accounted for that subject's failure.

In terms of the primary outcome measure, the statistically significant difference between the 2 groups in the time to confirmed HIV RNA ≥ 50 copies/mL is demonstrated in the Kaplan-Meier graph copied from the clinical overview section of the edr submission below:

6.1

Figure 1. Kaplan-Meier Graph of Time to First Detected HIV-1 RNA ≥ 50 copies/mL (Confirmed) by 24-Week Assessment (ITT Population)



Cross-reference: 24-Week Interim CSR [Figure3](#)

As noted in the demographics, despite the requirement that patients have HIV-1 RNA < 50 copies/mL for entry to the study, there was an imbalance in the number of patients with HIV-1 RNA ≥ 50 copies/mL. Twelve patients with QD dosing had a viral load ≥ 50 copies/mL at baseline compared with four patients with BID dosing. Similarly, for CD4+ T-cell %, nine patients with QD dosing had CD4+ T-cell % $\geq 40\%$ compared with 21 patients with BID dosing. These imbalances in HIV parameters suggest that patients

with BID dosing may have been less immunosuppressed at the start of the trial compared with patients with QD dosing. In the Agency sensitivity analyses once the statistical model was adjusted for these baseline imbalances as well as for other demographic characteristics such as weight, age, race and gender, the risk difference in the proportion with virologic failure as well as the 95% (b) (4)

The Applicant determined that based on the responses to adherence questionnaires provided to caregivers that adherence was the primary determinant of failure in almost all of the subjects and the development of resistance was the cause of failure in one subject (L90M).

It should be noted that the KONCERT study was powered to assess efficacy at 48 and not at 24 weeks. An abstract describing the week 48 results of the study (excerpt provided below) (b) (4)

12 QD vs 7 BID children had confirmed VL $\geq$ 50 c/mL within 48 weeks; the estimated percentage with VL rebound was 14% QD vs 8% BID: difference 6% (90% CI -2, 14; p=0.2); reducing to 4% (-4, 11) after adjustment for baseline CD4% and VL in a post-hoc analysis. No child died or had a new CDC C event. Two children (BID) had a major PI mutation at VL rebound (L90M, M46I+V82A); 3 QD vs 2 BID children had M184V, 2 QD vs 2 BID developed TAMs. 14 (4%) QD vs 6 (2%) BID children/careers reported missing a dose within 3 days of any clinic visit (p=0.2).

Conclusions: (b) (4)
. Resistance and safety data were similar in both arms. Although the results can be partly explained by chance VL imbalance at baseline, they do not support the routine use of LPV/r QD in children and adolescents.

Lyall H. Final results of Koncert: a randomized noninferiority trial of QD vs BD LPV/r dosing in children. [CROI abstract 74LB]. In Special Issue: Abstracts from the 2014 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med. 2014;22(e-1):34.

6.1.5 Analysis of Secondary Endpoints(s)

There were no significant differences between the 2 LPV/r dosing groups in change from Baseline to Week 24 in CD4+ T-cell % or CD4+ T-cell count. Results of secondary efficacy analyses can be found in the FDA Statistical Review by Dr. Fraser Smith.

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

Not applicable

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable to this submission

6.1.10 Additional Efficacy Issues/Analyses

No additional analyses were performed

7 Review of Safety

Safety Summary

Generally, the FDA's pooled Phase 3 safety data analyses replicated the Applicant's findings with few exceptions. The exceptions did not lead to a clinically meaningful difference, and were due to methods used in identifying the specific subject population of interest, pooling preferred terms outside of the MedDRA classification scheme or differences in attribution of treatment-relatedness.

The review of the 24 week safety data submitted with this NDA supplement did not identify any new or unexpected toxicity. The safety analyses of the KONCERT trial included all subjects who received at least one dose of study medication. The safety database was comprised of 173 subjects, 86 who received once daily LPV/r and 87 who received twice daily LPV/r as part of their HAART regimens.

Baseline demographics including gender, race, ethnicity, and age were comparable between the treatment arms. Subjects were predominantly female with a mean age of 11.3 years. All races were well represented.

Extent of exposure was also similar between treatment arms with almost 100% of subjects receiving the full 24 weeks of treatment. Only one subject was lost to follow-up during the trial (week 4 from the once daily treatment arm).

Through 24 weeks, 76.7 % of subjects (66) in the once daily group experienced any TEAE compared to 82.7% of subjects (72) in the twice daily group. Most reported adverse events were mild in severity. Grade 3 or 4 TEAEs were reported for six (7%) of once daily subjects compared to five (5.7%) of twice daily subjects. No Grade 3 or 4 AEs were reported for $\geq 1\%$ of subjects in any group. A total of 14 grade 3 or 4 TEAEs were reported. Only one TEAE in a once daily subject was considered grade 4, an event of headache. This subject also had a grade 3 event of herpes zoster. Both TEAEs were not considered treatment related.

Three events were considered treatment related (all grade 3). One was an event of diarrhea in a once daily treated subject (also an SAE), an event of hyperbilirubinemia in a once daily treated subject (with cholangitis), and an event of neutropenia in a twice daily treated subject (also on ZDV).

There was no trend in the types of grade 3 or 4 TEAEs by treatment arm. Most Grade 3 or 4 TEAEs were from the Investigations, Infections and Infestations and the Gastrointestinal Disorders SOC.

Two subjects on the once daily treatment arm discontinued once daily dosing and reverted back to twice daily dosing because of the TEAEs of nausea and vomiting.

The most common AE identified by MedDRA System Organ Class was “gastrointestinal disorders” occurring in 32.5% (28) of subjects on the once daily treatment arm compared to 16% (14) on the twice daily treatment arm. The most common AE from the gastrointestinal disorders SOC was diarrhea occurring in 18 (21%) once daily versus ten (11.4%) twice daily treated subjects followed by abdominal pain in 14 QD subjects (16%) versus six (7%) BID subjects, vomiting in nine (10%) QD subjects versus three (3.4%) BID subjects, and nausea in eight (9.3%) QD subjects versus one (1%) BID subject.

No deaths were reported.

Eleven SAEs were reported by eight subjects, five on the once daily and three on the twice daily treatment arms. All resulted in hospitalization but only one, an event of diarrhea on the once daily treatment arm, was considered possibly related to treatment by the investigator. None of the SAEs were classified as Grade 4.

There were no clinically significant differences between the two dosing frequencies in change from Baseline to Week 24 in safety laboratory values.

As expected and consistent with once daily treatment studies in adults, there was a higher incidence of gastrointestinal events in the once daily treatment group. Apart from this observation, the adverse event rates and laboratory findings suggest no clinically significant differences in the safety profile of LPV/r when dosed once or twice daily in pediatric subjects.

7.1 Methods

Review of this supplemental NDA included analysis of safety data through Week 24 for the KONCERT Phase 3b open label trial.

Multiple AEs were counted only once per subject for each preferred term while laboratory abnormalities were limited to subjects with at least one post-baseline

laboratory value for each test. Subjects were counted only once for their post-baseline maximum severity for each laboratory test.

Clinical adverse events and laboratory abnormalities were graded according to the NIH toxicity table for grading severity of adult and pediatric adverse events (December, 2004); Clarification August 2009)

All data analysis tables in this section were generated by the clinical reviewer from the provided datasets in the edr using JMP® statistical software version 9.0.2

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The review of this (b) (4) supplement focuses on the safety data from the KONCERT trial.

7.1.2 Categorization of Adverse Events

Overall the assessment of the quality and completeness of the data presented was adequate for conducting the safety review. Onset dates and time to resolution information was provided for adverse events. A well-recognized toxicity grading scheme was applied for laboratory abnormalities and is consistent with other HIV trials. The sample size of subjects included in the safety analysis is adequate to provide a reasonable assessment of safety in pediatric subjects who change their treatment regimen to once daily dosing.

The sponsor coded AEs using MedDRA version 16. An assessment of the Applicant's coding of events was carried out with attention given to assuring proper agreement between the investigators' verbatim terms and the selected MedDRA Preferred terms. Particular attention was given to adverse events that led to study drug discontinuation and serious adverse events judged related to study drug. Additionally, a random check of adverse events without respect to severity or causality of adverse events was performed. No issues of concern were identified

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The LPV/r tablets used contained the active ingredients of lopinavir 100 mg and ritonavir 25 mg or lopinavir 200 mg and ritonavir 50 mg and were manufactured by AbbVie. The tablets were packaged in bottles of 60 and 120 tablets per bottle respectively. The currently-approved dose of LPV/r was adjusted to follow the recommended FDA dosing plan based on body weight bands as necessary. Doses used can be seen in the following tables:

Table 7
LPV/r BID Dosing/KONCERT

Weight (kg)	Dose/number of tablets (H=100/25mg, F=200/50mg) AM		Dose/number of tablets (H=100/25mg, F=200/50mg) PM	
≥15 to ≤25	200/50mg	2H or 1F	200/50mg	2H or 1F
>25 to ≤35	300/75mg	3H or 1F, 1H	300/75mg	3H or 1F, 1H
>35	400/100mg	4H or 2F	400/100mg	4H or 2F

Source: csr

Table 8
LPV/r QD Dosing/KONCERT

Weight (kg)	Dose/number of tablets (H=100/25mg, F=200/50mg)	
≥15 to ≤25	400/100mg	4H or 2F
>25 to ≤35	600/150mg	6H or 3F
>35	800/200mg	8H or 4F

Source: csr

As noted previously, 86 subjects received LPV/r once daily and 87 received it twice daily as a component of their HAART regimen. Enrolled subjects had previously been on LPV/r. The mean number of weeks that they had been on LPV/r prior to randomization was 192.8 (min. 28, max. 552).

Only one subject on the once daily treatment arm was lost to follow-up at week 4. All others received LPV/r and were followed for the full 24 weeks (note: study is 48 week duration but Agency requested 24 week data).

A discussion of baseline demographics and baseline HIV characteristics can be found in section 6.1.2 of this review.

7.2.2 Explorations for Dose Response

As part of the 48-week safety and efficacy study, a PK substudy titled "Kaletra

ONCE daily Randomized Trial (KONCERT): QD vs. BID PK" was conducted. The results can be seen in section 4.4.3 of this review.

7.2.3 Special Animal and/or In Vitro Testing

No new data was submitted

7.2.4 Routine Clinical Testing

Routine clinical evaluations for safety in the KONCERT trial included medical history, and an assessment of adverse events and changes in concomitant medications at all scheduled visits (Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48). A complete physical exam at Weeks 24 and 48, symptom-directed physical exams as needed at the other scheduled visits, and safety laboratory assessments at all scheduled visits. Subjects with serious adverse events are followed through the last day of study and/or until the investigator and/or sponsor determined that the subject's condition was stable

7.2.5 Metabolic, Clearance, and Interaction Workup

No additional analyses were performed

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known safety profile of LPV/r was taken into consideration in the safety evaluation.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported.

7.3.2 Nonfatal Serious Adverse Events

Eleven SAEs were reported by eight subjects, five on the once daily and three on the twice daily treatment arms. All resulted in hospitalization but only one, an event of diarrhea on the once daily treatment arm, was considered possibly related to treatment by the investigator.

Table 9
Serious Adverse Events/KONCERT

Number of Subjects	LPV/r QD N = 86	LPV/r BID N = 87
Number of Subjects Experiencing Any Treatment-Emergent SAE	5 (5.8%)	3 (3.4%)

Number of Subjects Experiencing a Treatment Related SAE	1 (1.2%)	0
Number of Subjects with Events		
Abdominal pain	0	1 (1.1%)
Diarrhea	2 (2.3%)	0
Nausea	1 (1.2%)	0
Gastroenteritis	1 (1.2%)	0
Rotavirus Gastroenteritis	1 (1.2%)	0
Sinusitis	0	1 (1.1%)
Cholangitis	1 (1.2%)	0
Cholecystitis	1 (1.2%)	0
Herpes Zoster	1 (1.2%)	0
Dengue	0	1 (1.1%)

Source: CRfile09 section 5. Subjects may have had more than one event and ae.xpt

An independent assessment confirmed eight subjects with 11 reportable SAEs. None of the events led to treatment discontinuation. One subject on the once daily treatment arm reported four events including cholangitis, cholecystitis, diarrhea, and nausea. All other events were reported from one subject each.

None of the SAEs were classified as Grade 4. Seven events from seven subjects (four QD and 3 BID) were classified as grade three events. These included the events of sinusitis, cholangitis, herpes zoster, dengue, rotavirus infection, abdominal pain, rotavirus gastroenteritis, and diarrhea.

All SAEs resolved without treatment modification. Most events were from the Infections and infestations SOC (5), followed by the Gastrointestinal SOC (4) and the Hepatobiliary SOC (2).

Note: all narratives and CRFs for the eight subjects with SAEs were provided and independently reviewed. The MO agreed with the investigator's assessments of attribution.

7.3.3 Dropouts and/or Discontinuations

Two subjects on the once daily treatment arm developed adverse events that led to treatment modification. LPV/r was not permanently discontinued in any subject.

Two subjects on the once daily treatment arm developed nausea and vomiting which led to a change in treatment from once daily to twice daily with resolution of the AEs. These events occurred between 4 – 8 weeks after the switch to once daily treatment. The events were classified as grade 2 and as definitely related to treatment.

Table 10
Treatment-Emergent Adverse Events Leading to Premature Study Drug Discontinuation/KONCERT

Number of Subjects	LPV/r QD N = 86	LPV/r BID N = 87
Number (%) of Subjects Experiencing Any TEAE Leading to Premature Study Drug Discontinuation	0	0
Number (%) of Subjects Experiencing Any TEAE Leading to Study Drug Modification	2 (2.3%)	0
Nausea	2 (2.3%)	0
Vomiting	2 (2.3%)	0

Source: CRfile09 section 5.

7.3.4 Significant Adverse Events

Most reported adverse events were mild in severity. A slightly lower percentage of subjects experienced any Grade 1 or 2 treatment- emergent AE (77% (66) of subjects) in the once daily group compared to 71 (82%) in the twice daily group). Grade 3 or 4 TEAEs were reported for six (7%) of once daily subjects compared to five (5.7%) of twice daily subjects. No Grade 3 or 4 AEs were reported for $\geq 1\%$ of subjects in any group. A total of 14 grade 3 or 4 TEAEs were reported.

Only one TEAE in a once daily subject was considered grade 4, an event of headache. This subject also had a grade 3 event of herpes zoster. Both TEAEs were not considered treatment related.

Three events were considered treatment related (both grade 3). One was an event of diarrhea in a once daily treated subject (also an SAE), an event of hyperbilirubinemia in a once daily treated subject, and an event of neutropenia in a twice daily treated subject.

There was no trend in the types of grade 3 or 4 TEAEs on with treatment arm. Most Grade 3 or 4 TEAEs were from the Investigations, Infections and Infestations and the Gastrointestinal Disorders SOC. Grade 3 and 4 TEAEs can be seen in the following table:

Table 11
Grades 3 and 4 Treatment-Emergent Adverse Events

Number of Subjects	LPV/r QD N = 86	LPV/r BID N = 87
Number (%) of Subjects Experiencing Any Grade 3 or 4 TEAE	6 (7%)	5 (5.7%)
Number (%) of Subjects Experiencing Any Grade 3 or 4 Drug-Related TEAE	2 (2.2%)	1 (1%)

Verbatim Term, n (%)		
Investigations	2 (2.2%)	2 (2%)
Hyperbilirubinemia	1 (1.1%)	0
Hypercholesterolemia	0	1 (1%)
Hypertriglyceridemia	1	0
LDL Increased	0	1 (1%)
Gastrointestinal Disorders	1 (1.1%)	2 (2%)
Diarrhea	1 (1.1%)	0
Abdominal Pain	0	2 (2%)
General Disorders	1 (1.1%)	1 (1%)
Pain	1 (1.1%)	0
Influenza like illness	0	1 (1%)
Infections and Infestations	2 (2.2%)	2 (2%)
Gastroenteritis rotavirus	1(1.1%)	0
Dengue Fever	0	1 (1%)
Herpes Zoster	1 (1.1%)	0
Sinusitis	0	1 (1%)
Hepatobiliary Disorders	1 (1.1%)	0
Cholangitis	1 (1.1%)	0
Nervous System Disorders	1 (1.1%)	0
Headache	1 (1.1%)	0
Blood and Lymphatic system disorders	0	1 (1%)
Neutropenia	0	1 (1%)

Source: CRfile09 section 5.

In the original and subsequent NDA reviews events of hepatitis and pancreatitis along with metabolic complications, specifically new onset diabetes and fat redistribution were evaluated in detail. These events were reviewed to determine if changes to the package insert were warranted. No new significant or clinically relevant adverse events warranting changes to the package insert were identified in the current submission.

7.3.5 Submission Specific Primary Safety Concerns

The adverse event profile identified in this trial is consistent with other LPV/r studies. Therefore no additional search strategies were conducted.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Through 24 weeks, 76.7 % of subjects (66) in the once daily group experienced any TEAE compared to 82.7% of subjects (72) in the twice daily group.

The most common AEs in by System Organ Class on the once daily treatment arm were from the Gastrointestinal disorders SOC (32.5%, 28 subjects vs. 16%, 14 subjects on the twice daily arm) followed by the 'infections and infestations' SOC (22%, 19 subjects both arms). No substantive differences in incidence of 'infections and infestations' were noted when comparing the treatment groups.

The following table summarizes all AEs that occurred in at least 2% of subjects (by preferred term) in the either group, regardless of causality.

Table 12
Treatment-Emergent Adverse Events that Occurred in at Least 2% of Subjects/KONCERT

Number of Subjects	LPV/r QD N = 86	LPV/r BID N = 87
Number of Subjects Experiencing Any TEAE	66 (76.7%)	72 (82.7%)
MedDRA Preferred Term n (%)		
DIARRHEA	18 (21%)	10 (11%)
ABDOMINAL PAIN	13 (15%)	6 (7%)
VOMITING	8 (9%)	3 (3%)
NAUSEA	8 (9%)	1 (1%)
TONSILITIS	1 (1%)	3 (3%)
URI	4 (5%)	6 (7%)
LIPODYSTROPHY	2 (2%)	3 (3%)
HEADACHE	5 (6%)	1 (1%)

As can be appreciated from both the table of TEAEs and the one below for TRAEs, gastrointestinal TE and TRAEs were more frequent on the once daily treatment arm. The most frequent event was diarrhea followed by abdominal pain, nausea, and vomiting. The increased frequency of gastrointestinal adverse events with once daily LPV/r administration is consistent with that seen in adults.

28% of subjects (24) in the once daily group experienced TRAEs compared to 17% of subjects (15) in the twice daily treatment group.

Table 13
Treatment-Related Adverse Events that Occurred in ≥ 2% Subjects/KONCERT

Number of Subjects	LPV/r QD N = 86	LPV/r BID N = 87
Number of subjects with TRAE	24 (28%)	15 (17%)
Treatment Emergent Adverse Events, n	38	19

MedDRA Preferred Term by subject n (%)		
NAUSEA	6 (7%)	1 (1%)
DIARRHEA	13 (15%)	5 (6%)
ABDOMINAL PAIN	7 (8%)	1 (1%)
VOMITING	3 (3%)	1 (1%)
LIPDYSTROPHY	1 (1%)	3 (3%)

7.4.2 Laboratory Findings

This review focused primarily on the comparative incidences of grade three and four laboratory abnormalities and reported associated adverse events for selected laboratory tests as reported by the Applicant. The proportion of patients with grade three and four laboratory abnormalities was independently verified by FDA and the results presented below are accurate and acceptable for inclusion in the package insert.

Comment: Generally it can be stated that similar percentages of subjects developed laboratory abnormalities across the treatments arms and that the switch to once daily LPV/r did not lead to an increased frequency of laboratory abnormalities.

As expected most events were Grade 1 or 2. There were no grade 4 abnormalities reported. There was one report of a grade 3 neutropenia in a once daily treated subject. This event resolved without treatment discontinuation and was thought to be due to ZDV administration. In addition there was one grade 3 report of hyperbilirubinemia which was described in the SAE section of this review. This event was associated with an episode of cholangitis and was not associated with LFT abnormalities. There were two reports of hypertriglyceridemia in twice daily treated subjects. As noted above, none of these events led to treatment discontinuation.

Although there were 2 reports of grade 3 hypertriglyceridemia in the lab datasets only one of these was reported as a grade 3 adverse event in table 11 of this review (Grades 3 and 4 Treatment-Emergent Adverse Events) because of the varying ways the sites reported such events depending on their location (Europe vs Thailand etc.).

There were no significant changes in hemoglobin or other hematologic parameters during the 24 week study on either treatment arm.

Similarly there were no clinically significant differences between treatment arms with regards to renal or hepatic function. More twice daily treated subjects had increases in total cholesterol (22 QD vs. 25 BID) and LDL cholesterol (11 QD vs. 21 BID).

7.4.3 Vital Signs

During the 24 weeks of treatment, the mean changes from baseline for each vital sign parameter was generally small and similar between treatment groups and were not clinically meaningful.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed.

7.4.5 Special Safety Studies/Clinical Trials

Additional special safety studies were not included in this supplemental NDA nor required for review.

7.4.6 Immunogenicity

Immunogenicity effects were not anticipated and therefore not specifically assessed for during the clinical trial.

7.5 Other Safety Explorations

Additional analyses for dose dependency, time dependency drug-disease, drug demographics, and drug-drug interactions were not conducted with this review. This was deemed acceptable for this study performed only in pediatric subjects.

7.5.1 Dose Dependency for Adverse Events

Not applicable

7.5.2 Time Dependency for Adverse Events

Not applicable

7.5.3 Drug-Demographic Interactions

Not applicable

7.5.4 Drug-Disease Interactions

Not applicable

7.5.5 Drug-Drug Interactions

Not applicable

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information with regard to human carcinogenicity was included. Please see the USPI for this information.

7.6.2 Human Reproduction and Pregnancy Data

No new data with regard to human reproduction and pregnancy data were included. LPV/r is a pregnancy category C agent. No pregnancies were reported.

7.6.3 Pediatrics and Assessment of Effects on Growth

With this (b) (4) supplement submitted in response to a PREA/PMC the Applicant seeks to update the labeling pertaining to pediatric use (section 8.4) as follows:

The safety, efficacy, and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 14 days have not been established. KALETRA should not be administered once daily (b) (4)

A prospective multicenter, randomized, open-label study evaluated the (b) (4) efficacy, and safety of twice-daily versus once-daily dosing of KALETRA (b) (4) dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, ≥ 15 kg in weight, receiving cART that included KALETRA, HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 24, the efficacy (b) (4)

Section 12, CLINICAL PHARMACOLOGY, Special Populations, Pediatric Patients was updated as follows:

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses were reported.

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarketing Experience

A 120 day safety update was not required for this submission because of the consistency of the reported safety from the studies reviewed to those previously reviewed and included in the USPI.

9 Appendices

9.1 Literature Review/References

Not applicable

9.2 Labeling Recommendations

As noted in section 7.6.3, the sponsor proposed the following labeling changes

To the pediatric use (section 8.4) as follows:

The safety, efficacy, and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 14 days have not been established. KALETRA should not be administered once daily (b) (4) in pediatric patients.

A prospective multicenter, randomized, open-label study evaluated the (b) (4) efficacy, and safety of twice-daily versus once-daily dosing of KALETRA (b) (4) tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, ≥ 15 kg in weight, receiving cART that included KALETRA, HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 24, (b) (4)

Section 12, CLINICAL PHARMACOLOGY, Special Populations, Pediatric Patients was updated as follows:

(b) (4)

The DAVP determined that the proposed changes did not adequately represent the results of the KONCERT study with regards to the large number of treatment failures on the once daily treatment arm compared to the twice daily. Further as no comparative efficacy studies were performed between adults and pediatric subjects, statements regarding comparative efficacy cannot be made. The following changes were proposed:

A prospective multicenter, randomized, open-label study evaluated the efficacy, and safety of twice-daily versus once-daily dosing of KALETRA tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, ≥ 15 kg in weight, receiving cART that included KALETRA, HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 24, efficacy (defined as the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL) was significantly higher in subjects receiving twice daily dosing compared to subjects receiving once daily dosing. The safety profile was similar between the two treatment arms although there was a greater incidence of diarrhea in the once daily treated subjects.

In addition changes were made to the pregnancy (8.1) and nursing mothers (8.3) sections of section 8 of the capsule label in order to make it consistent with that of the tablet and the oral solution.

At the time of completion of this review, labeling negotiations were ongoing.

9.3 Advisory Committee Meeting

Not applicable

9.4 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: 21906/S-0146, 21251/S-0138, 21226/S-0041

Submission Date(s): September 17, 2014

Applicant: AbbVie

Product: Kaletra (LPV/r)

Reviewer: Regina Alivisatos, MD

Date of Review: September 30, 2014

Covered Clinical Study (Name and/or Number): PENTA-18 (KONCERT)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>50</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA		

3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒ x	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒ x	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐ x	No ☐ (Request explanation from applicant)

The Applicant adequately disclosed financial interests and arrangements with clinical investigators for a study not conducted by the Applicant. None of the investigators had disclosable financial interests. It should be noted that AbbVie was unable to provide a financial disclosure form for one investigator, (b) (6) of the PENTA committee who did not enroll any patients.

9.5 DDIs

Proposed changes:

The following additions have been proposed by the Applicant to Table, 8 which provides a listing of established or potentially clinically significant drug interactions. The Medication Guide was also updated accordingly.

7.3 Established and Other Potentially Significant Drug Interactions

Non-nucleoside Reverse Transcriptase Inhibitor:	etravirine	(b) (4)
etravirine	required.	no dose adjustment is required. (b) (4)

Non-nucleoside Reverse Transcriptase Inhibitor:	↑	(b) (4)
<u>rilpivirine</u>	rilpivirine	but no dose adjustment is required. (b) (4)

HCV-Protease Inhibitor:	↑	(b) (4)
<u>simeprevir</u>	simeprevir	It is not recommended to co-administer KALETRA and simeprevir.

REVIEW:

Rilpivirine (EDURANT):

Rilpivirine is an NNRTI that is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients with HIV-1 RNA $\leq$ 100,000 copies/mL. Rilpivirine is primarily metabolized by CYP3A, and drugs that inhibit or induce CYP3A may result in increased or decreased plasma concentrations of rilpivirine.

The USPI for rilpivirine states that "Co-administration of EDURANT with drugs that induce or inhibit CYP3A may affect the plasma concentrations of rilpivirine." However, the USPI also states "No dose adjustment is required when EDURANT is co-administered with lopinavir/ritonavir."

Rilpivirine is also a component of Complera FDC. The Complera USPI states that "Drugs that induce or inhibit CYP3A4 may affect the plasma concentrations of rilpivirine" and that "Coadministration of rilpivirine and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine." The Complera USPI further states that "Complera is a complete regimen for treatment of HIV-1 infection; therefore, Complera should not be administered with other antiretroviral medications for treatment of HIV-1 infection."

In support of the proposed changes the Applicant submitted the results of a pharmacokinetic study between LPV/r and rilpivirine as well as evidence from the literature and their postmarketing safety database.

The PK study was an open label, randomized, 2-period crossover trial conducted to investigate the potential pharmacokinetic interaction between rilpivirine and LPV/r. Sixteen healthy volunteers were randomized to receive rilpivirine 150 mg once daily (QD) or LPV/r 400/100 mg BID plus rilpivirine 150 mg QD. The 150 mg dose of rilpivirine is 6-fold greater than the recommended dose of 25 mg QD.

Co-administration resulted in rilpivirine C_{max} , AUC_{24h} , and C_{min} increases of 29%, 52%, and 74%, respectively, compared with rilpivirine administered alone. Rilpivirine did not significantly affect lopinavir or ritonavir exposures, and only marginally decreased lopinavir C_{min} by 11%. The increase in rilpivirine exposure was smaller than that observed for the DRV/r (800 mg plus 100 mg once daily) interaction, which resulted in 79%, 130%, and 178% increases in rilpivirine C_{max} , AUC_{24h} , and C_{min} , respectively.

Concomitant use of rilpivirine with LPV/r resulted in increased plasma concentrations of rilpivirine. Nevertheless, the potential increase in rilpivirine exposure with the recommended dose of 25 mg is expected to be lower than the exposures observed in the Phase 2b study in which higher doses of rilpivirine (75 mg and 150 mg) were evaluated and found to be well-tolerated. Therefore, as stated in the USPI, no dose adjustments are warranted when either rilpivirine or Complera is co-administered with LPV/r.

The Applicant's review of the published literature revealed no articles that described adverse events resulting from the potential DDI between LPV/r and rilpivirine.

One report was retrieved from the AbbVie postmarketing safety database of a DDI between LPV/r and rilpivirine. In that report a female patient receiving Complera developed lactic acidosis. Treatment dates were unspecified. It was thought that the acidosis was attributable to tenofovir. Outcome was not reported.

Summary:

In summary the published literature, PK data, and postmarketing safety information support the recommendation that no dosage adjustments are necessary when rilpivirine is co-administered with LPV/r. Based on the above it is reasonable to update the LPV/r label to indicate that no dosage adjustment is necessary. The Clinical Reviewer agrees with the changes proposed by the Clinical Pharmacology Reviewer.

Etravirine (INTELENCE):

Etravirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated for the treatment of HIV-1 infection in treatment-experienced patients 6 years of age and older with viral strains resistant to an NNRTI and other antiretroviral agents. It is a substrate of CYP3A4, CYP2C9, and CYP2C19. Drugs that induce or inhibit CYP3A, CYP2C9, and CYP2C19 may alter the plasma concentrations of etravirine. Etravirine is also a (b) (4) inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19.

The USPI for Intelence states, "Co-administration of INTELENCE with drugs that inhibit or induce CYP3A, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of etravirine."

In support of the proposed changes the Applicant submitted the results of a pharmacokinetic study between RTV and etravirine as well as evidence from the literature and their postmarketing safety database.

The PK study was a Phase 1, open-label, 2-period, 2-way crossover interaction study conducted in 16 healthy volunteers to evaluate the DDI of etravirine and LPV/r. All subjects received both treatments in a randomized, crossover fashion: etravirine 200 mg twice daily (BID) alone for 8 days and LPV/r tablets 400/100 mg BID for 16 days with etravirine 200 mg BID co-administered from days 9 to 16, with a 14-day washout between periods.

Co-administration resulted in decreases in etravirine C_{max}, AUC_{12h}, and C_{min} of 30%, 35%, and 45%, respectively. Lopinavir exposures were slightly decreased with co-administered etravirine; lopinavir C_{max}, AUC_{12h}, and C_{min} were decreased by 11%, 13%, and 20%, respectively.

The decreases in lopinavir exposure on co-administration of etravirine are considered small (< 20%) and do not require dosage adjustment for LPV/r. The extent of decrease in etravirine exposures was similar to that observed for the interaction of etravirine with co-administered DRV/r (600 mg plus 100 mg twice daily) in another study, which showed decreases in etravirine C_{max}, AUC_{12h}, and C_{min} of 32%, 37%, and 49%, respectively. No dose adjustments for any of the drugs are recommended when they are co-administered. The decrease in etravirine exposures did not negatively impact the antiretroviral efficacy of etravirine.

The Applicant's review of the published literature revealed no articles that described adverse events resulting from the potential DDI between LPV/r and etravirine.

One report was retrieved from the AbbVie postmarketing safety database of a DDI between LPV/r and etravirine. In that case virologic failure occurred in a subject receiving both drugs. However provided information was limited and no conclusions regarding causality could be drawn.

Summary:

Review of published literature and of AbbVie's global postmarketing safety database did not identify a potential safety signal resulting from the LPV/r/etravirine DDI. No case reports were found in the literature that described clinically significant DDIs with their co-administration. Based on the above it is reasonable to update the LPV/r label to indicate that no dosage adjustment is necessary. The Clinical Reviewer agrees with the changes proposed by the Clinical Pharmacology Reviewer.

Simeprevir (OLYSIO):

Simeprevir is protease inhibitor active against hepatitis C. It undergoes hepatic metabolism primarily by CYP3A. Co-administration of simeprevir with inhibitors or inducers of CYP3A may affect the systemic exposures of simeprevir. The daily recommended simeprevir dose is 150 mg once daily (QD), and simeprevir shows more than a dose proportional increase in concentrations at the dose range of 75 to 200 mg QD.

(b) (4) Applicant submitted the results of a pharmacokinetic study between RTV and simeprevir as well as evidence from the literature and their postmarketing safety database

The PK study was a Phase 1 open-label, single-arm, two-period, sequential crossover study carried out in 12 healthy subjects to investigate the effect of ritonavir (100 mg BID) on simeprevir (200 mg QD). Simeprevir 200 mg QD was administered alone for 7 days, followed by a washout period of at least 7 days. Subsequently, ritonavir 100 mg BID was administered for 15 days, and simeprevir 200 mg QD was co-administered on Days 6 through 12. Co-administration of multiple doses of simeprevir with ritonavir resulted in increases in simeprevir maximum observed concentration (C_{max}), area under the concentration time curve (AUC_{24h}), and minimum observed concentration (C_{min}) by 4.7-, 7.2-, and 14.4-fold, respectively, compared with simeprevir alone. Similar increases occurred when DRV/RTV was co-administered with simeprevir.

As per the Applicant, exploratory exposure-response analysis using safety data from three simeprevir Phase 3 trials, showed that higher simeprevir exposures (AUC_{24}) were significantly associated with an increased risk of adverse events such as rash, pruritus, anemia, photosensitivity, and increased bilirubin.

The Applicant also stated that “When darunavir plus ritonavir (800 mg plus 100 mg QD) were administered with simeprevir 50 mg QD, the increases in simeprevir C_{max} , AUC_{24h} , and C_{min} were 1.8-, 2.6-, and 4.6-fold, respectively, compared with 150 mg QD simeprevir administered alone.”

The simeprevir USPI cautions that ritonavir-boosted or unboosted HIV protease inhibitors should not be co-administered with simeprevir.

The Applicant’s review of the published literature revealed no articles that described adverse events resulting from the potential DDI between RTV and simeprevir. In addition no case reports of DDIs were retrieved from AbbVie’s postmarketing safety database.

Summary:

This Applicant proposes the addition of wording to the LPV/r USPI regarding a potential safety concern for a DDI between LPV/r and simeprevir when co-administered. Such co-administration could lead to increased simeprevir concentrations. To date there have

been no adverse events reported with coadministration and there are no literature reports describing potential safety signals. This could be because simeprevir was recently approved in the US. There is however PK data that shows that co-administration results in increased simeprevir exposures and therefore increased risk of developing adverse events. Finally the simeprevir label states that "It is not recommended to co-administer Olysio with boosted or unboosted PIs".

Based on the above it is reasonable to update the LPV/r label to include information on the potential for a DDI between LPV/r and simeprevir. The Clinical Reviewer agrees with the changes proposed by the Clinical Pharmacology Reviewer.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

M R ALIVISATOS
04/14/2015

ADAM I SHERWAT
04/14/2015

I am in complete agreement with Dr. Alivisatos' clinical review.