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Title:	APV20002: A 48 Week Phase II, Open-label, 2-cohort, Multicentre Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of GW433908 and GW433908/RTV When Administered to HIV-1 Infected Protease Inhibitor (PI) Naïve and PI-Experienced Pediatric Subjects aged 4 weeks to <2 years

Compound Number: GW433908

Effective Date: 20-NOV-2019

Protocol Amendment Number: 12

Subject: HIV infection, pediatric, protease inhibitor, fosamprenavir, GW433908

Author: PPD

Revision Chronology:

GD2001/00007/00	2002-SEP-20	Original
GD2001/00007/01	2003-AUG-05	Amendment No. 1: Study Design changes including lowering of the age limit from 6 weeks to 4 weeks Revision of study objectives and endpoints Update schedule of assessments and interim analyses Addition of new data from other FPV studies Changes related to initial dose selection and dose adjustment criteria To update the definition of study drug overdose To update the subject management options
GD2001/00007/02	2004-MAY-10	Amendment No. 2: To change the Exclusion Criteria No 8 to any Grade 3 or greater laboratory abnormality
GD2001/00007/03	2005-JUL-01	Amendment No. 3: To add a new dose recommendation for Cohort 1A To temporarily close Cohort 1B To revise the study design to allow simultaneous enrolment of Cohort 2 Arm A and B To update the dose adjustment guidance To provide details pertaining to study visit beyond 48 weeks To clarify that subjects enrolled in Cohort 1B or 2B may have their treatment switched to a boosted regimen only in countries where RTV solution is locally available for long-term use To provide clarification regarding the maximum age allowed for each cohort in Inclusion Criteria No 1.

GD2001/00007/04	2005-AUG-03	Amendment No. 4: To add information regarding the removal of the unboosted FPV Cohort 1 Arm B from the study. This amendment was sent to the Food and Drug Administration (FDA) only and was not sent to the sites for implementation.
GD2001/00007/05	2007-JUL-05	Amendment No. 5: Defers enrolment of subjects in the unboosted FPV cohorts (Cohort 1 Arm B and Cohort 2 Arm B) Increases the dose of FPV to 60 mg/kg at the Week 2 visit for subjects in Cohort 1 Arm A Revises the PK visits and sampling times for subjects in Cohort 1 Arm A and adds plasma samples for determining unbound APV concentrations Increases the single doses for Cohort 2 Arm A SDV to FPV 45 mg/kg and RTV 7 mg/kg Revisions to the concurrent medications; rifabutin and phenytoin no longer excluded Updates information on rash and abacavir hypersensitivity reaction Updates sponsor contact information Updates the DAIDS toxicity grading tables (2004) Updates background information, removes redundancies and corrects minor inconsistencies in the protocol.
GD2001/00007/06	2007-NOV-20	Amendment No. 6: Corrects the inaccuracies in the study drug dosing tables and an inconsistency in exclusion criteria no. 9 (per amendment 5)

GD2001/00007/07	2009-JUN-02	Amendment No. 7: To add a dose recommendation for subjects recruited into Cohort 2 Arm A. Update to the number of subjects to be recruited into Cohort 2 Arm A. Remove the Single Dose Visit from the assessment flow chart for subjects in Cohort 2 Arm A. Include the option to use local laboratories for haematology and clinical chemistry with Sponsor approval.
GD2001/00007/08	2009-NOV-23	Amendment No. 8: To revise the dose recommendation for new subjects enrolled into Cohort 1, Arm A to FPV/RTV 45/7 mg/kg BID, with no increase to 60/7 mg/kg BID at Week 2. To update the number of subjects to be recruited into Cohort 1, Arm A. To provide additional dosing advice for existing subjects in Cohort 1, Arm A receiving FPV/RTV 60/7 mg/kg. To provide guidance on dosing for subjects when reaching 2 years and 6 years of age during the study. Allows for individual dose adjustment on a case by case basis. Provision for a single repeat test for liver enzymes in the event of grade 3 or > value to determine eligibility
GD2001/00007/09	2010-OCT-25	Amendment No. 9: To specify a change of study sponsor. To provide information on an external review committee. To update recruitment status. To clarify guidance on dosing for subjects reaching 2 years and 6 years

		of age during the study
GD2001/00007/10	2011-MAR-28	Amendment No. 10: To amend information on propylene glycol content in FPV oral suspension to include contribution from liquid flavours. To close unboosted FPV Cohorts 1B and 2B and amend study objectives and endpoints accordingly. To correct study sponsor information.
GD2001/00007/11	2012-OCT-26	Amendment No. 11: To include information on 3TC and ABC tablets to be provided by GSK as background NRTI options. To update the list of drugs not to be co-administered with FPV and RTV. To provide option to discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis once a subject has reached and exceeded 2 years and has initiated the 23/3 mg/kg BID dosing regimen To update section on posting of information on publicly available clinical trials registers and publication
GD2001/00007/12	20-NOV-2019	Amendment No.12 To include additional RTV formulation options as the oral solution is being discontinued in South Africa and provide updated FPV and RTV dosing tables for children >6 years of age To update the list of drugs not to be co-administered with FPV and RTV and provide additional information on rash management and suspected abacavir hypersensitivity 1. FPV Pediatric

		Clinical Data references to pediatric study results published after amendment 11 have been added; sites are also now advised to refer to these and local labels for summaries of the available data The section regarding reporting of SAES was moved to Section 7.9 and the previous Section 7.9 (Regulatory Reporting Requirements For SAEs) was moved to Section 7.8 After 2013, viral load measurements, are being performed using the Abbott Realtime HIV-1 assay due to manufacturer discontinuation of the Roche Amplicor assay Assent forms will be obtained from subjects still enrolled in the study as of Nov 1, 2019 as the subjects are now of an age where they can provide assent (consent originally provided by the careers)

Sponsor Signatory:	Signature:	Date:
PPD Sherene Min, MD Vice President Clinical Development, ViiV Healthcare	PPD	PPD

SPONSOR INFORMATION PAGE

Title: A 48 Week Phase II, Open-label, 2-cohort, Multicentre Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of GW433908 and GW433908/RTV When Administered to HIV-1 Infected Protease Inhibitor (PI) Naïve and PI-Experienced Pediatric Subjects aged 4 weeks to <2 years.

Study Number: APV20002

This study is sponsored by ViiV Healthcare UK Limited and ViiV Healthcare Company. GlaxoSmithKline is responsible for implementing and managing all aspects of this study.

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INVESTIGATOR AGREEMENT PAGE

For protocol number APV20002

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Signature	Date

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ABBREVIATIONS

3TC	lamivudine, EPIVIR
ABC	abacavir sulfate, ZIAGEN
AE	adverse event
AGN	Agenerase, amprenavir
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
APV	amprenavir
ART	antiretroviral therapy
AST	aspartate aminotransferase (SGOT)
AUC_{∞}	area under the plasma concentration versus time curve from time 0 and extrapolated to infinity
AUC_{last}	area under the concentration versus time curve from time 0 until the last quantifiable concentration during a dosing interval
$AUC_{last,ss}$	area under the concentration versus time curve from time 0 until the last quantifiable concentration during a dosing interval at steady-state
$AUC_{\tau,ss}$	area under the concentration versus time curve during a dosing interval, τ, at steady- state
BID	twice daily
$C_{avg,ss}$	The average concentration during a dosing interval, τ, at steady-state
CD4+	helper-inducer T-lymphocyte surface antigen
CD8+	cytotoxic-suppressor T-lymphocyte surface antigen
CDC	Centers for Disease Control and Prevention
CL_{ss}	the apparent plasma clearance at steady-state
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum concentration at steady-state
$C_{min,ss}$	minimum concentration during a dosing interval
CPMP	Committee for Proprietary Medicinal Products
CPK	creatine phosphokinase
CRF	case report form
$C_{\tau,ss}$	concentration at the end of a dosing interval, τ, at steady-state
CVb	coefficient of variability
CYP	cytochrome P450
DQ	data query
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eDQ	electronic data query
EFZ	efavirenz
EISR	Expedited Investigator Safety Report
ERC	External Review Committee
FDA	Food and Drug Administration (US)
FPV	fosamprenavir, GW433908, 908, Telzir, Lexiva
GCP	good clinical practice

GLP	Good Laboratory Practices
GSK	GlaxoSmithKline
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV-1	human immunodeficiency virus type 1
HSR	hypersensitivity reaction
ICF	informed consent form
IDV	indinavir
IEC	independent ethics committee
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
LDL	low density lipoprotein
LOD	limit of detection
LPV/RTV	lopinavir/ritonavir, Kaletra
LSLV	last subject's last visit
MCV	mean corpuscular volume
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
PCR	polymerase chain reaction
PI	protease inhibitor
PK	pharmacokinetics
PRO	viral protease
QD	once daily
RNA	ribonucleic acid
RT	reverse transcriptase
RTV	ritonavir, Norvir
SAE	serious adverse event
SCA	standard clarification agreement
SDV	single dose visit
$t_{1/2}$	the associated apparent terminal elimination half-life
t_{max}	the first time to reach C_{max}
$t_{max,ss}$	the first time to reach $C_{max,ss}$
$t_{min,ss}$	the time that C_{min} occurs
WBC	white blood cell
λ_z	The apparent terminal plasma elimination rate-constant
ZDV	zidovudine

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PROTOCOL SUMMARY

Agenerase (AGN, amprenavir, APV) was a protease inhibitor (PI) developed for the treatment of HIV disease. Although AGN demonstrated antiviral activity and was generally safe when given in combination with other antiretroviral agents to subjects at all stages of HIV infection, the pill count with the capsule formulation and substantial volume of oral solution required (1.5mL/kg BID) was less than optimal and could impact long term adherence to therapy. To reduce the pill burden of APV delivered as AGN, a tablet and oral suspension formulation of fosamprenavir (FPV, GW433908, LEXIVA™/ TELZIR™), the phosphate ester prodrug of APV, was developed to facilitate dosing of adult and pediatric HIV-1 infected patients. The safety and efficacy of FPV-containing regimens was demonstrated in three Phase III clinical trials in adults.

The use of combination therapy with 3 drugs, including either a PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor, plus a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone is the current standard of care for and is recommended for initial treatment of most HIV-infected adults and children [DHHS, 2019; EACS, 2018; Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children; 2019]. There remains a need for additional therapies for HIV infected children, in particular there are limited choices for a third agent to be given in combination with two NRTIs, and the choices are even more limited in children <2 years of age.

Amprenavir, delivered as Agenerase oral solution, required large dosing volumes and was approved for restricted use by children of at least 4 years of age who were unable to swallow AGN capsules. This restriction in use was due mainly to concerns about the large volume of excipients, including PEG400 and propylene glycol, required for dosing [Agenerase Package Insert, 2005]. Further, due to the high propylene glycol content in AGN oral solution and the high ethanol content of ritonavir (RTV) oral solution, co-administration of AGN oral solution and RTV oral solution was contraindicated. At the holder's request, the Marketing Authorisation for AGN was withdrawn in the EU on April 29, 2010 and in the USA on August 18, 2009.

The FPV oral suspension incorporates less propylene glycol than AGN oral solution thereby facilitating its administration to children of all ages and allows co-administration with RTV oral solution. The FPV oral suspension is also easier to formulate than APV with an increased concentration (50 mg/mL vs. 15 mg/mL) allowing a significant reduction in the total volume of FPV oral suspension required per dose compared to AGN solution.

APV20002 is evaluating the pharmacokinetics (PK), safety, tolerability and antiviral activity of FPV when administered to HIV-1 infected PI-naïve and PI-experienced pediatric subjects aged 4 weeks to <2 years. FPV will be administered as either the sole PI or in combination with low dose RTV. Subjects in this study will be enrolled in 2 age cohorts (Cohort 1: 6 months to <2 years, and Cohort 2: 4 weeks to <6 months) in order to determine FPV and FPV/RTV dosage regimens for pediatric subjects at various stages of physiologic development.

Dose Rationale

Given the young age of the children enrolled into this study, subjects will receive the FPV oral suspension formulation. In children, the FPV oral suspension is recommended to be administered with food.

APV20002 was designed to determine FPV/RTV regimens for pediatric subjects 4 weeks to <2 years of age that would deliver plasma APV exposures proven to be safe and effective in adults.

In a small subset of five subjects aged 6 months to <2 years (Cohort 1, Arm A) who received FPV/RTV 45/7 mg/kg BID, plasma APV AUC(0-τ) was approximately 48% lower, Cmax 26% lower, and Cτ 29% lower than the adult target values. Conversely, RTV levels appeared to be similar between these pediatric subjects and adult comparators. Based on these results, Amendment 5 (05-Jul-2007) was undertaken to initiate dosing with FPV/RTV 45/7 mg/kg BID for two weeks (to allow collection of additional data on this regimen) and then increase the dose to FPV/RTV 60/7 mg/kg BID (to collect data on a higher dose regimen) for the duration of the study.

Subsequent to Amendment 5, eleven additional subjects have been enrolled in Cohort 1, Arm A. APV PK was evaluated at Week 2 (sampling predose, 2h, and 4h post dose) for the FPV/RTV 45/7 mg/kg BID regimen and at Week 8 (sampling predose, 1, 2, 4, 6, 8h post dose) for the FPV/RTV 60/7 mg/kg BID regimen. Plasma APV Cτ values were collected at all subsequent visits. APV PK parameters for newly enrolled subjects in Cohort 1A (6 months to <2 years) are compared to those for the subjects of this age group previously report as well as adult counterparts.

APV Cmax and Cτ following FPV/RTV 45/7 mg/kg BID were higher in the eleven newly enrolled subjects than in the original five subjects who received the same dose. However, upon re-evaluation of data for the original subjects who received 45/7 mg/kg BID, one subject (PPD) had extremely low PK parameter values at Week 2 that appear to have affected the statistical point estimate of each parameter. Excluding that one subject from the originally enrolled group, the geometric mean Cmax for the remaining 4 subjects is increased from 4.16µg/mL to 6.07µg/mL, more consistent with adult values and more similar to the geometric mean Cmax at 7.5ug.mL of the newly enrolled subjects receiving 45/7 mg/kg BID at Week 2. Geometric mean AUC(0-τ) is increased from 19.3µg*h/mL (n=5) to 31.2µg*h/mL (n=4), again much closer to the adult target values; AUC(0-τ) following 45/7 mg/kg BID could not be determined at Week 2 for newly enrolled subjects due to limited sampling scheme. Overall geometric mean (95% CI) Cτ was increased from 1.54µg/mL (1.13, 2.09µg/mL, n=5) to 1.81µg/mL (1.40, 2.33µg/mL n=4), also closer to adult targets and newly enrolled subjects.

APV parameters following FPV/RTV 60/7 mg/kg BID in subjects 6 months to <2 years were significantly higher than adult target parameters. Geometric mean APV AUC(0-τ) and Cmax following FPV/RTV 60/7 mg/kg BID were 1.8-fold and 2.6-fold higher than the geometric mean values in adults.

Per protocol amendment 8, since APV parameters following FPV/RTV 45/7 mg/kg BID were closer to adult targets in the newly enrolled subjects and in the original 6 month to 24 month olds upon exclusion of the one low outlier and since APV parameters following FPV/RTV 60/7 mg/kg BID were significantly higher than adult targets, subjects enrolled in the future will receive FPV/RTV 45/7 mg/kg BID continuously without an increase to FPV/RTV 60/7 mg/kg BID at Week 2. Some subjects with consistently high Cτ values following FPV/RTV 60/7 mg/kg BID have had their dose reduced to FPV/RTV 45/7 mg/kg BID. Other subjects previously enrolled and currently receiving FPV/RTV 60/7 mg/kg may have their dose modified at the discretion of the investigator and GSK.

Plasma APV PK data are available from the first 12 subjects enrolled in Cohort 2 Arm A (4 week to <6 month age group). All 12 subjects received FPV/RTV 45/7 mg/kg as a single dose, and 11 subjects underwent repeat administration of FPV/RTV BID at individualized dosage regimens ranging from FPV 30-60 mg/kg and RTV 7-10 mg/kg based on each subject's single dose PK data. On both single dose and repeat dose administration of FPV/RTV, pediatric subjects 4 weeks to <6 months of age had higher plasma APV Cmax and AUC values, but similar C12 (single dose) and lower Cτ (repeat dose) values compared with those historically observed for adults. Repeat dose plasma RTV Cmax and AUC values were similar to historical adult data, but plasma RTV Cτ values were lower in the pediatric subjects. As plasma APV Cτ is important for long-term efficacy and minimization of resistance development, it is important to try to achieve plasma APV Cτ values in pediatric subjects similar to those achieved with the approved FPV/RTV 700/100 mg BID regimen in adults. It is possible that the lower plasma RTV Cτ values are responsible for the lower plasma APV Cτ values; therefore per Protocol Amendment 7, an increase in the RTV dose from 7 mg/kg BID to 10 mg/kg BID for all subsequently enrolled subjects was recommended. These subjects will initiate dosing with FPV/RTV 45/10 mg/kg BID and have serial PK sampling at Week 2 and trough sampling on subsequent visits. Additionally, a single dose visit (SDV) is no longer required for newly enrolled subjects 4 weeks to <6 months of age (Cohort 2 Arm A).

Per Protocol Amendment 10, enrolment in the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is closed. Based on the PK data from the age-specific FPV/RTV cohorts, the dose volumes of unboosted FPV oral suspension necessary to administer the calculated therapeutic dose in children aged <2 years would be approximately twice the boosted dose volumes. Enrolment into the unboosted FPV cohorts is therefore not advised due to these large volumes of FPV oral suspension that would need to be administered as they could result in poor adherence, likely leading to an inadequate virologic response and subsequent resistance.

Per Protocol Amendment 12, as sale of RTV oral solution is being discontinued by the manufacturer in South Africa, additional RTV formulation options have been added for the South African sites. The RTV dosing is based upon the weight of the child and include RTV supplied as 100 mg tablets, capsules or powders/sachets.

STUDY OBJECTIVES

Primary

- To define the FPV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected PI-naïve pediatric subjects aged 4 weeks to <2 years (deferred per amendment 5). **This objective has been removed with enrolment into the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) closed as per Protocol Amendment 10.**
- To define the FPV/RTV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the safety and tolerability of FPV/RTV when administered as a component of combination therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years. **The objective to evaluate the safety and tolerability of FPV BID dosage regimens has been removed as per Protocol Amendment 10.**

Secondary

- To evaluate the antiviral activity of FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the immunologic activity of FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess systemic exposure to FPV when administered to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess plasma RTV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- To investigate the relationship of steady-state plasma APV PK parameters to changes in plasma HIV-1 RNA concentrations, CD4+ percentages and/or the occurrence of adverse events
- To assess subject adherence and parent/guardian perceptions of study medications
- To assess viral resistance patterns and to compare these patterns with treatment outcome (where permissible by blood volumes)

The secondary objectives to evaluate the antiviral and immunologic activity of FPV have been removed as per Protocol Amendment 10.

STUDY ENDPOINTS

Primary

- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV BID (deferred per amendment 5). **This endpoint has been removed with enrolment into the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) closed as per Protocol Amendment 10.**

- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- Plasma unbound APV Cτ,ss and percent protein binding
- The incidence and nature of adverse events, laboratory abnormalities, and treatment –limiting toxicities
- Proportion of subjects who permanently discontinue FPV/RTV due to adverse events. **The endpoint 'Proportion of subjects who permanently discontinue FPV due to adverse events' has been removed as per Protocol Amendment 10.**

Secondary

- Proportions of subjects with plasma HIV-1 RNA levels <400copies/mL at each study visit
- Change from Baseline in plasma HIV-1 RNA at each study visit (absolute values and time-averaged)
- Proportion of subjects with ≥1.0 log10 decrease in plasma HIV-1 RNA at each study visit
- Change from Baseline in the percentage of CD4+ lymphocytes at each study visit (absolute values and time-averaged)
- Plasma FPV concentrations
- Plasma RTV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- Relationship of steady-state plasma APV PK parameters to changes in plasma HIV-1 RNA concentrations, CD4+ percentages and/or the occurrence of adverse events
- Subject adherence and parent/guardian perceptions of study medications
- Incidence of viral resistance (where permissible by blood volumes)

STUDY DESIGN

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART. Per protocol amendment 12; only subjects at sites in South Africa remain enrolled as supplies of oral FPV suspension are not commercially available in South Africa. Subjects successfully completing 48 weeks of therapy and receiving clinical benefit who weigh less than 39 kg may continue to receive FPV oral suspension provided by GSK. Once subjects reach a weight of 39 kg, South African treatment guidelines permit the use of the FPV tablets in children weighing ≥39 kg and these subjects will be withdrawn as FPV tablets are commercially available in South Africa.

Single dose PK data for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Enrolment into Arm B (unboosted FPV cohorts 1 and 2) as per amendment 10 has been closed.

Recruitment Status for APV20002 – from Oct 2003 (FSFV) to Jul 2011 (cutoff for 48 week CSR

Age (yrs) Cohorts	No. of Subjects originally planned	Cumulative enrolment and current status
1A 6 months - <2yr PI-naïve/exp FPV/RTV (boosted)	12	26[1] enrolled 11 ongoing[2]
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	12	28[1] enrolled 14 ongoing[2]

1. A total of 59 patients were enrolled but 5 discontinued after receiving single dose of FPV; current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments
2. Ongoing as of cutoff for 48 week CSR (July 2011)

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 10, enrolment in the Arm B cohorts (unboosted FPV) is closed.

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments.

Refer to Section 3.1 (Figure 1 and Figure 2) for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 8, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit and will undergo plasma PK serial sampling at Week 2 (over 4 hours) and Week 8 (over 8-12 hours; 12 hour sample optional).

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence multiple dosing with FPV 45 mg/kg BID + RTV 10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is based on the Week 2 plasma PK data from the initial 12 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo plasma PK serial sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit. Approximately 8-12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 2 Arm A to receive this dosing regimen.

Enrolment of Arm B (FPV BID)

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 10, enrolment in the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is closed. Based on the PK data from the age-specific FPV/RTV cohorts, the dose volumes of unboosted FPV oral suspension necessary to administer the calculated therapeutic dose in children aged <2 years would be approximately twice the boosted dose volumes. Enrolment into the unboosted FPV cohorts is therefore not advised due to these large volumes of FPV oral suspension that would need to be administered as they could result in poor adherence, likely leading to an inadequate virologic response and subsequent resistance.

PLANNED SAMPLE SIZE

The sample size of 48 subjects was selected as an appropriate number to allow an accurate description of plasma APV PK, safety and tolerability of FPV BID, (N=24 for PK and safety; enrolment closed per Amendment 10) and FPV/RTV BID, Arm A (N=24 for PK and safety). Safety and tolerability assessment of the FPV/RTV BID regimen (Arm A) will be for the duration of the study or until a subject permanently discontinues study drug. If less than 8 subjects in a cohort and dosage regimen complete the steady-state PK analysis on Week 2, additional subjects may be enrolled as replacement subjects. Additionally, if dose modification to the cohort dose is warranted, a further 8 subjects in each arm may be recruited to provide steady-state PK data on the revised dose.

Revisions to the sample size have been made in view of required dose adjustments as specified in previous amendments.

STUDY POPULATION

HIV-1 infected pediatric subjects 4 weeks to <2 years of age with screening plasma HIV -RNA ≧400copies/mL and who meet the eligibility criteria will be recruited into the study.

Following Amendments 5 and 8, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 25 subjects in total to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 29 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is closed.

Subjects enrolled to receive FPV/RTV (Arm A) may be PI-naïve or PI-experienced. PI-experienced subjects will be eligible for Arm A if they have previously been treated with ≤3 PIs. Prior therapy with a RTV-boosted PI regimen will be considered as only 1 prior PI as long as the RTV dose was below that recommended for use as an antiretroviral agent.

Prior treatment with NRTIs is permitted and subjects are eligible if an active background regimen of two NRTIs can be constructed. For treatment-experienced subjects, prior treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PIs is permitted, however, to be eligible for this study subjects must discontinue their NNRTI use at least 14 days prior and, for subjects undergoing SDV, must discontinue their PI at least 5 days prior to administration of FPV. Subjects will NOT be permitted to receive concurrent NNRTI therapy while participating in this study. In addition, concurrent PI therapy other than the study treatments described in this protocol will NOT be permitted during the course of this study.

STUDY DRUGS AND DOSAGES

Study drugs are defined as FPV and RTV. FPV will be administered as a 50 mg/mL (43.2mg/mL APV molar equivalents) oral suspension. RTV will be administered as an 80 mg/mL oral solution, as a 100 mg capsule or tablet, or as a 100 mg powder packet/sachet. Choice of appropriate formulation will depend on participant's weight, availability of formulation and participant/caregiver preference. Both the FPV and RTV oral formulations should be administered with food. If vomiting or spitting up occurs within 30 minutes of administration, parents/guardians should be instructed to re-administer the study medications.

Refer to the Dose Rationale section of the Protocol Summary for information on dosing in each cohort.

Background Antiretroviral Therapy Options Provided by GlaxoSmithKline

ABC and 3TC will be provided as **optional** background therapy. Refer to local prescribing information for use of ABC and 3TC.

MEASUREMENTS AND EVALUATIONS

Schedules showing the timing of study procedures and laboratory evaluations for all subjects are shown in Section 10. Subjects will attend the clinic at Screening (within approximately 21 days prior to Baseline/Day 1), Day 1 (Baseline), and Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects who successfully complete 48 weeks on therapy may continue to receive FPV oral suspension provided by GSK until they no longer derive clinical benefit, weigh 39 kg or more, or according to prior agreements between GSK and participating study sites for provision of ART. A follow-up visit will be performed 4 weeks after the permanent discontinuation of study drug.

Cohort 1 (6 months to <2 years) Arm A: Plasma samples for evaluation of PK parameters will be collected over 4 hours at Week 2 and over 8-12 hours (12 hour sample optional) at Week 8. Plasma trough PK samples will be collected at Weeks 12, 16, 24, 36, 48 and

every 12 weeks thereafter. Protocol amendment 11 (effective date October 26, 2012) provided the option to discontinue PK sampling once a subject had reached and exceeded 2 years and had initiated the 23/3 mg/kg FPV/RTV BID dosing regimen. PK sampling was discontinued after approval of the amended protocol in South Africa.

Cohort 2 (4 weeks to <6 months) Arm A: Plasma PK samples will be collected over 8-12 hours (12 hour sample optional) at Week 2. Plasma trough PK samples will be collected at Weeks 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter. PK sampling was subsequently discontinued after approval of APV20002 protocol amendment 11, by which time the last enrolled subject had been enrolled in the study for more than 48 weeks.

To measure the unbound concentration of APV, additional plasma trough PK samples will be collected prior to FPV/RTV BID dosing at Weeks 2, 16 and 36 for Cohort 1 Arm A subjects and at Weeks 8 and 16 for Cohort 2 Arm A subjects.

Plasma storage samples may be collected from all study participants, where permitted by blood volume restrictions, at the Day 1, Weeks 12, 24, 36, 48, every 12 weeks thereafter, and premature discontinuation visits. These samples may be used for retrospective HIV-1 viral resistance analysis or for repeat laboratory evaluations as needed. A plasma sample for viral resistance analysis may be collected from subjects at the Screening visit per the investigator's discretion if needed to guide selection of an active NRTI background regimen. An additional plasma sample for viral resistance analysis may be collected 1 to 4 weeks after a subject meets one of the subject management criteria listed in Section 3.3.8.

The scheduled laboratory evaluations will involve collection of a maximum blood volume of 7mL/kg in any 56-day period. A maximum of 3mL/kg of blood will be collected at any one study visit from children 4 weeks to <6 months. Lastly, as defined in Section 5.6, subject adherence to study medications will be measured at Day 1, Weeks 2, 12, 24, 48**,** and at the time of premature discontinuation visits, and parent/guardian perceptions of study medications will be measured at Weeks 2, 24, and 48, and at the time of premature discontinuation visits.

1. INTRODUCTION

1.1. Background

Agenerase (AGN, amprenavir, APV) was a protease inhibitor (PI) for the treatment of HIV disease. Although AGN demonstrated antiviral activity and was generally safe when given in combination with other antiretroviral agents to subjects at all stages of HIV infection, the pill count with the capsule formulation and substantial volume of oral solution required (1.5mL/kg BID) were less than optimal and may have impacted long term adherence to therapy. To reduce the pill burden of APV delivered as AGN, a tablet and oral suspension formulation of fosamprenavir (FPV, GW433908, LEXIVA/ TELZIR), the phosphate ester prodrug of APV, were developed to facilitate dosing of adult and pediatric HIV-1 infected patients.

The safety and efficacy of three FPV-containing regimens has been demonstrated in three Phase III clinical trials, APV30001 (antiretroviral [ART]-naïve subjects), APV30002 (ART-naïve subjects), and APV30003 (PI-experienced subjects). [GlaxoSmithKline Document Number GM2002/00054/00, Study APV30002; GlaxoSmithKline Document Number RM2002/00088/00, Study APV30001; GlaxoSmithKline Document Number RM2002/00140/00, Study APV30003]. Based on these studies, four dosing regimens in adults are approved in the United States (US) for ART-naïve subjects: FPV 1400 mg BID, FPV 700 mg BID + ritonavir (RTV) 100 mg BID or FPV 1400 mg QD + RTV 200 mg QD or FPV 1400 mg QD + RTV 100 mg QD and for PI-experienced subjects: FPV 700 mg BID + RTV 100 mg BID. In Europe, the FPV 700 mg BID + RTV 100 mg BID regimen was approved for PI-naïve or experienced HIV-1 infected adults. A further study in ART-naïve adults (ESS100732, KLEAN) demonstrated non-inferiority of FPV 700 mg BID + RTV 100 mg BID compared to lopinavir (LPV)/ RTV (Kaletra) BID [GlaxoSmithKline Document Number RM2006/00010/00, Study ESS100732].

1.2. Rationale

The use of combination therapy with 3 drugs, including either a PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor, plus a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone is the current standard of care for and is recommended for initial treatment of most HIV-infected adults and children [DHHS, 2019; EACS, 2018; Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children; 2019]. There remains a need for additional therapies for HIV infected children, in particular there are limited choices for a third agent to be given in combination with two NRTIs, and the choices are even more limited in children <2 years of age.

At the time the APV20002 study was collecting the primary outcome data (through Week 48), in the NNRTI class, efavirenz (EFZ) and nevirapine (NVP) were available as liquid formulations. NVP is associated with rare but potentially life threatening adverse reactions whilst EFZ is associated with neuropsychiatric adverse reactions [Viramune Package Insert, 2010] [Sustiva Package Insert, 2010].

Similarly, at the time the APV20002 study was collecting the primary outcome data (through Week 48), in the PI class, six agents - APV, indinavir (IDV), nelfinavir (NFV), RTV lopinavir/ritonavir (LPV/RTV), and darunavir were approved for use in HIV-1 infected children. APV has subsequently been discontinued. The lower age limits for which these PIs were approved for use varies between countries.

LPV/RTV is a PI combination frequently used in children. Several studies support the use of LPV/RTV in children. An early study in children 6 months to 12 years of age demonstrated the antiviral activity of LPV/RTV over a 24 week period, with plasma HIV-1 RNA levels of <400 copies/mL being achieved in 82% of ART-naïve children and 66% of children with a mixture of NRTI-experience and NRTI + PI-experience, and accompanying improvements in CD4+ lymphocyte counts, after 24 weeks of therapy [Violari, 2000]. In a later study, 100 children ages 6 months to 12 years who were either ART naïve or ART-experienced but NNRTI naïve, received LPV/RTV as part of an ART regimen. At Week 48, 79% of subjects had plasma HIV-1 RNA levels of <400 copies/mL with corresponding mean increases in CD4+ cell counts from baseline [Post, 2010; Ross, 2015; Saez-Llorens, 2003]. Recently, data on the use of LPV/RTV in infants <6 weeks of age has been presented. In this study, 8 infants ages ≥14 days to ≤6 weeks received standard dose LPV/RTV over 24 weeks. LPV/RTV AUCs were significantly lower than seen in an older cohort ages 6 weeks to 6 months, yet the regimen resulted in virological suppression (plasma HIV-1 RNA <400 copies/mL) in 7/8 subjects [Pinto, 2007].

Although these PI therapies available for the treatment of HIV-1 infected children effectively inhibit HIV replication, most display limitations, such as lack of suitable formulations, inflexible dosing schedules and clinical side effects. For instance, no liquid formulation is available for indinavir and it is more difficult to assure adequate fluid intake to avoid renal complications in children than in adults. The powder formulation of nelfinavir is difficult to administer to children, and consequently the adult tablets are used which results in a restrictive dosing schedule [Gibb, 2000b]. The major limitations to the pediatric formulation of RTV are the taste, vomiting as an adverse event and high alcohol content [Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Use of Antiretroviral Agents in Pediatric HIV Infection. Updated April 16, 2019. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed August 20, 2019.

Pelton, 1998]. Although Kaletra is now widely used in treating HIV infected children, the pediatric liquid formulation of LPV/RTV does have a similar alcohol content (42%) to that in the RTV liquid (43%) [Kaletra Package Insert, 2019; Norvir, Package Insert, 2019].

These limitations exemplify the need for new and improved potent PI antiretroviral therapies with pediatric formulations.

The FPV oral suspension incorporates less propylene glycol than AGN oral solution which allows administration to children of all ages and co-administration with RTV oral solution. FPV is easier to formulate than AGN, with an increased concentration (50 mg/mL vs. 15 mg/mL) allowing a significant reduction in the total volume of FPV oral suspension required per dose compared to AGN solution. Thus, FPV oral suspension offers an improved vehicle for delivering amprenavir compared to AGN oral solution.

The safety, tolerability, pharmacokinetic characteristics, and antiviral activity of FPV in combination with RTV in HIV-1 infected pediatric subjects between 2 to 18 years of age were studied in protocols APV20003 and APV29005.

APV20002 is evaluating the pharmacokinetics (PK), safety, tolerability and antiviral activity of FPV when administered to HIV-1 infected PI-naïve and PI-experienced pediatric subjects aged 4 weeks to <2 years. FPV will be administered as either the sole PI or in combination with low dose RTV. Subjects in this study are enrolled in 2 age cohorts (Cohort 1: 6 months to <2 years, and Cohort 2: 4 weeks to <6 months) in order to determine FPV and FPV/RTV dosage regimens for pediatric subjects at various stages of physiologic development.

1.3. Fosamprenavir

FPV is the phosphate ester prodrug of APV which is hydrolyzed to APV and inorganic phosphate as it is absorbed through the gut epithelium. Plasma FPV exposure (AUC) was <0.6% of the corresponding plasma APV exposure when FPV was administered for 2-4 weeks in HIV-1 infected, treatment-naïve adult subjects [GlaxoSmithKline Document Number RM2001/00021/00, Study Report for APV20001].

1.3.1. FPV Neonatal Toxicology

Toxicity studies of up to 13 weeks duration have been performed with FPV in neonatal and juvenile rats [GlaxoSmithKline Document Number RD1999/02344/00, Study R40576; GlaxoSmithKline Document Number RD2000/02506/00, Study R40877; GlaxoSmithKline Document Number RD2002/00045/01]. In these studies, administration of FPV to neonatal and juvenile rats (starting at 4 days of age) at doses up to 300 mg/kg/day (213 mg/kg/day APV equivalents) resulted in only slight changes indicative of an effect on the liver (increased serum liver enzymes and increased liver weights). Renal hyaline droplet accumulation seen in male rats was due to α_{2u}-globulin nephropathy, and hence of limited toxicological relevance to humans [Durham, 2002]. FPV doses ≥553 mg/kg/day (389 mg/kg/day APV equivalents) led to high mortality.

The ages of animals during both the initial phases of the FPV general toxicity studies and the specific studies investigating effects in juvenile animals, are considered representative of administration to pediatric patients in the clinic. In these studies, there were no effects on the development of young animals and no evidence of an increased susceptibility of young animals to the effects of FPV. Therefore, no such effects were predicted, nor have

they been observed, during clinical use. Thus, the results from toxicology studies in both juvenile and adult animals indicate that the safety profile of FPV in children is unlikely to be different to that seen in adult patients and support the safe clinical use of FPV in HIV-infected infants and children.

1.3.2. FPV Pediatric Clinical Data

Pharmacokinetic, safety, and antiviral response data in pediatric subjects 2 to 18 years of age receiving FPV with or without RTV are available from Study APV29005 [Fortuny, 2014], and Study APV20003 [Chadwick, 2007]. Additionally, 48 week data from the pediatric subjects <2 years of age receiving FPV/RTV in Study APV20002 have also been reported [Cotton, 2014;Ross, 2015]. Overall the safety profile of fosamprenavir with and without ritonavir in paediatric patients was comparable to that observed in adult clinical studies. Refer to the local product information for summaries of the available data from these studies.

1.4. Ritonavir

Ritonavir (Norvir, RTV) is an HIV protease inhibitor discovered and developed by Abbott Laboratories. RTV is most commonly used at reduced dosages in combination with other protease inhibitors as a pharmacokinetic enhancer. In this study, RTV will be used to enhance plasma concentrations of APV. Because the dose of RTV as a pharmacokinetic enhancer in this study will be a small fraction of the approved dose for antiviral effect, selective pressure and the development of RTV resistant HIV-1 is unlikely.

RTV has been licensed for use as an antiretroviral agent in subjects >1 month of age or older and is also licensed for use in combination with lopinavir (Kaletra) in boosted PI regimens in subjects of at least 6 months and 2 years of age in the USA and Europe, respectively.

Refer to the local Norvir prescribing information for complete information regarding RTV.

1.5. Abacavir

Abacavir (ZIAGEN™, ABC) is a carbocyclic 2',3'-ene nucleoside analog that inhibits replication of HIV-1. It is triphosphorylated intracellularly to a carbocyclic guanosine analog which is a potent inhibitor of the viral reverse transcriptase (RT).

The most commonly reported adverse events include nausea, fever, lethargy, fatigue, headache, vomiting, diarrhea, rash and decreased appetite. In general, adverse events have not been treatment limiting and the majority were mild or moderate in severity. Grade 3 or 4 laboratory abnormalities are uncommon and no specific treatment-related laboratory trends have been detected to date. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral

nucleoside analogues either alone or in combination, including abacavir. A majority of these cases have been in women.

In clinical studies, approximately 5% of patients receiving ABC develop a hypersensitivity reaction which in rare cases has proved fatal. See Section 3.3.7.4 for specific information regarding Hypersensitivity Reaction identification and management.

ZIAGEN is licensed for treatment of pediatric subjects of at least 3 months of age in the USA, the European Union, and South Africa. Refer to local ZIAGEN prescribing information for complete information regarding ABC.

1.6. Lamivudine

Lamivudine (EPIVIR™, 3TC), is a dideoxynucleoside analogue (negative enantiomer) inhibitor of HIV reverse transcriptase approved as a treatment for HIV-infection in combination with other antiretrovirals. It is phosphorylated intracellularly to its triphosphate form and acts as a chain terminator.

Lamivudine is generally safe and well tolerated, with the most commonly reported clinical adverse experiences being headache, nausea, vomiting, diarrhea, fatigue, malaise, insomnia, fever, abdominal pain, arthralgias, alopecia, and rash. Laboratory abnormalities reported for patients receiving the 3TC/ZDV combination include anemia, neutropenia and/or thrombocytopenia. Pancreatitis has been observed in some patients receiving lamivudine although it is unclear whether this was due to the drug treatment or the underlying HIV disease. Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of anti-retroviral nucleoside analogues alone or in combination, including lamivudine, in the treatment of HIV infection. In some patients, these events have occurred within a few weeks of initiating combination therapy.

EPIVIR is licensed for treatment of subjects of at least 3 months of age in the USA, Europe, and South Africa. Refer to local EPIVIR prescribing information for complete information regarding 3TC.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

Primary

- To define the FPV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected PI-naïve pediatric subjects aged 4 weeks to <2 years (deferred per amendment 5). **This objective has been removed with enrolment into the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) closed as per Protocol Amendment 10.**
- To define the FPV/RTV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected pediatric subjects aged 4 weeks to <2 years

- To evaluate the safety and tolerability of FPV/RTV when administered as a component of combination therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years. **The objective to evaluate the safety and tolerability of FPV BID dosage regimens has been removed as per Protocol Amendment 10.**

Secondary

- To evaluate the antiviral activity of FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the immunologic activity of FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess systemic exposure to FPV when administered to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess plasma RTV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- To investigate the relationship of steady-state plasma APV PK parameters to changes in plasma HIV-1 RNA concentrations, CD4+ percentages and/or the occurrence of adverse events
- To assess subject adherence and parent/guardian perceptions of study medications
- To assess viral resistance patterns and to compare these patterns with treatment outcome (where permissible by blood volumes)

The secondary objectives to evaluate the antiviral and immunologic activity of FPV have been removed as per Protocol Amendment 10.

2.2. Study Endpoints

Primary

- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV BID (deferred per amendment 5). **This endpoint has been removed with enrolment into the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) closed as per Protocol Amendment 10.**
- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- Plasma unbound APV Cτ,ss and percent protein binding
- The incidence and nature of adverse events, laboratory abnormalities, and treatment-limiting toxicities
- Proportion of subjects who permanently discontinue FPV/RTV due to adverse events. **The endpoint 'Proportion of subjects who permanently discontinue FPV due to adverse events' has been removed as per Protocol Amendment 10.**

Secondary

- Proportions of subjects with plasma HIV-1 RNA levels <400copies/mL at each study visit
- Change from Baseline in plasma HIV-1 RNA at each study visit (absolute values and time-averaged)
- Proportion of subjects with ≥1.0 log10 decrease in plasma HIV-1 RNA at each study visit
- Change from Baseline in the percentage of CD4+ lymphocytes at each study visit (absolute values and time-averaged)
- Plasma FPV concentrations
- Plasma RTV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- Relationship of steady-state plasma APV PK parameters to changes in plasma HIV-1 RNA concentrations, CD4+ percentages and/or the occurrence of adverse events
- Subject adherence and parent/guardian perceptions of study medications
- Incidence of viral resistance (where permissible by blood volumes)

3. INVESTIGATIONAL PLAN

3.1. Study Design

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART. Per protocol amendment 12; only subjects at sites in South Africa remain enrolled as supplies of oral FPV suspension are not commercially available in South Africa. Subjects successfully completing 48 weeks of therapy and receiving clinical benefit who weigh less than 39 kg may continue to receive FPV oral suspension provided by GSK. Once subjects reach a weight of 39 kg, South African treatment guidelines permit the use of the FPV tablets in children weighing ≥39 kg and these subjects will be withdrawn as FPV tablets are commercially available in South Africa.

Single dose visits (SDVs) for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in previous protocol amendments (3, 5, 7 and 8). Protocol amendment 10 allows for the discontinuation of collection of samples for

PK analysis after the age of the subjects exceeds 2 years and the subjects have successfully completed 48 weeks of treatment. Therefore, the evaluable PK data for approximately 50 to 60 subjects will be analysed when it is available for all subjects successfully completing 48 weeks of therapy and will include subjects who have been on different dosing regimens.

Arm B (unboosted FPV cohorts 1 and 2) as per amendment 10 has been closed.

Table 1 Recruitment Status for APV20002 – from Oct 2003 (FSFV) to Jul 2011 (cutoff for 48 week CSR)

Age (yrs) Cohorts	No. of Subjects originally planned	Cumulative enrolment and current status
1A 6 months - <2yr PI-naïve/exp FPV/RTV (boosted)	12	26[1] enrolled 11 ongoing[2]
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	12	28[1] enrolled 14 ongoing[2]

1. A total of 59 patients were enrolled but 5 discontinued after receiving single dose of FPV; current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments
2. Ongoing as of cutoff for 48 week CSR (July 2011)

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2 years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 10, enrolment in the Arm B cohorts (unboosted FPV) is closed.

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments.

Refer to Figure 1 and Figure 2 for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 8, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit and will undergo plasma PK serial sampling at Week 2 (over 4 hours) and Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Existing subjects in Cohort 1 Arm A whose dose of FPV was increased to 60 mg/kg BID at Week 2 as per amendment 5 may have their dose adjusted based on ongoing viral load, pharmacokinetic and safety assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence appropriate multiple dosing with FPV 45 mg/kg BID + RTV 10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is be based on the Week 2 plasma PK data from the initial 12 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo serial plasma PK sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit.

Enrolment of Arm B (FPV BID)

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 10, enrolment in the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is closed. Based on the PK data from the age-specific FPV/RTV cohorts, the dose volumes of unboosted FPV oral suspension necessary to administer the calculated therapeutic dose in children aged <2 years would be approximately twice the boosted dose volumes. Enrolment into the unboosted FPV cohorts is therefore not advised due to these large volumes of FPV oral suspension that would need to be administered as they could result in poor adherence, likely leading to an inadequate virologic response and subsequent resistance.

Figure 1 Study Design for Cohort 1 Arm A: PI-naïve or PI-experienced subjects 6 months to <2 years of age

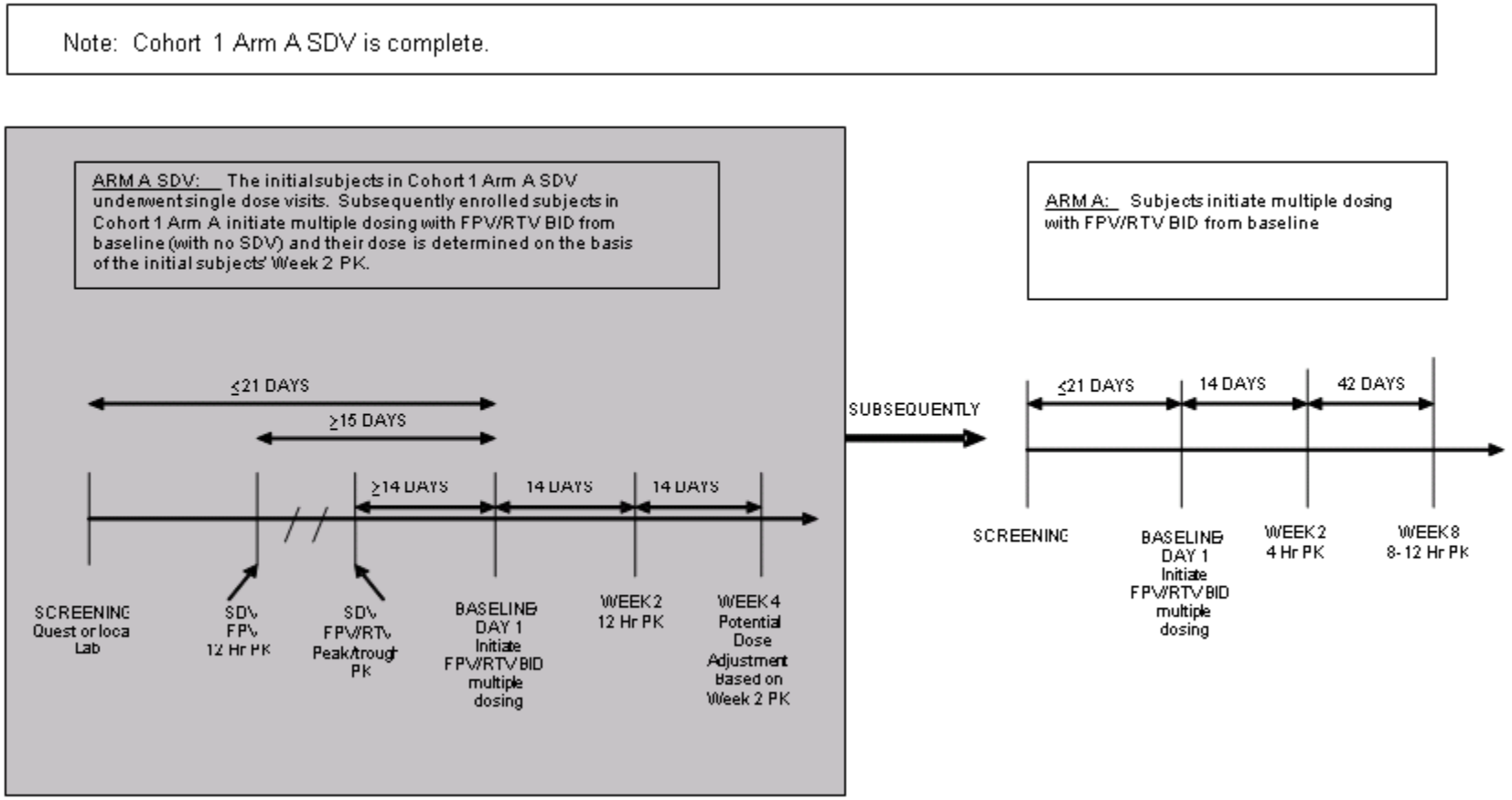
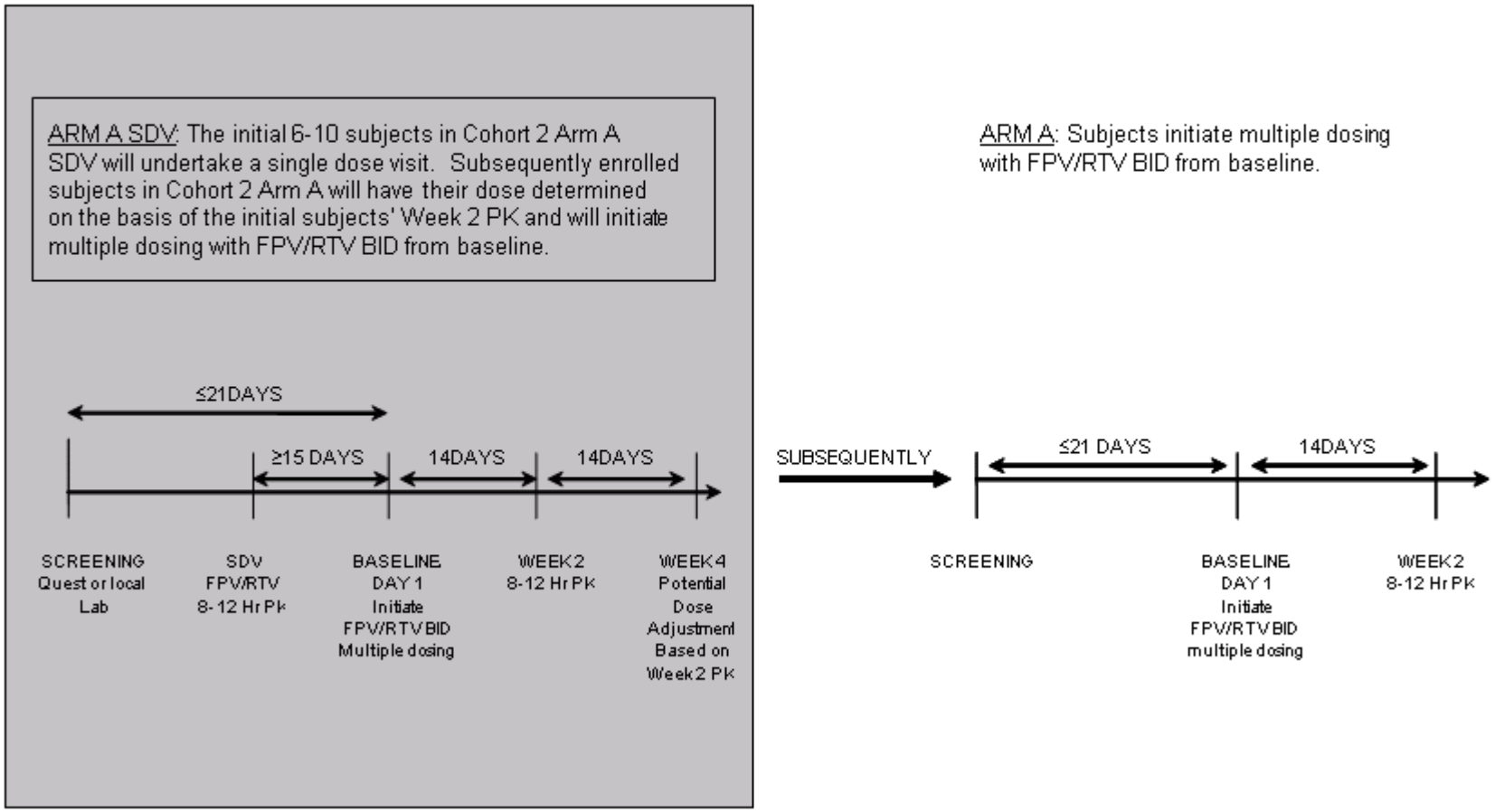


Figure 2 Study Design for Cohort 2 Arm A: PI-naïve or PI-experienced subjects 4 weeks to <6 months of age

Note: Cohort 2 Arm A SDV is complete.



3.2. Study Population

HIV-1 infected pediatric subjects 4 weeks to <2 years of age with screening plasma HIV-RNA ≧400copies/mL and who meet the eligibility criteria will be recruited into the study. As of Amendment 8, Cohort 1 Arm A (6 months to <2 years) was to enrol approximately 4 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 20-25 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is closed.

Subjects enrolled to receive FPV/RTV (Arm A) may be PI-naïve or PI-experienced. PI-experienced subjects will be eligible for Arm A if they have previously been treated with ≤3 PIs. Prior therapy with a RTV-boosted PI regimen will be considered as only 1 prior PI as long as the RTV dose was below that recommended for use as an antiretroviral agent.

Prior treatment with NRTIs is permitted and subjects are eligible if an active background regimen of two NRTIs can be constructed. For treatment-experienced subjects, prior treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PIs is permitted, however, to be eligible for this study subjects must discontinue their NNRTI use at least 14 days prior and, for subjects undergoing SDV, must discontinue their PI at least 5 days prior to administration of FPV. Subjects will NOT be permitted to receive concurrent NNRTI therapy while participating in this study. In addition, concurrent PI therapy other than the study treatments described in this protocol will NOT be permitted during the course of this study.

3.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male or female 4 weeks to <2 years of age.

   Cohort 1 (6 months - <2 years): Subjects must be <2 years of age at the Week 2 visit therefore the maximum age at screening is 22 months.

   Cohort 2 (4 weeks - <6 months): Subjects must be <6 months of age at the Week 2 visit, therefore the maximum age at screening is 4 months for entry into this cohort.
2. Parent or legal guardian is willing and able to provide written informed consent for the subject to participate in the trial.
3. Screening plasma HIV-1 RNA level ≥400 copies/mL.
4. Subjects, who, in the investigator's opinion, and following viral resistance testing if conducted, are able to construct an active NRTI backbone regimen consisting of 2 NRTIs.
5. Subjects must meet one of the following criteria:
   - Therapy-naïve or PI-naïve subjects (defined as having received less than one week of any PI).

- PI-experienced subjects defined as having prior experience with no more than three PIs. Prior RTV-boosted PI therapy will be considered as only one PI as long as the RTV dose was lower than that recommended for use of RTV as an antiretroviral agent.

3.2.2. Exclusion Criteria

A subject will **not** be eligible for inclusion in this study if any of the following criteria apply:

1. Prior history of having received AGN.
2. NNRTI therapy within 14 days prior to study drug administration (single or multiple-dose) or anticipated need for concurrent NNRTI therapy during the study period.
3. PI therapy within 5 days prior to study drug administration (applicable only for subjects undergoing single dose visits)
4. Subjects and/or parents/legal guardians who, in the investigator's opinion, are not able to comply with the requirements of the study.
5. Subject is in the initial acute phase of a CDC Clinical Category C event or infection (per 1994 classification) at Baseline. Subject may be enrolled provided they are receiving treatment for the infections, such treatment not being contraindicated with FPV, and subjects are clinically improving at the Baseline visit.
6. Presence of a malabsorption syndrome or other gastrointestinal dysfunction which might interfere with drug absorption or render the subject unable to take oral medication.
7. Presence of any serious medical condition (e.g., hemoglobinopathy, chronic anemia, diabetes, cardiac dysfunction, hepatitis, or clinically relevant pancreatitis) which, in the opinion of the investigator, might compromise the safety of the subject.
8. Any acute laboratory abnormality at screen which, in the opinion of the investigator, should preclude the subject's participation in the study of an investigational compound. If subjects are found to have an acute Grade 4 laboratory abnormality at screening, this test may be repeated once within the screening window. Any verified Grade 4 laboratory abnormality would exclude a subject from study participation.
9. Grade 3 or higher (>5x ULN) serum aminotransferase levels (alanine aminotransferase, ALT and/or aspartate aminotransferase, AST) within 28 days prior to study drug administration and / or clinically relevant hepatitis within the previous 6 months. A single repeat test is allowed to determine eligibility.
10. Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 28 days of study drug administration or an anticipated need for such treatment within the study period.
11. Treatment with immunomodulating agents (e.g., systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV activity (e.g., hydroxyurea or foscarnet) within 28 days of study drug administration.

12. Treatment with any of the following medications within 28 days prior to receiving study medication or the anticipated need during the study:

    - Amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, simvastatin, terfenadine, and triazolam (these drugs have been excluded for safety reasons).
    - Carbamazepine, dexamethasone, phenobarbital, primidone, rifampin, St Johns Wort, (these drugs have been excluded because they have the potential to decrease plasma protease inhibitor concentrations).

    Note: per Protocol Amendment 11, the list of drugs not to be co-administered with FPV and RTV has been updated (see Section 3.3.10, "Concurrent Medications and Non-Drug Therapies"). As recruitment is closed, the exclusion criteria have not been amended.

13. Treatment with other investigational drugs/therapies within 28 days prior to receiving study medication (note: treatments available through a Treatment IND or other expanded-access mechanism will be evaluated on a case-by-case basis in consultation with GSK).
14. History of drug or other allergy which, in the opinion of the investigator, contraindicates participation in the trial or known hypersensitivity to any study medications (e.g. documented hypersensitivity to a nucleoside analogue).

3.2.3. Other Study Eligibility Criteria Considerations

In order to assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drugs: Such documents may include, but are not limited to, the local product information or the International Product Information.

3.3. Treatment During Study

3.3.1. Study Drugs

Study drugs are defined as only the medications under study (FPV and RTV). Other antiretroviral therapies (including ABC and 3TC provided by GSK) will not be considered study drugs but will be considered background antiretroviral therapy (NRTIs) and thus a concurrent medication. Record background NRTIs, including ABC and 3TC, on the Background Antiretroviral Therapy page in the case report form (CRF).

In this study FPV, oral suspension will be provided by GSK. In all countries, RTV oral solution, powder, tablets or capsules will be obtained locally and reimbursed if acceptable to regulatory authorities. GSK will provide RTV by other means where reimbursement is not acceptable, or GSK may provide RTV if local supplies are not available and RTV is able to be obtained from other countries. Both FPV and RTV will be considered study

drugs. Therefore, in the event that a subject permanently discontinues FPV oral suspension, the subject will discontinue from this protocol and GSK will no longer supply FPV or RTV for that subject.

The FPV 50 mg/mL (43.2mg/mL APV molar equivalents) suspension is a white to off-white bubblegum and peppermint flavoured suspension for oral administration using a dosing syringe. Each mL of suspension contains 50 mg of FPV**,** equivalent to 43.2 mg/mL of APV. The suspension contains the following inactive ingredients: hydroxypropylmethyl cellulose, polysorbate 80, methylparaben, propylparaben, propylene glycol (overall 20 mg/mL), sucralose, calcium chloride, flavours and purified water. The FPV oral suspension is manufactured by GSK in Mississauga, Ontario, Canada.

The RTV oral solution manufactured by Abbvie contains 80 mg/mL of RTV in a peppermint and caramel flavoured vehicle and will be administered via a dosing syringe. The RTV solution contains the following inactive ingredients: ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid, saccharin sodium, peppermint oil, creamy caramel flavouring and FD&C Yellow No. 6.

The RTV 100 mg oral powder/sachets manufactured by Abbvie also contains the inactive ingredients: copovidone, sorbitan monolaurate, and colloidal silicon dioxide, and are sugar-free.

The 100 mg RTV tablets manufactured by Abbvie contains the inactive ingredients copovidone, anhydrous dibasic calcium phosphate, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The film coating contains: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, polyethylene glycol 3350, colloidal silicon dioxide, and polysorbate 80. The 100 mg RTV tablets are white, film-coated, ovaloid tablets and are sugar-free.

The 100 mg soft gelatin RTV capsules manufactured by Abbvie contains ritonavir 100 mg (SSSS enantiomer); other ingredients include ethanol (12 % v/v), butylated hydroxytoluene (antioxidant), oleic acid, polyoxyl 35 castor oil, water, gelatin, sugar, sorbitol, glycerin, titianium dioxide, medium chain triglycerides, lecithin and black ink.

3.3.2. Background NRTI Options Provided by GlaxoSmithKline

Abacavir and 3TC will be provided by GSK as optional background NRTIs for subjects of at least 3 months of age who are determined to be susceptible to ABC and/or 3TC. Susceptibility will be determined by investigator discretion and/or investigator interpretation of screening resistance viral genotype data, if available.

ABC and 3TC oral solutions are licensed for the treatment of pediatric subjects of at least 3 months of age in the USA, the European Union, and South Africa. Scored 3TC tablets are licensed in the USA, the European Union, and South Africa for the treatment of pediatric subjects weighing greater than or equal to 14 kg for whom a solid dosage form is appropriate. Scored ABC tablets are licensed in the USA and the European Union for the treatment of pediatric subjects weighing greater than or equal to 14 kg for whom a

solid dosage form is appropriate. Scored ABC tablets will only be provided by GSK for subjects in South Africa when a license has been granted there.

The ABC oral solution contains 20 mg/mL of ABC in aqueous solution and the inactive ingredients strawberry and banana flavours, citric acid (anhydrous), methylparaben, propylparaben, propylene glycol, saccharin sodium, sodium citrate, and sorbitol solution. The ABC oral solution is manufactured by GSK in Mississauga, Ontario, Canada.

The ABC tablet contains ABC sulfate equivalent to 300 mg ABC and the inactive ingredients colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate, Type A. The tablet is coated with a film that is made of methylhydroxypropylcellulose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin. ABC tablets are manufactured by GSK in Ware, Hertfordshire, United Kingdom.

The 3TC oral solution contains 10 mg/mL of 3TC in aqueous solution and the inactive ingredients strawberry and banana flavours, citric acid (anhydrous), methylparaben, propyparaben, propylene glycol, sodium citrate (dihydrous) and sucrose (20% w/v). The 3TC oral solution is manufactured by GSK in Mississauga, Ontario, Canada.

The 3TC tablet contains 150 mg of 3TC and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablet is coated with a film that is made of hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, titanium dioxide, and polysorbate 80. 3TC tablets are white, diamond-shaped and scored and manufactured by GSK in Ware, Hertfordshire, United Kingdom.

In the event that a subject permanently discontinues study medication, GSK will no longer provide background 3TC and ABC medications.

3.3.3. Background ART Not Provided by GlaxoSmithKline/ViiV Healthcare

GSK/ViiV Healthcare will not provide or reimburse background ART other than ABC or 3TC.

3.3.4. Rationale for Study Drug Dose Selection

Given the young age of the children enrolled into this study, subjects will receive the FPV oral suspension formulation. In children, the FPV oral suspension is recommended to be administered with food due to the following considerations:

- Children tend to eat frequently throughout the day
- Parents may wish to enhance adherence, medication intake and mask taste by offering medication with food

- FPV will be co-administered with ritonavir, which is recommended to be administered with food.

In adults, the FPV oral suspension formulation delivered an equivalent plasma APV AUC(0-∞) and 14.5% higher Cmax compared to the FPV tablet formulation [GlaxoSmithKline Document Number RM2006/00240/00, Study APV10024] Administration of the FPV suspension with food reduced plasma APV AUC(0-∞) by 29% and C_{max} by 46% [GlaxoSmithKline Document Number RM2002/00048/00, Study APV10016].

3.3.4.1. Rationale for Drug Dose Selection for Cohort 1 (6 months to 2 years)

APV20002 was designed to determine FPV/RTV regimens for pediatric subjects 1 to 24 months of age that would deliver plasma APV exposures proven to be safe and effective in adults.

In a small subset of five subjects aged 6 months to <2 years (Cohort 1, Arm A) who received FPV/RTV 45/7 mg/kg BID, plasma APV AUC(0-τ) was approximately 48% lower, Cmax 26% lower, and Cτ 29% lower than the adult target values. Conversely, RTV levels appeared to be similar between these pediatric subjects and adult comparators. Based on these results, Amendment 5 (5 July 2007) was undertaken to initiate dosing with FPV/RTV 45/7 mg/kg BID for two weeks (to allow collection of additional data on this regimen) and then increase the dose to FPV/RTV 60/7 mg/kg BID (to collect data on a higher dose regimen) for the duration of the study.

Subsequent to Amendment 5, eleven additional subjects have been enrolled in Cohort 1, Arm A. APV PK was evaluated at Week 2 (sampling predose, 2h, and 4h post dose) for the FPV/RTV 45/7 mg/kg BID regimen and at Week 8 (sampling predose, 1, 2, 4, 6, 8h post dose) for the FPV/RTV 60/7 mg/kg BID regimen. Plasma APV Cτ values were collected at all subsequent visits. APV PK parameters for newly enrolled subjects in Cohort 1A (6 months to <2 years) are compared to those for the subjects of this age group previously report as well as adult counterparts in Table 2.

Table 2 Summary of Plasma APV PK in pediatric subjects for Cohort 1 (6 months to 2 years)

APV Parameter	Newly enrolled 6 months to <2 years		Original 6 months to <2 years		Historical Adult
	FPV/RTV 45/7 mg/kg BID (n=11)	FPV/RTV 60/7 mg/kg BID (n=7)[2]	FPV/RTV 45/7 mg/kg BID (n=5)[3]	FPV/RTV 45/7 mg/kg BID (n=4)[4]	FPV/RTV 700/100 mg BID (n=159)[5]
AUC(0-τ) μg*h/mL[1]	NA	66.9 (31.5, 142) [82] (19.2 – 140)	19.3 (4.64, 79.9) [165] (2.77 – 58.1)	31.2 (15.7, 62.1) [45] (21.8 – 58.1)	37.0 (35.1, 38.9) [33] (15.7 – 95.9)
Cmax μg/mL[1]	7.50 (5.27, 10.7) [56] (4.54 – 28.6)	14.8 (8.09, 27.1) [73.0] (4.79 – 29.6)	4.16 (1.35, 12.8) [113] (0.92 – 9.29)	6.07 (3.27, 11.3) [40] (4.07 – 9.29)	5.62 (5.35, 5.92) [33] (2.47 – 13.3)
Cτ μg/mL[1]	1.92 (1.12, 3.31) [96] (0.48 – 5.28)	3.57 (2.42, 5.25) [99] (1.09 – 16.4)	1.54 (1.13, 2.09) [117] (0.055 – 8.15)	1.81 (1.40, 2.33) [80] (0.246 – 8.15)	2.17 (2.05, 2.30) [38] (0.75 – 5.83)

1. Geometric Mean (95% CI) [CVb%] (min – max)
2. N=6 for AUC(0-τ) and N=20 for Cτ (across Weeks 8 -24)
3. N=38 for Cτ (across Weeks 2 -48)
4. N=32 for Cτ (across Weeks 2 -48)
5. N=158 for AUC(0-τ)

APV Cmax and Cτ following FPV/RTV 45/7 mg/kg BID were higher in the eleven newly enrolled subjects than in the original five subjects who received the same dose. However, upon re-evaluation of data for the original subjects who received 45/7 mg/kg BID, one subject (PPD) had extremely low PK parameter values at Week 2 that appear to have affected the statistical point estimate of each parameter. Excluding that one subject from the originally enrolled group, the geometric mean Cmax for the remaining 4 subjects is increased from 4.16 μg/mL to 6.07 μg/mL, more consistent with adult values and more similar to the geometric mean Cmax at 7.5 ug/mL of the newly enrolled subjects receiving 45/7 mg/kg BID at Week 2. Geometric mean AUC(0-τ) is increased from 19.3 μg*h/mL(n=5) to 31.2 μg*h/mL(n=4), again much closer to the adult target values; AUC(0-τ) following 45/7 mg/kg BID could not be determined at Week 2 for newly enrolled subjects due to limited sampling scheme. Overall geometric mean (95% CI) Cτ was increased from 1.54 μg/mL (1.13, 2.09μg/mL, n=5) to 1.81 μg/mL (1.40, 2.33 μg/mL, n=4), also closer to adult targets and newly enrolled subjects.

APV parameters following FPV/RTV 60/7 mg/kg BID in subjects 6 months – 2 years old were significantly higher than adult target parameters. Geometric mean APV AUC(0-τ) and Cmax following FPV/RTV 60/7 mg/kg BID were 1.8-fold and 2.6-fold higher than the geometric mean values in adults.

Per protocol amendment 8, since APV parameters following FPV/RTV 45/7 mg/kg BID were closer to adult targets in the newly enrolled subjects and in the original 6 month to 24 month olds upon exclusion of the one low outlier and since APV parameters following FPV/RTV 60/7 mg/kg BID were significantly higher than adult targets, subjects enrolled in the future will receive FPV/RTV 45/7 mg/kg BID continuously without an increase to FPV/RTV 60/7 mg/kg BID at Week 2. Some subjects with consistently high Cτ values following FPV/RTV 60/7 mg/kg BID have had their dose reduced to FPV/RTV 45/7 mg/kg BID. Other subjects previously enrolled and currently receiving FPV/RTV 60/7 mg/kg may have their dose modified at the discretion of the investigator and GSK.

3.3.4.2. Rationale for Drug Dose Selection for Cohort 2 (4 weeks to 6 months)

Plasma APV PK data are available from the first 12 subjects enrolled in Cohort 2 Arm A (4 week to <6 month age group). All 12 subjects received FPV/RTV 45/7 mg/kg as a single dose, and 11 subjects underwent repeat administration of FPV/RTV BID at individualized dosage regimens ranging from FPV 30-60 mg/kg and RTV 7-10 mg/kg based on each subject's single dose PK data. On both single dose and repeat dose administration of FPV/RTV, pediatric subjects 4 weeks to <6 months of age had higher plasma APV Cmax and AUC values, but similar C12 (single dose, Table 3) and lower Cτ (repeat dose, Table 4) values compared with those historically observed for adults. Repeat dose plasma RTV Cmax and AUC values were similar to historical adult data, but plasma RTV Cτ values were lower in the pediatric subjects (Table 5). As plasma APV Cτ is important for long-term efficacy and minimization of resistance development, it is important to try to achieve plasma APV Cτ values in pediatric subjects similar to those achieved with the approved FPV/RTV 700/100 mg BID regimen in adults. Although FPV/RTV 60/10 mg/kg exhibited APV Cτ,ss, most similar to adults (Figure 3), the APV Cmax for this regimen was considered unnecessarily high (Figure 4). The RTV 10 mg/kg in the FPV/RTV 60/10 mg/kg regimen provided the most consistently high RTV Cτ,ss values as compared to 30/7 and 45/7 mg/kg (Figure 5). It is possible that the lower plasma RTV Cτ values are responsible for the lower plasma APV Cτ values; therefore per Protocol Amendment 7, an increase in the RTV dose from 7 mg/kg BID to 10 mg/kg BID for all subsequently enrolled subjects was recommended. These subjects will initiate dosing with FPV/RTV 45/10 mg/kg BID and have serial PK sampling at Week 2 and trough sampling on subsequent visits. Additionally a SDV is no longer required for newly enrolled subjects 4 weeks to <6 months of age (Cohort 2 Arm A).

Table 3 Summary of Single Dose Plasma APV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma APV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV 45/7 mg/kg (N=11)[1,3,4]	Adult Subjects FPV/RTV 700/100 mg (N=17)[2]
Cmax (μg/mL)	9.74 (5.67, 16.2)	3.65 (2.54, 6.76)
AUC(0-∞) (μg.h/mL)	57.5 (20.2, 111)	35.2 (20.8, 114)
C8h (μg/mL)	2.64 (0.819, 5.86)	1.10 (0.451, 2.20)
C12h (μg/mL)[2]	1.13 (0.41, 3.76)	1.19 (0.659, 1.92)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10013
3. Data for pediatric Subject PPD was excluded because exposures were very high: Cmax: 30.9μg/mL, AUC(0-∞): 335μg.h/mL, C8hr: 16.9μg/mL.
4. C12h is extrapolated value for pediatric subjects and observed value for adult subjects

Table 4 Summary of Repeat Dose Plasma APV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma APV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV BID (N=9) [1,3-5]	Adult Subjects FPV/RTV 700/100 mg (N=14)[2]
Cmax (μg/mL)	8.90 (2.07, 12.1)	4.76 (2.47, 7.68)
AUC(0-τ) (μg.h/mL)	41.0 (16.2, 70.4)	28.3 (17.9, 43.1)
C8h (μg/mL)	2.05 (1.10, 3.25)	1.58 (0.816, 2.64)
Cτ (μg/mL)[3]	0.970 (0.438, 1.95)	1.46 (1.06, 2.20)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10013
3. Pediatric FPV/RTV dosage regimens included: 30/7 mg/kg BID (N=2), 45/7 mg/kg BID (N=4), 45/10 mg/kg BID (N=1), and 60/10 mg/kg BID (N=4).
4. Data for pediatric Subject PPD was excluded because pre-dose APV concentration was non-quantifiable (NQ).
5. Cτ calculated as the mean of the pre-dose and C12h (extrapolated) values.

Table 5 Summary of Repeat Dose Plasma RTV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma RTV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV BID[1]		Adult Subjects FPV/RTV 700/100 mg BID[2]
	(N=9)[3-5]	(N=8)3-5	(N=24)
Cmax (μg/mL)	1.28 (0.228, 7.70)	0.999 (0.228, 2.11)	1.24 (0.520, 3.84)
AUC(0-τ) (μg.h/mL)	6.66 (0.922, 28.8)	4.67 (0.922, 14.30)	5.59 (2.88, 14.4)
C8h (μg/mL)	0.270 (0.021, 1.05)	0.239 (0.021, 1.05)	0.260 (0.068, 0.614)
Cτ (μg/mL)[6]	0.075 (NQ, 0.496)	0.069 (NQ, 0.496)	0.165 (0.010, 0.610)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10010
3. Pediatric FPV/RTV dosage regimens included: 30/7 mg/kg BID (N=2), 45/7 mg/kg BID (N=4), 45/10 mg/kg BID (N=1), and 60/10 mg/kg BID (N=4).
4. Data for pediatric Subject PPD was excluded because pre-dose APV concentration was non-quantifiable (NQ).
5. Data summarized excluding Subject PPD who had high RTV Cmax and AUC values.
6. Cτ calculated as the mean of the pre-dose and C12h (extrapolated) values.

Figure 3 Week 2 Plasma APV Ctau,ss Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)

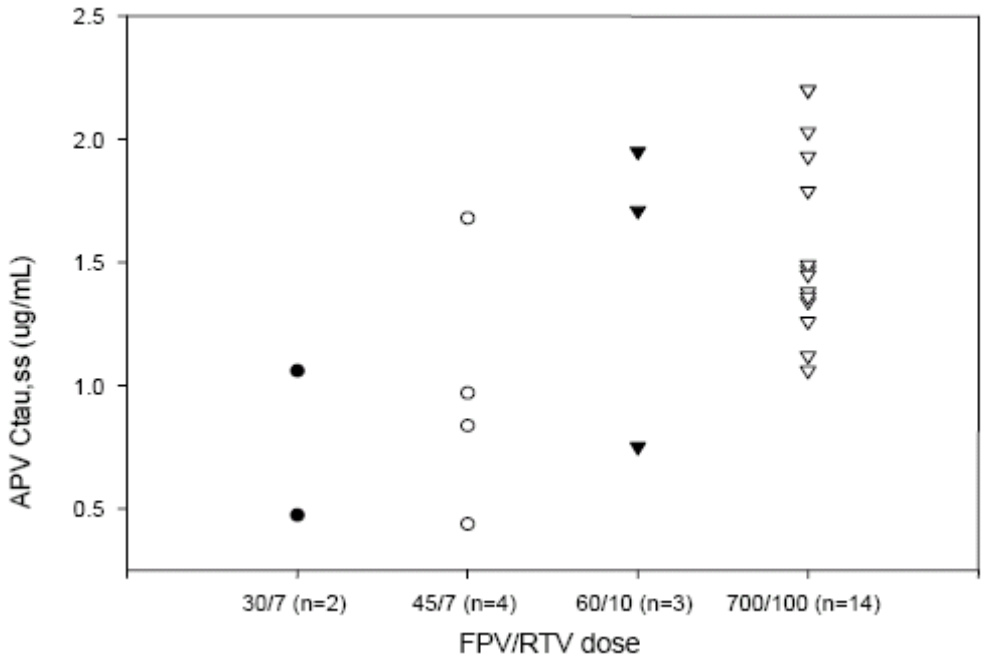


Figure 4 Week 2 Plasma APV Cmax Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)

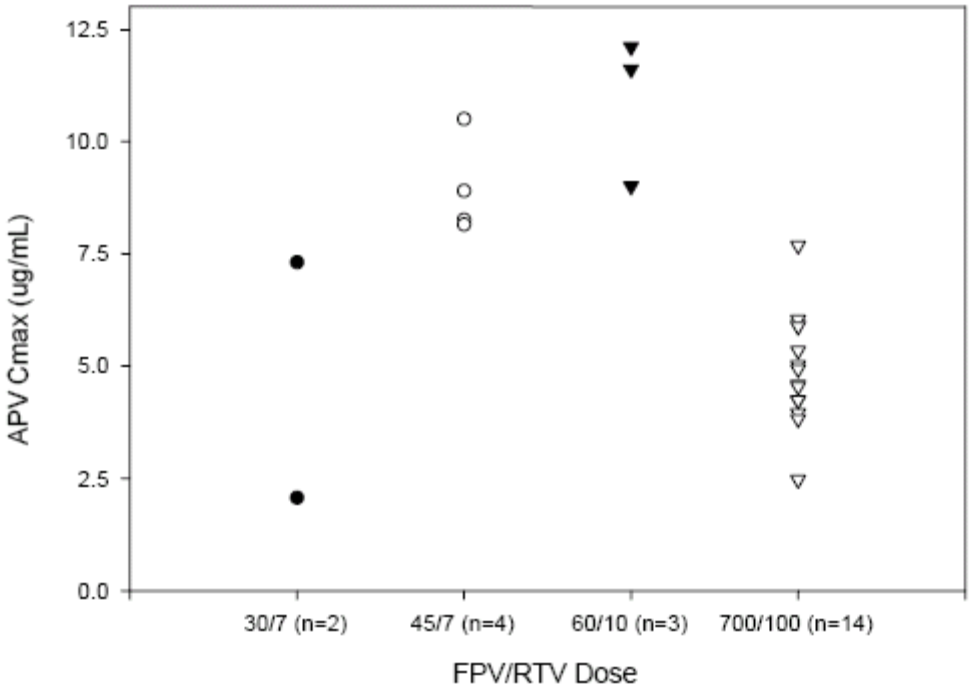
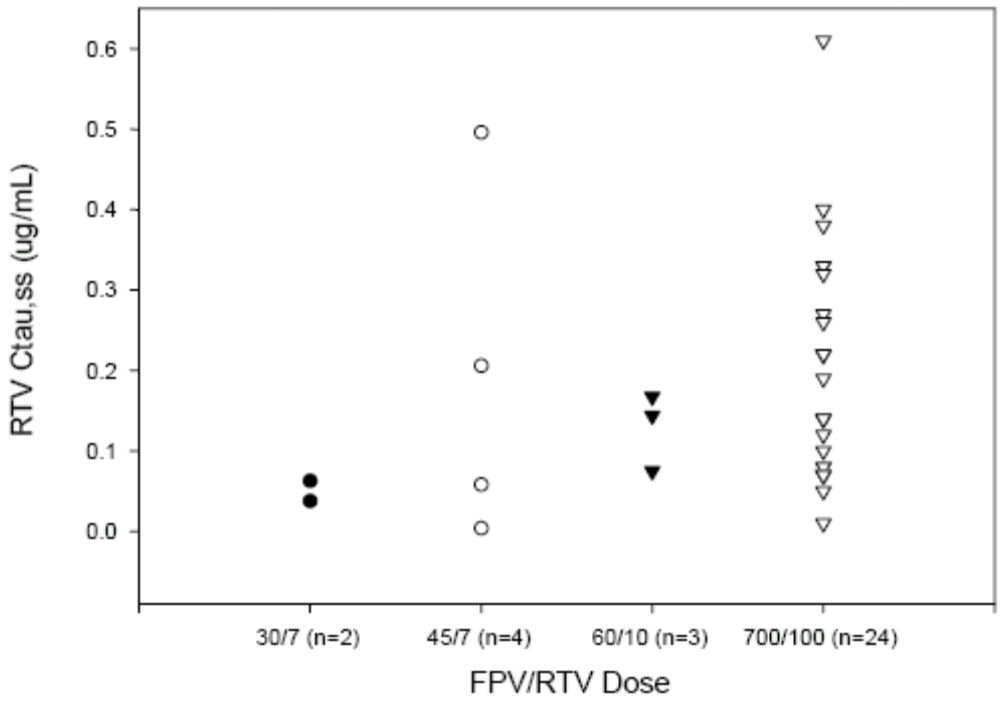


Figure 5 **Week 2 Plasma RTV Ctau,ss Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)**



Per Protocol Amendment 10, enrolment of the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is closed.

Following receipt and review of PK results from subjects in Cohorts 1 or 2, individual dose adjustment may be made on a subject by subject basis.

3.3.5. Dosages and dosing

FPV and RTV will be administered according to the doses described in Section 3.3.4 and in Section 3.3.5.1.

Both the FPV and RTV formulations should be administered with food. If vomiting or spitting up occurs within 30 minutes of administration, parents/guardians should be instructed to re-administer the study medications.

The recommended dose of ABC solution is 8 mg/kg BID (up to a maximum of 600 mg/day).

For ABC tablets, the recommended dose is one-half of a scored tablet taken twice daily in children weighing between 14 kg and 21 kg and one-half of a scored tablet taken in the

morning and one whole tablet taken in the evening in children weighing between 21 kg and 30 kg.

The recommended dose of 3TC solution is currently 4 mg/kg BID (up to a maximum of 300 mg/day). The dosing recommendation in the local label should be followed.

For 3TC tablets, the recommended dose is one-half of a scored tablet taken twice daily in children weighing between 14 kg and 21 kg and one-half of a scored tablet taken in the morning and one whole tablet taken in the evening in children weighing between 21 kg and 30 kg.

3.3.5.1. Dosage Regimen Adjustment Criteria

Dose Adjustment Due to Subject Weight

Due to subjects' growth throughout the duration of the study, the dose of all drugs administered must be recalculated at each visit and the total daily dose adjusted according to the child's weight and the recommended dosage regimen. Dose adjustments should occur when the dose would change by ≥10% from the subject's prior calculated dose.

Dose adjustments due to weight change should be delayed until after completion of the PK sampling to ensure that sampling is conducted at steady-state.

Dose Adjustment Due to Subject Physiological Development

Subjects will not automatically change dosage regimens as they increase in age between 4 weeks and 2 years and grow out of their age assigned cohort. However, because subjects may require dose adjustments as they grow and develop, plasma PK samples collected throughout the study will be assayed on an ongoing basis, and if individualized dose adjustments are needed to maintain target concentrations, data will be provided to the investigators.

Dose Adjustment Due to Subject Age exceeding 2 and 6 years

Subjects reaching and exceeding 2 years of age during the study should transition to the lower dose of FPV and RTV to 23 mg/kg and 3 mg/kg BID respectively. The change in dosage can be staged gradually over multiple visits and will be based on ongoing viral load, pharmacokinetic and safety assessments, at the investigator's discretion.

Subjects reaching and exceeding 6 years of age may transition to the lower dosage regimen (FPV 18 mg/kg and RTV 3 mg/kg BID) in accordance with the regimen approved for this age group. This dose change can be implemented gradually as the subject 'grows into' the new dose or at the time of their 6th birthday at the investigator's discretion.

In consultation with the investigator, GSK may discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis once a subject has reached and exceeded 2 years and has initiated the 23/3 mg/kg BID dosing regimen after Week 48. Any further dosing changes would follow the approved dosing recommendations without PK sampling, including a transition to FPV/RTV 18/3mg/kg BID at 6 years. Note: after Protocol Amendment 11 became effective, PK sampling and

monitoring of plasma APV, FPV and RTV concentration on an individual basis was discontinued.

3.3.6. Target Plasma APV Exposure

3.3.6.1. Pharmacokinetic Targets for a Dose Increase

Single Dose

The lower limit of the target plasma APV exposure for subjects receiving a single dose of FPV is defined as a plasma APV AUC_{∞} value of ≥16.8μg.h/mL. This target represents the 25th percentile observed in adults receiving FPV 1395 mg in APV20001.

The lower limit of the target plasma APV exposure for subjects receiving single doses of FPV + RTV is a 12-hour concentration of 0.800μg/mL. This target represents the 25th percentile observed in adults receiving single doses of FPV 700 mg + RTV 100 mg in APV10013.

Steady-State

The lower limit of the target plasma APV exposure for subjects receiving a FPV (without RTV) regimen is defined as a plasma APV $C_{\tau,ss}$ value of ≥0.25μg/mL. This target represents the 25th percentile observed in adult subjects receiving FPV 1395 mg BID for 2-4 weeks in APV20001.

The lower limit of the target plasma APV exposure for subjects receiving a FPV/RTV regimen is defined as a plasma APV $C_{\tau,ss}$ value of ≥1.48μg/mL. This target represents the 25th percentile observed in adult subjects FPV 700 mg BID + RTV 100 mg BID in APV10010, APV10011, APV10012, APV10013, and APV10022.

3.3.6.2. Pharmacokinetic Targets for a Dose Reduction

No dose-limiting toxicities have been observed in adults receiving FPV or FPV + RTV. However, to ensure that children in this study, APV20002, do not maintain concentrations higher than those observed in adults, an upper limit to the plasma APV PK target has been set. The upper limit of the target is a plasma APV $AUC_{\tau,ss}$ value of 61.68 h*ug/mL at the Week 2 visit and a plasma APV $C_{\tau,ss}$ value of 3.52ug/mL at subsequent visits (where only trough sampling is conducted). Plasma APV $AUC_{\tau,ss}$ and $C_{\tau,ss}$ values are highly correlated, supporting the use of $C_{\tau,ss}$ values at visits subsequent to Week 2.

3.3.7. Overdose and Toxicity management

3.3.7.1. Overdose

Experience with either FPV or AGN overdose is very limited, therefore GSK does not recommend any specific treatment in the event of an overdose. It is not known whether

APV can be removed by hemodialysis. The investigator should use clinical judgment in treating the overdose.

Experience of acute overdose with RTV is limited. One patient in a clinical trial took RTV 1500 mg/day for 2 days. The patient reported parasthesias, which resolved after the dose was decreased. A post-marketing case of renal failure with eosinophilia has been reported with RTV overdose. The approximate lethal dose was found to be greater than 20 times the related human dose in rats and 10 times the related dose in mice. In case of an overdose, general supportive measures should be given. If indicated, elimination of unabsorbed drug may be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since RTV is highly protein bound, dialysis is unlikely to significantly remove drug from blood.

Single doses up to 1200 mg and daily doses up to 1800 mg of ABC have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

Limited data are available on the consequences of ingestion of acute 3TC overdoses in humans. No fatalities occurred, and patients recovered. No specific signs or symptoms have been identified following such overdose. Since lamivudine is dialyzable, continuous hemodialysis could be used in the treatment of overdose, although this has not been studied. Investigators should refer to local prescribing information for further information.

There are currently no known antidotes for FPV**,** RTV, ABC, or 3TC. If overdosage occurs, the subject should be monitored for evidence of toxicity and standard supportive treatment applied as required.

An overdose is any dose greater than those described below for each study drug. For the purposes of this study, an overdose is not considered an adverse event (AE, see Section 7.1) unless it is accompanied by a clinical manifestation associated with the overdose.

Definition of Overdose

FPV: An overdose of FPV will be defined as 1.5 x individualized dose recommended for the first 6-10 subjects or 1.5 x the overall dose recommendation made for the remaining subjects in cohort.

RTV: a daily dose of >300 mg

ABC: a daily dose of >600 mg

3TC: a daily dose of >300 mg

3.3.7.2. Toxicity Management

For the purpose of toxicity management, information is provided pertaining to the antiretroviral medications supplied for this study by GSK (i.e., FPV**,** RTV, ABC and 3TC). All Adverse Events and Serious Adverse Events must be recorded and reported according to Section 7 of this protocol.

The following toxicity management guidelines are intended to ensure the safety of each subject. Should the investigator have compelling evidence that an adverse event does **NOT** appear to be causally related to the study drug(s), dosing with study drug(s) may remain unaltered. Application of these guidelines is discretionary; a stepwise approach to the evaluation or management of a subject with severe findings may not be consistent with best clinical care.

Decisions regarding sequential reintroduction of study drugs or temporary interruption of one or more but not all drugs within the antiretroviral therapy (ART) regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Every effort should be made to minimize the time that less than the full combination of study drugs is being administered. Subjects undergoing toxicity management should be evaluated at weekly intervals. Interruption of PI therapy may be allowed for evaluation of adverse events. Subjects intolerant to their study PI should be discontinued from the study.

Subjects who are intolerant to any component of their background NRTI therapy may change to another NRTI as directed by the investigator. All changes to the treatment regimen must be accurately recorded on the study drug changes page and the background antiretroviral therapy page of the CRF.

General management guidelines based on the protocol Toxicity Grades follow. For a detailed discussion about specific events, please see Section 3.3.7.3 “Specific Events”. Specific events covered include rash management, nausea/vomiting and hypertriglyceridemia/ hypercholesterolemia. Adverse events that occur during the trial should be evaluated by the investigator and graded according to the toxicity grades provided in Section 11.3, Appendix 3 and in Section 11.4, Appendix 4 (2004 DAIDS Tables).

Grade 1 or Grade 2 Toxicity/Adverse Event

Subjects who develop a Grade 1 or 2 AE or toxicity may continue all study drugs and background antiretroviral drugs without alteration of the dose at the discretion of the investigator (see Section 3.3.7.2). Subjects who choose to withdraw from study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Grade 3 Toxicity/Adverse Event

In general, subjects who develop a Grade 3 AE or toxicity should have all study drugs and background antiretroviral drugs withheld and be re-evaluated each week until the AE returns to Grade 2 or less. Specific events (rash, nausea and vomiting, hyperlipidemia/ hypercholesterolemia) are discussed in Section 3.3.7.3. If the investigator has compelling

evidence that the AE has not been caused by the study drug(s), dosing may continue. Once the AE returns to Grade 2 or lower, study treatment may be re-instated at the discretion of the investigator or according to standard practice.

For those subjects whose regimen includes ABC, reinitiation of drug should be undertaken with caution. In the event of a discontinuation of ABC for any reason, health care providers should obtain a complete history of the events surrounding the discontinuation of ABC. If there are symptoms consistent with a hypersensitivity reaction, ABC should not be reinitiated. If there is no evidence of a prior reaction, the subject may restart treatment with ABC. The subject and health care provider should be aware of the possibility of a rapid-onset hypersensitivity reaction upon reinitiation of ABC, which may be life-threatening, and the subject should be able to, if necessary, receive prompt medical evaluation.

Should the same Grade 3 AE recur *after* 4 weeks, the management scheme outlined above may be repeated. However, if the same Grade 3 AE recurs *within* 4 weeks, study drug(s) must be permanently discontinued if the investigator considers the AE related to study drug. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of study drug therapy should be followed weekly until resolution of the AE and encouraged to have withdrawal study evaluations completed. A follow-up visit should be performed 4 weeks after the last dose of study drug.

Subjects who develop Grade 3 clinically asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes and study drug(s) may be continued if the investigator has compelling evidence that the abnormality is not related to the study drug(s).

Grade 4 Toxicity/Adverse Event

Study drug will be permanently discontinued in subjects who develop a Grade 4 AE or toxicity. However, if the investigator has compelling evidence that the AE is not causally related to the study drug(s), dosing may continue after discussion with and assent from GSK. Subjects experiencing Grade 4 AEs requiring permanent discontinuation of study drug therapy should be followed weekly until resolution of the AE and encouraged to complete the withdrawal study evaluation. A follow-up visit should be performed 4 weeks after the last dose of study drug.

Subjects with Grade 4 clinically asymptomatic laboratory abnormalities should be investigated for all potentially non-drug related causes and study drug(s) may be continued if the investigator has compelling evidence that the toxicity is NOT related to the study drug, following discussion with GSK.

3.3.7.3. Specific Events

Rash

Erythematous or maculopapular cutaneous eruptions, with or without pruritus, may occur during therapy with FPV. Most rashes are mild or moderate in severity and will generally resolve spontaneously. Appropriate antihistamine (e.g. cetirizine dihydrochloride) may reduce pruritus and hasten the resolution of rash.

Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, were reported in less than 1% of subjects included in the FPV clinical development program. FPV should be permanently discontinued in case of severe rash, or in case of rash of moderate intensity with systemic or mucosal symptoms.

A total of 700 adult subjects received FPV either alone or in combination with RTV in Phase III clinical trials. Rash, regardless of causality or grade, occurred in 25% and 9% of ART-naïve adult subjects receiving FPV BID (Study APV30001) and FPV/RTV QD (Study APV30002), respectively. In PI-experienced adult subjects in Study APV30003, 7% of subjects receiving FPV/RTV experienced rash. Within the FPV treatment arm of APV30002, three subjects (<1%) were permanently discontinued due to rash. No permanent discontinuations due to rash were reported in APV30001 or APV30003.

In an integrated safety analysis of pediatric studies APV29005 and APV20003 in subjects 2 to 18 years of age receiving FPV or FPV/RTV, rash (all grades, regardless of causality) occurred in 19% (27/144) of subjects, when all rash-related preferred terms were considered. There were few cases of drug-related rash events. Most rash events were Grade 1 or 2 in severity and no subjects discontinued treatment due to rash.

The appearance of rash in the absence of other symptoms or signs is not indicative of hypersensitivity to ABC. Subjects receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information. Subjects should be instructed to contact the Investigator as soon as possible if they develop a rash while on study.

Subjects who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Erythema Multiforme. SJS, TEN and Erythema Multiforme have been reported very rarely in patients taking ABC-containing products. These patients generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC HSR, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, ABC (and / or all other concurrent medication(s) suspected in the Investigators causality assessment) should be discontinued, and the subject should not be re-challenged with any ABC-containing medicinal product (i.e., TRIUMEQ, ZIAGEN, TRIZIVIR, EPZICOM or KIVEXA).

As many products other than abacavir also cause rash and/or serious skin reactions, all other medicinal products that the subject is receiving should also be reviewed and discontinued as appropriate.

Study treatment should be managed as outlined in the following table:

Rash Management

Event	Action to be Taken		
	FPV BID or FPV/RTV BID	**ABC**	**3TC**
Grade 1 rash alone	Therapy can continue	Evaluate for the possibility of hypersensitivity. If there is no evidence of any other organ system involvement and the subject has no constitutional symptoms (fever, malaise, fatigue, headache), ABC may be continued at the investigators discretion with the warning to discontinue immediately and permanently if other signs and/or symptoms consistent with HSR appear. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.	Therapy can continue
Grade 1 rash with symptoms indicating multi-organ involvement[1]	Discontinue FPV BID or FPV/RTV BID. Therapy should not be reinitiated unless the investigator has compelling evidence that the rash is not caused by FPV.	Discontinue ABC immediately and permanently[2] Subjects should be treated as clinically appropriate and followed until resolution of the AE.	Therapy can continue
Grade 2 rash alone	Therapy can continue	Follow Grade 1 rash alone instructions	Therapy can continue
Grade 2 rash with symptoms indicating multi-organ involvement[1]	Discontinue FPV BID or FPV/RTV BID. Therapy should not be reinitiated unless the investigator has compelling evidence that the rash is not caused by FPV.	Discontinue ABC immediately and permanently[2] The subject should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.	Discontinue 3TC. Therapy should not be reinitiated unless the investigator has compelling evidence that the rash is not caused by 3TC.
Grade 3/4 rash alone or with symptoms indicating multi-organ involvement[1]	Discontinue FPV BID or FPV/RTV BID and do not reinitiate therapy[3] Subjects should be treated as clinically appropriate and followed until resolution of the AE.	Discontinue ABC immediately and permanently[3] Subjects should be treated as clinically appropriate and followed until resolution of the AE.	Discontinue 3TC[3] Subjects should be treated as clinically appropriate and followed until resolution of the AE.

1. Symptoms include: systemic symptoms (fever, GI symptoms including nausea, vomiting, diarrhea or abdominal pain) or allergic symptoms, or mucosal involvement, or severe tiredness, achiness or generally ill feeling.
2. ABC therapy should be permanently stopped and another NRTI therapy should be initiated.
3. Medications should be permanently stopped and the subject withdrawn from the trial. .

Adjunctive treatment:

- For Grade 1 or 2 rash, antihistamines (see Section 3.3.10 for potential interactions) or topical corticosteroids may be prescribed. Systemic corticosteroids are not recommended for Grade 1 or 2 rash, as steroid therapy may mask the appearance of other symptoms leading to the diagnosis of hypersensitivity to ABC.
- Subjects who develop a Grade 3 (vesiculation, moist desquamation, or ulceration) or 4 rash (exfoliation, mucosal involvement, or target lesions [erythema multiforme]) or any evidence of Stevens-Johnson Syndrome should have all study drugs discontinued and assessed appropriately. If Grade 3 or 4 rash is accompanied by systemic symptoms, study medications should be permanently discontinued. Steroids may be used for treatment of the event.

Nausea and vomiting

Upper gastrointestinal adverse events may be reduced by taking medications with a meal, and by maintaining a steady oral intake, e.g., pretzels or other dry bread. Subjects who experience potentially treatment limiting nausea or vomiting should be treated with anti-emetics. No dose reduction or modification of any study medication (i.e., FPV or RTV) will be allowed for the management of adverse events.

Hypertriglyceridemia/ hypercholesterolemia

There is currently no guidance available for the treatment and/or occurrence of cardiovascular disease in HIV-1 infected children. Please see recent recommendations [Dube, 2003] for full discussion of management of hyperlipidemia in the context of HIV therapy.

During the study, management of these events should be at the investigator's discretion.

3.3.7.4. Abacavir Hypersensitivity Reaction

In clinical studies, conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5% of subjects receiving ABC develop a hypersensitivity reaction (HSR) that in rare cases has proved fatal. However, in the PENTA 5 study [Gibb, 2000a] only 1 of the 92 ART-naïve, symptomatic children, aged 3 months to 16 years who were treated with a regimen containing ABC developed a classical hypersensitivity reaction. In CNAA3006, which utilized an ABC containing backbone, ABC HSR was observed in 2% of pediatric subjects. The risk for abacavir HSR to occur is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of *HLA-B*5701* and subsequently avoiding ABC in *HLA-B*5701* positive patients, significantly reduced the incidence of clinically suspected ABC HSR from 7.8% (66 of 847) to 3.4% (27 of 803) ($p<0.0001$) [Mallal, 2008]. In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of subjects who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively [Post, 2010; Squires, 2010].

It is recommended that any HIV-infected patient without prior exposure to abacavir be screened for HLA-B*5701 allele. Screening is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended. In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision making. Even in the absence of the HLAB* 5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

The ABC hypersensitivity reaction is characterized by the appearance of symptoms indicating multi-organ involvement. The majority of patients have fever and/or rash as part of the syndrome; however reactions have occurred without rash or fever.

Symptoms can occur at any time during treatment with ABC, but the symptoms usually appear within the first six weeks of initiation of treatment (median time to onset 11 days). The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve shortly after discontinuation of ABC.

Frequently observed signs and symptoms include fever, rash, malaise or fatigue, gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain, and respiratory symptoms such as dyspnea, sore throat, cough. Other signs and symptoms include myalgia, arthralgia, edema, pharyngitis, headache, paresthesia or myolysis.

Some subjects with hypersensitivity were initially thought to have onset respiratory diseases (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis, or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in ABC being continued or re-introduced, leading to more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. If hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC (ZIAGEN, TRIZIVIR, KIVEXA, TRIUMEQ or any other ABC-containing product) should be restarted.

Physical findings may include rash (usually maculopapular or urticarial), lymphadenopathy or mucous membrane lesions (conjunctivitis, mouth ulceration). Abnormal chest x-ray findings may also present (predominantly infiltrates, which can be localized). Laboratory abnormalities may include elevated liver function tests (such as hepatic transaminases), increased creatine phosphokinase or creatinine levels, and lymphopenia.

Anaphylaxis, hypotension, liver failure, renal failure, adult respiratory distress syndrome or respiratory failure may occur.

Subjects who develop a hypersensitivity reaction must discontinue ABC and must NEVER be rechallenged with any medicinal product that contains ABC (ZIAGEN, TRIZIVIR, KIVEXA, TRIUMEQ or any ABC-containing product). Restarting any ABC-containing product following a hypersensitivity reaction results in a prompt return of symptoms within hours. **This recurrence of the hypersensitivity reaction may be**

more severe than on initial presentation and may include life-threatening hypotension and death.

There have been infrequent reports of hypersensitivity reactions following reintroduction of ABC, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal or a respiratory symptom).

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms of a hypersensitivity reaction (i.e., patients previously considered to be abacavir tolerant).

Management of Hypersensitivity Reactions

Patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice.

If a hypersensitivity reaction is diagnosed the ABC-containing product MUST be discontinued immediately. The subject's parent/legal guardian should be asked to return all unused supplies of the ABC-containing product for disposal to prevent an accidental re-challenge.

An ABC-containing medicinal product (ZIAGEN, TRIZIVIR or any ABC-containing fixed dose combination), MUST NEVER be administered following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, the ABC-containing product should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications).

Symptomatic support for ABC hypersensitivity may be indicated. This should include, for example, administration of intravenous fluids to patients who develop hypotension. Antihistamines or corticosteroids have been used in cases of ABC hypersensitivity, however there are no clinical data demonstrating the benefit of these in the management of the reaction.

Laboratory and other investigations which may be useful in the evaluation and treatment of ABC hypersensitivity include, but may not be limited to, measurement of ALT, AST, creatine phosphokinase, serum creatinine and white blood cell differential count and chest x-ray, if respiratory symptoms are present.

Special considerations following an interruption of abacavir therapy

If therapy with ABC has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC (ZIAGEN, TRIZIVIR, KIVEXA, TRIUMEQ or any ABC-containing fixed dose combination) should be restarted.**

There have been infrequent reports of hypersensitivity reaction following reintroduction of an ABC-containing product where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart any ABC-containing product in these patients, this should be done only under direct medical supervision.

Rarely, patients who have stopped ABC for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re- initiating abacavir therapy. Subjects must be made aware that HSR can occur with reintroduction of ABC or any other medicinal product containing abacavir and that reintroduction of ABC or any other medicinal product containing abacavir should be undertaken only if medical care can be readily accessed.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of ABC in patients of unknown HLA-B*5701 status who have previously tolerated ABC. Re-initiation of ABC in such patients who test positive for the HLA B*5701 allele is not recommended.

Essential Patient Information

Investigators must ensure that subject's parents/legal guardians are fully informed regarding the following information on the hypersensitivity reaction:

- Subjects' parents/legal guardians must be made aware of the possibility of a hypersensitivity reaction to ABC that may result in a life threatening reaction or death.
- Parents/legal guardians of subjects developing signs or symptoms possibly linked with a hypersensitivity reaction MUST CONTACT their doctor IMMEDIATELY.
- Parents/legal guardians must be reminded that subjects who are hypersensitive to ABC must never take any ABC-containing medicinal products (ZIAGEN, TRIZIVIR, KIVEXA, TRIUMEQ or any ABC-containing fixed-dose combination) again.
- In order to avoid restarting the ABC-containing product, the parents/legal guardians of subjects who have experienced a hypersensitivity reaction should be asked to return the remaining oral solution to the pharmacy.
- Parents/legal guardians of subjects, who have stopped an ABC-containing product for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.
- Each parent/legal guardian should be reminded to read the Package Leaflet included in the pack.
- Parents/legal guardians should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

Reporting of Hypersensitivity Reactions

All cases of potential ABC hypersensitivity should be reported as Serious Adverse Events (SAE) (see Section 7.8). In addition to reporting the case as an SAE, the HSR CRF should be completed and sent to GSK within one week of the onset of the hypersensitivity reaction.

Stevens Johnson Syndrome, Toxic Epidermal Necrolysis or Erythema Multiforme

Serious skin reactions such as Stevens Johnson Syndrome, Toxic Epidermal Necrolysis or Erythema Multiforme have been reported very rarely in patients taking ABC-containing products. These patients generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC hypersensitivity reaction, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, the ABC-containing product should be discontinued, and the patient should not be rechallenged with any ABC-containing medicinal product (ZIAGEN, TRIZIVIR, KIVEXA, TRIUMEQ or any ABC-containing fixed dose combination).

As many products other than ABC also cause these serious skin reactions, all other medicinal products that the patient is receiving should also be reviewed and discontinued as appropriate.

Management of Rash That is Not Accompanied by Systemic Symptoms

Subjects receiving ABC who develop rash of any grade should be evaluated for the possibility of a hypersensitivity reaction or a serious skin reaction such as Stevens Johnson Syndrome, Toxic Epidermal Necrolysis or Erythema Multiforme and managed appropriately as outlined above. Rash may be caused by therapies in any of the major antiretroviral classes, or by other therapies commonly used as concurrent medications, such as cotrimoxazole. As it is not possible to provide an exhaustive list of products that may cause rash in this protocol, please consult the product information leaflets for other products for information relating to rash.

The rash and any associated symptoms should be reported as adverse events (See Section 7.1) and appropriate toxicity ratings should be used to grade the events.

If the etiology of the rash can be definitively diagnosed as being due to a specific medical event or a concomitant medicinal product, routine management should be performed and documentation of the diagnosis provided.

3.3.8. Subject Management Options

If subjects experience the following criteria**:**

- less than 1 log10 copies/mL reduction in plasma HIV-1 RNA by Week 12, or
- ≥0.7 log10 copies/mL rise from the nadir of plasma HIV-1 RNA, or

- a persistent decrease of five percentiles in CD4% in children with a baseline CD4% of less than 15%, or criteria as specified in local guidelines, the investigator should consider whether a change in therapy and study discontinuation is warranted.

Investigators are urged to follow country specific guidelines where they exist when making decisions about the management of subjects (e.g., when to switch therapy).

Subjects meeting one of the criteria defined above (first occurrence only and providing that the subject's plasma HIV-1 RNA is at least 1000copies/mL) should return, at the discretion of the investigator, to the clinic within 1 to 4 weeks to have a blood sample drawn for resistance testing.

If a subject develops an AIDS diagnosis (CDC stage C) or other evidence of disease progression such that the treating clinician believes that changing therapy is required even though the above criteria have not been met, the investigator should contact ViiV Healthcare for further discussion on a case by case basis.

3.3.9. Study Treatment Assignment

Subject Number

After the parent/guardian has signed the informed consent form (ICF), each subject being screened for study enrolment will be assigned a subject number. This number will be given sequentially in chronological order of subject presentation according to a numerical roster provided to the site by GSK. The subject number will be used to identify each subject for the duration of the study. Once a subject number has been assigned to a subject, it cannot be re-assigned to any other subject.

Treatment Number

The treatment number will be used to identify the specific study drug regimen initiated by the subject. Once a treatment number has been assigned to a subject, it cannot be reassigned to any other subject.

Allocation of treatment numbers and consequently treatment assignments will be made via a 24-hour central registration telephone system according to the treatment code provided by GSK.

Subjects undergoing SDV will be assigned a treatment number at the SDV. Subjects not undergoing SDV will be assigned a treatment number at Baseline.

3.3.10. Concurrent Medications and Non-Drug Therapies

All concurrent medications, including non-prescription medications and herbal supplements, should be administered only as medically necessary during the study. Chemoprophylaxis for HIV-associated conditions is encouraged, if deemed appropriate by the investigator. All concurrent medications administered during the study must be recorded on the CRF for the duration of the trial.

Hematological supportive therapy with G-CSF, GM-CSF, or erythropoietin will be permitted.

Other experimental agents, immunomodulators, cytotoxic chemotherapy or radiation therapy may not be administered during the study (see Section 3.2.2. Exclusion Criteria); an exception will be made for local therapy or radiation treatment for Kaposi's sarcoma.

Because vaccines may cause a temporary increase in the level of plasma HIV-1 RNA, it is recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit. This approach will minimize the risk of non-specific increases in the level of plasma HIV-1 RNA at the next scheduled assessment. HIV immunotherapeutic vaccines are not permitted at any time point during the study.

IMPORTANT: For other potential interactions always refer to the product information for any drug used in combination therapy.

Fosamprenavir and Ritonavir

FPV and RTV are metabolized in the liver by cytochrome P450 3A4 (CYP3A4). APV and RTV are predominantly CYP3A4 inhibitors. When FPV and RTV are co-administered, the ritonavir metabolic drug interaction profile may predominate because ritonavir is a more potent CYP3A4 inhibitor. The full prescribing information for ritonavir must therefore be consulted prior to initiation of therapy with FPV and RTV.

Caution should be used when co-administering medications that are substrates, inhibitors, or inducers of CYP3A4. In addition, RTV has an affinity for other cytochrome P450 isozymes including CYP2D6, CYP2C9, CYP2C19, CYP2A6, CYP1A2 and CYP2E1, and appears to increase the activity of glucuronosyl transferases.

FPV and RTV should not be co-administered with alfuzosin, amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, halofantrine, lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, ketaconazole, rifampicin, PDE5 inhibitors including sildenafil, simvastatin, terfenadine and triazolam. Co-administration may result in competitive inhibition of metabolism of these medications and may cause serious or life-threatening adverse events. Co-administration of FPV or FPV/RTV with rifabutin results in significant increases in plasma rifabutin levels, therefore the dose of rifabutin should be reduced by at least 50% when co-administered with FPV and by at least 75% when co-administered with FPV/RTV. Caution should be used and subjects should be monitored closely for signs of toxicity.

Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this interaction is also expected with other corticosteroids metabolized via the P450 3A pathway.

Concomitant use of fluticasone propionate and ritonavir should be avoided unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

FPV and RTV should not be co-administered with carbamazepine, dexamethasone, phenobarbital, primidone, rifampin and St. John's Wort because the PI concentrations may be significantly decreased, reducing efficacy. FPV and RTV should also not be co-administered with hepatitis C virus (HCV) protease inhibitors telaprevir and boceprevir because both APV and HCV PI concentrations may be significantly decreased, with the possibility of sub-therapeutic concentrations.

APV and RTV interact with CYP3A4 and are predominantly CYP3A4 inhibitors. Medications which interact with CYP3A4, either as substrates, inhibitors, or inducers of the isozyme, or medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP 3A4) should be used with caution include, but are not limited to: alprazolam, amlodipine, atorvastatin, cerivastatin, cimetidine, clarithromycin, clindamycin, clonazepam, codeine, dapsone, diltiazem, disopyramide, erythromycin, estrogens and progestogens, felodipine, fluvastatin, glucocorticoids, imipramine, isradipine, itraconazole, loratadine, miconazole, nicardipine, nifedipine, nimodipine, nisoldipine, pravastatin, verapamil and zolpidem.

The following medications are examples of drugs that require concentration and therapeutic effect monitoring when administered in combination with FPV and RTV due to the potential for serious and/or life-threatening drug interactions: cyclosporine, systemic lidocaine, rapamycin, tacrolimus, tricyclic antidepressants, theophylline, and warfarin. International Normalized Ratio (INR) monitoring is recommended when warfarin is used concomitantly with FPV and RTV.

RTV is not recommended for use with digoxin, voriconazole, blonanserin, salmeterol and other drugs not recommended for use with FPV above. RTV is an inhibitor of CYP2D6 and an inducer of CYP1A2, CYP2C9 and glucuronosyl transferase. Medications which interact with CYP2D6, CYP1A2, CYP2C9, and/or glucuronosyl transferase should be used with caution and include but are not limited to: bisoprolol, codeine, chlorpromazine, cyclobenzaprine, desipramine, doxepin, fluphenazine, fluoxetine, haloperidol, hydrocodone, methamphetamine, metoprolol, mexilitine, morphine, propranolol, oxycodone, paroxetine, perphenazine, risperidone, thioridazine, timolol, tramadol, trazodone, and venlafaxine.

Because RTV oral solution contains alcohol, drugs such as metronidazole that may inhibit alcohol metabolism should be avoided.

IMPORTANT: For further information refer to local product information or the International Product Information for more complete information.

3.3.10.1. GSK Supplied Background NRTI Options

Interactions Relevant to Abacavir

Based on the results of in vitro experiments and the known major metabolic pathways of ABC, the potential for drug interactions involving ABC is low.

ABC shows no potential to inhibit metabolism mediated by the cytochrome P450 3A4 enzyme. It has also been shown in vitro not to interact with drugs that are metabolised by

CYP 3A4, CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for drug interactions with antiretroviral protease inhibitors and other drugs metabolised by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between ABC, zidovudine and 3TC.

Ethanol - The metabolism of ABC is altered by concomitant ethanol resulting in an increase in AUC of ABC of about 41%. Given the safety profile of ABC, these findings are not considered clinically significant. ABC has no effect on the metabolism of ethanol.

Methadone - In a PK study, co-administration of 600 mg ABC twice daily with methadone showed a 35% reduction in ABC Cmax and a one hour delay in tmax, but AUC was unchanged. The changes in ABC PK are not considered clinically relevant. In this study, ABC increased the mean methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.

Retinoids - Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with ABC is possible but has not been studied.

Refer to the local prescribing information for additional information on concurrent therapies.

Interactions Relevant to Lamivudine

The likelihood of interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system, e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

Active substances shown to be predominately excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.

Zidovudine - A modest increase in Cmax (28%) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of lamivudine.

Trimethoprim/sulphamethoxazole - Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see Dosage and Administration). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of

co-trimoxazole for the treatment of Pneumocystis carinii pneumonia and toxoplasmosis has not been studied.

Zalcitabine - Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

Emtricitabine: Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicines are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these medicines in combination therapy may be limited. 3TC is not recommended for use in combination with emtricitabine.

Refer to the local prescribing information for additional information on concurrent therapies.

Packaging and Labeling of GSK Supplied Background NRTI Options

GSK will provide ABC and/or 3TC as optional background NRTIs for subjects whose screening HIV-1 genotype, if available, shows susceptibility to ABC and/or 3TC, or per investigator discretion.

The contents of the label will be in accordance with all applicable regulatory requirements.

ABC and 3TC will be supplied in their own bottle and labeled with the following information: protocol number, container contents, batch/inventory number, quantity, dosing instructions and storage conditions/instructions. Qualified study site personnel should calculate the drug dose at the site.

GSK supplied background NRTIs will be packaged such that the site investigator or pharmacist can dispense sufficient drug for each subject until the next scheduled study visit.

Handling of GSK Supplied Background NRTI Options

GSK supplied background NRTIs will be dispatched to a site only after receipt of required documents in accordance with all applicable regulatory requirements and GSK procedures. These documents include, but are not limited to the signed FDA Form 1572 or equivalent, signed Financial Disclosure Agreement, signed protocol agreement and IEC/IRB approval letter.

ABC and 3TC will be shipped to the investigational sites by GSK. At each visit the investigator or designated site staff should dispense sufficient amount of background NRTIs to provide adequate supply for each subject until the next scheduled visit. All GSK supplied background NRTIs that are not utilized during the study will be destroyed at the completion of the trial. Drug disposition records will be regularly reviewed by the study monitor.

GSK supplied background NRTIs must be dispensed or administered according to procedures described below. Only subjects whose HIV-1 genotype shows susceptibility to ABC and/or 3TC and who meet the minimum age requirements may receive GSK supplied background NRTIs, in accordance with all applicable regulatory requirements. Only authorized site personnel may supply or administer GSK supplied background NRTIs. All GSK supplied background NRTIs must be stored in a secure area with access limited to the investigator and authorized study site personnel and under physical conditions that are consistent with study drug-specific requirements.

All GSK supplied background NRTIs should be stored until the time of dispensing as follows:

Abacavir oral solution	**US/Canada/Latin America** – Store between 20°C - 25°C (68°F - 77°F) **DO NOT FREEZE.** May be refrigerated**.** **Europe/ South Africa** – Store below 30°C **DO NOT FREEZE**
Abacavir tablet*	**South Africa** – Store at or below 30°C.
Lamivudine oral solution	**US/Canada/Latin America** – Store in tightly closed bottles at 25°C (77°F) **Europe/ South Africa** – Store at or below 25°C
Lamivudine tablet	**South Africa** – Store at or below 30°C.

*Only supplied when licensed in South Africa.

Accountability Procedures for GSK Supplied Background NRTI Options

The investigator is responsible for GSK supplied background NRTIs accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study site personnel must maintain drug accountability records throughout the course of the study. This person(s) will document the amount of background NRTIs received from GSK, the amount supplied and/or administered to and returned by subjects, if applicable.

All GSK supplied background NRTIs will be handled and stored in accordance with the product label or information provided by GSK.

Within each subject's CRF, start and stop dates of each background ART (both GSK supplied and those supplied by the subject via prescription) must be recorded on the background antiretroviral therapy page. In addition, dose changes and interruptions of greater than **24** hours duration must be recorded.

Separate from the CRF, the site will maintain GSK Supplied Background NRTI Accountability Logs to include the following:

- subject number
- treatment number

- quantity of drug dispensed/returned (the unit of accountability will be full/partial/empty bottles)
- dispensing/return date
- signature or initials of individual dispensing the drug
- comment area for noting discrepancies

Subjects must be instructed to return all GSK supplied background NRTIs to the site at each study visit for volume assessments. This includes bottles that are empty, partially full and completely full.

At the end of the study and at appropriate intervals during the study, all unused background NRTIs must be returned to GSK according to procedures dictated by the study monitor or destroyed at site and adequately documented.

The investigator is responsible for assuring that GSK supplied background NRTIs are stored, dispensed and returned appropriately. GSK monitors will regularly access pharmacy/dispensing records. Cases of suspected negligence will be investigated.

4. STUDY DRUG MANAGEMENT

4.1. Study Drug Packaging and Labeling

The contents of the label on all study drugs will be in accordance with all applicable regulatory requirements.

FPV 50 mg/mL oral suspension will be supplied in its own bottle and labeled with the following information: protocol number, container contents, batch/inventory number and quantity, storage conditions/instructions, dosing instructions and shaking instructions to ensure adequate redispersal of the oral suspension prior to dosing. Qualified study site personnel should calculate the drug dose at the site.

RTV oral solution, powder, tablets or capsules will be provided locally by the investigator as required and should be stored according to the local product information. GSK will provide RTV by other means where reimbursement is not acceptable, or GSK may provide RTV if local supplies are not available and RTV is able to be obtained from other countries.

In this trial, ‘study drugs’ are defined as FPV and RTV for the purposes of recording adverse events and serious adverse events. The FPV oral suspension will be packaged such that the site investigator or pharmacist can dispense sufficient drug for each subject until the next scheduled study visit.

4.2. Study Drug Handling

Study drug will be dispatched to a site only after receipt of required documents in accordance with all applicable regulatory requirements and GSK procedures. These documents include but are not limited to the signed FDA Form 1572 or equivalent, signed Financial Disclosure Agreement, signed protocol agreement and IEC/IRB approval letter.

FPV will be shipped to the investigational sites by GSK. In all countries, RTV oral solution, powder, tablets or capsules will be obtained locally and reimbursed if acceptable to regulatory authorities. GSK will provide RTV by other means where reimbursement is not acceptable, or GSK may provide RTV if local supplies are not available and RTV is able to be obtained from other countries. At each visit, the investigator or designated site staff should dispense sufficient amount of study drug to provide adequate supply for each subject until the next scheduled visit. All study drug that is not utilized during the study will be destroyed at the completion of the trial. Drug disposition records will be regularly reviewed by the study monitor.

Study drug must be dispensed or administered according to procedures described below. Only subjects enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized site personnel may supply or administer study drug. All study drugs must be stored in a secure area with access limited to the investigator and authorized study site personnel and under physical conditions that are consistent with study drug-specific requirements.

The FPV suspension should be shaken as per the label instructions prior to measuring. Site staff designated to dispense FPV oral suspension will also be instructed to rigorously shake all bottles at the point of dispensing for a minimum of 20 seconds. The time the bottles were shaken for should be recorded in the Study Drug Accountability Log and this information will be transcribed into the corresponding page of the subject's CRF.

Both FPV oral suspension and RTV oral solution should be measured and administered using separate appropriately sized oral dosing syringes. Administration via dosing cups is not allowed as residual FPV oral suspension and RTV oral solution could remain in the cups.

Note per Amendment 12; for subjects weighing less than 33 kg, if RTV oral solution is not available, the RTV powder can be substituted. For doses less than 100 mg or partial doses between 100 mg increments the following instructions should be followed. Mix 1 packet/sachet of oral powder (100 mg) with 9.4 mL of liquid (such as water, chocolate milk, or infant formula) in a mixing cup. Once mixed, use an oral dosing syringe to measure and administer the prescribed volume. Once the powder is mixed, the dosage must be consumed within 2 hours. Discard any mixture remaining in the mixing cup. Additional guidance is provided in Section 11.6.

IMPORTANT: Do NOT mix FPV with RTV or other background NRTI medications in the same syringe.

Study medications should be stored until the time of dispensing as follows:

FPV 50 mg/mL oral suspension	Store below 30°C (86°F) **DO NOT FREEZE**
RTV 80 mg/mL oral solution	Store according to local product information
RTV oral powder	Store according to local product information
RTV 100 mg tablet	Store according to local product information
RTV 100 mg soft gelatin capsules	Store according to local product information

4.3. Study Drug Accountability Procedures

The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study site personnel must maintain study drug accountability records throughout the course of the study. This person(s) will document the amount of study drug received from GSK, the amount supplied and/or administered to and returned by subjects, if applicable.

All study drugs will be handled and stored in accordance with the product label or information provided by GSK.

Within each subject's CRF, the Study Drug Record page will list the name and dose regimen of each study drug. Start and stop dates of each study drug must be recorded on this page. In addition, dose changes and interruptions of greater than **24** hours duration must be recorded.

Separate from the CRF, the site will maintain a Study Drug Accountability Log to include the following:

- subject number
- treatment number
- batch/inventory number
- quantity of drug dispensed/returned (the unit of accountability will be full/partial/empty bottles)
- dispensing/return date
- signature or initials of individual dispensing the drug
- comment area for noting discrepancies

Subjects must be instructed to return all study drug to the site at each study visit for volume assessments. This includes bottles that are empty, partially full and completely full.

At the end of the study and at appropriate intervals during the study, all unused drug must be returned to GSK according to procedures dictated by the study monitor or destroyed at site and adequately documented.

The investigator is responsible for assuring that study medications are stored, dispensed and returned appropriately. GSK monitors will regularly access pharmacy/dispensing records. Cases of suspected negligence will be investigated.

5. MEASUREMENTS AND EVALUATIONS

5.1. Time and Events Schedule

Schedules showing the timing of study procedures and laboratory evaluations for all subjects are shown in Section 10.

After determining that a subject is potentially eligible for enrolment, written informed consent from each subject's parent/guardian must be obtained before any investigations are performed which are for the sole purposes of this study.

Subjects will attend the clinic at Screening, Day 1 (Baseline), and Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART. A follow-up visit will be performed 4 weeks after the permanent discontinuation of study drug.

The scheduled laboratory evaluations will involve collection of a maximum blood volume of 7mL/kg in any 56-day period in all subjects. Additionally, a maximum of 3mL/kg of blood will be collected at any one study visit from children 4 weeks to <6 months old.

5.2. Screening and Enrolment

Subjects will undertake the procedures listed in the schedules in Section 10. Screening will be within approximately 21 days of Baseline/Day 1 for all subjects. As per amendments 5 and 7, SDV assessments are no longer required for Cohort 1 Arm A and Cohort 2 Arm A.

Reports of screening assessments of lymphocyte subsets, HIV-1 RNA PCR and HIV-1 resistance testing (if performed) should be reviewed prior to Baseline/Day 1 to confirm that the subject meets the full eligibility criteria.

5.3. Demographic and Baseline Characteristics

- Demography: Subject date of birth, gender and race will be collected at the Screening visit.
- Baseline characteristics:

  Information to be collected will include:

  - HIV risk factors and mode of transmission (collected at Screening visit)
  - CDC classification (collected at the Screening visit and summarised at Baseline)
  - Current medical conditions (collected at Day 1)
  - HIV-associated conditions (collected from Day 1)
  - Prior antiretroviral therapy (collected at Day 1 or the initial Single Dose Visit if applicable)
  - Background antiretroviral therapy (collected from Day 1 or the initial Single Dose Visit if applicable)

- Height, weight, head circumference and vital signs (blood pressure and pulse, collected at all visits)

5.4. Study Drugs and Background NRTIs

The start and stop date for all study drugs and background NRTIs, any temporary interruptions or dose changes >24 hours, and information on premature discontinuation of study drug and background NRTIs will be collected on Day 1 and throughout the study period. In this trial, study drugs are defined as FPV and RTV, whereas ABC and 3TC are GSK supplied background NRTIs.

5.5. Efficacy

All evaluations listed below will be performed at Screening, Day 1 and at Weeks 4, 12, 24, 36, 48, every 12 weeks thereafter, and Withdrawal. Refer to the study manual provided by the central laboratory for specific instructions on sample collection, preparation and shipment.

- Quantitative plasma HIV-1 RNA (Roche Amplicor HIV-1 Monitor Test; version 1.5, ultrasensitive limit of detection (LOD) = 50 copies/mL). Samples with >75,000 copies/mL will be retested using the Roche Amplicor HIV-1 Monitor Test, version 1.5, standard assay LOD = 400 copies/mL. (NOTE: At the Screening and Baseline (Day 1) visits, the Roche Amplicor HIV-1 Monitor Test, version 1.5, standard assay will be used). Per Protocol Amendment 12: the Roche Amplicor HIV-1 Monitor Test Version 1.5 was subsequently discontinued after the July 2011 cut-off date for the week 48 CSR. By January 2013, only two APV20002 study sites, both in South Africa had actively enrolled subjects; and efficacy for these subjects was evaluated using the Abbott Realtime HIV-1 Test, which has a LOD of 40 copies/mL.
- Lymphocyte subsets to include total lymphocytes, absolute and percent CD4+ and CD8+ cell counts.
- HIV associated conditions: The subject will be assessed for any new or recurring HIV-associated conditions at all study visits from Baseline.
- Genotypic HIV-1 resistance testing: Plasma samples may be collected at the Screening visit at the investigator's discretion if needed to guide selection of background ART. Resistance analysis will also include an assessment of the HIV-1 protease (PRO) coding region. Where blood volumes permit, a sample will also be collected if the subject meets one of the criteria described in Section 3.3.8 with results provided to the investigator.
- Additional storage samples may be collected at Day 1, Weeks 12, 24, 36, 48, every 12 weeks thereafter, and Withdrawal and stored for possible HIV genotype/phenotype testing in the future or for repeat laboratory assessments as needed.

5.6. Health Outcomes

5.6.1. Humanistic Outcomes

Adherence Questionnaire

Medication adherence will be measured by the subject's parent or guardian via completion of an adherence questionnaire. The adherence questionnaire will be completed in order to quantify the number of doses of FPV BID and/or FPV/RTV BID that were missed during the course of the study. The adherence questionnaire will be administered on Day 1 (Baseline practice questionnaire), Weeks 2, 12, 24, 48 and at the time of premature study discontinuation.

Parent/Guardian Perception of Study Medication

Parent/guardian's attitude or perceptions of medications can impact on the acceptability of a medication to a child, affecting adherence and the subsequent drug efficacy in the pediatric population. Parent/guardian perceptions of FPV BID and FPV/RTV BID will be assessed using a Parent/Guardian Perception of Study Medication assessment administered during Weeks 2, 24 and 48/premature study discontinuation.

Administration of the Humanistic Questionnaires

Completeness and Accuracy of Subject Questionnaire Responses

The parent/guardian should be asked to complete the questionnaires as completely and as accurately as possible. If a parent/guardian is unable to complete a questionnaire by him or herself, study site personnel may administer the questionnaire via an interview at the discretion of the investigator. With the exception of helping parents/guardians identify which antiretroviral drugs the subjects are supposed to be taking, the investigator will not provide an answer to any question nor interpret any portion of the question. If the parent/guardian requests help or clarification of any question, he or she should be asked to read the instructions again, or to listen again as the instructions and question are repeated if administration is undertaken via interview, and to give the best answer possible to each question. Parents/guardians should be encouraged that it is their experiences and opinions that are requested, and that the subject's treatment during the study will not be affected by their answers.

Recording of Data

Black ink should be used to complete the questionnaires. Parents/guardians must be instructed to make any changes by drawing a line through the undesired response, dating the change, and then recording the desired response.

Collection and Storage of Subject Questionnaires

Upon completion of the questionnaires, the investigator will retrieve the questionnaires from the parent/guardian, check that the header sections (Subject Number, Visit Date, etc.) are complete, ensure the parent/guardian did not *unintentionally* skip questions or a

page of questions, and return them to the subject's CRF notebook. At this point, the subject questionnaires are considered complete, and they should not be given back to the parent/guardian. No changes should be registered once they have been completed and returned to the investigator. Investigators are to record the method of administration of the questionnaires on the "Method of Administration for Questionnaires and Subject Dosing Card" CRF page. If respondents experience difficulties or are unable to answer any question, then the investigator should document the reason in the investigator comments log. Possible reasons for not completing the questionnaires are the parent/guardian refused, parent/guardian unable to understand a question or other.

Source Documents and Monitoring Procedures for Subject Questionnaires

Each questionnaire completed by the subject's parent/guardian serves as a source document; therefore there are no other source documents for data validation by the clinical research team member.

No attempt should be made by the investigator to reconcile data recorded on the subject's parent/guardian questionnaire booklets with data recorded on the clinical CRF, except for subject identification data (e.g., Subject Number, Treatment Number, Visit Date, Gender, etc.). Neither the investigator nor any member of the clinical research team is under any obligation to validate the accuracy of the parent/guardian completed sections of the questionnaires.

5.7. Bioanalysis and Pharmacokinetic Samples

Cohort 1 (6 months to <2 years) Arm A: Plasma samples for evaluation of PK parameters will be collected over 4 hours at Week 2 and over 8-12 hours (12 hour sample optional) at Week 8. Plasma trough PK samples will be collected at Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter.

Cohort 2 (4 weeks to <6 months) Arm A: Plasma PK samples will be collected over 8-12 hours (12 hour sample optional) at Week 2. Plasma trough PK samples will be collected at Weeks 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.

To measure the unbound concentration of APV, additional plasma trough PK samples will be collected prior to FPV/RTV BID dosing at Weeks 2, 16 and 36 for Cohort 1 Arm A subjects and at Weeks 8 and 16 for Cohort 2 Arm A subjects.

A maximum of 7mL/kg of blood for PK, safety, and virological assessments will be collected during any 56-day period for all subjects. A maximum of 3mL/kg of blood will be collected at any one study visit for subjects 4 weeks to <6 months old.

Single Dose Visit (SDV)

Cohort 1 (6 months - <2 years)

Per protocol amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks - <6 months)

Per protocol amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Week 2 PK Sampling

Subjects enrolled in both cohorts (Arm A, FPV/RTV BID) will undergo plasma PK sampling on Week 2. Plasma concentrations of APV, FPV and RTV will be determined:

- Cohort 1 Arm A: A plasma trough PK sample of 1.0mL whole blood will be collected prior to FPV/RTV dosing. A 2.0mL whole blood sample will be collected prior to dosing to determine plasma concentrations of unbound APV. Three 1.0mL whole blood samples will be collected at 0, 2, and 4 hours post-dosing.
- Cohort 2 Arm A: Seven whole blood samples of 0.5mL each will be collected at 0, 1, 2, 4, 6, 8, and 12 hours post-dosing (optional 12-hour sample).

Week 4 PK Sampling

No PK sampling will be collected at Week 4 for either Cohort.

Week 8 PK Sampling

Subjects in Cohort 1 Arm A will undergo serial plasma PK sampling on Week 8. Plasma concentrations of APV, FPV and RTV will be determined. Seven whole blood samples will be collected at 0, 1, 2, 4, 6, 8, and 12 hours post-dosing (optional 12 hour sample). One mL whole blood samples will be drawn at each time point specified.

Subjects in Cohort 2 Arm A will have a plasma trough PK sample of 1.0mL whole blood collected prior to FPV/RTV BID dosing. A 2.0mL whole blood sample will be collected prior to dosing to measure the unbound APV concentration.

Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter

All subjects will undergo additional plasma trough PK sampling of 1.0mL of whole blood (just prior to receiving a scheduled dose of FPV/RTV BID) at Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter.

In addition, at Week 16 (both Cohorts) and Week 36 (Cohort 1 only), subjects will have a plasma trough PK sample of 2.0mL whole blood collected (prior to receiving the scheduled dose of FPV/RTV BID) to determine the unbound concentration of APV.

In consultation with the investigator, GSK may discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis once a subject has reached and exceeded 2 years and has initiated the 23/3 mg/kg BID dosing regimen after Week 48. Any further dosing changes would follow the approved dosing recommendations without PK sampling, including a transition to FPV/RTV 18/3 mg/kg BID at 6 years.

Directly Observed Therapy

Because plasma PK sampling needs to occur at steady-state, it is imperative that subjects consistently receive their medications prior to PK sampling. To improve the quality of the serial PK samples, it is strongly recommended that the administration of study drugs on the evening prior to the serial PK visits and on the morning of the serial PK visits (after the pre-dose PK sample is collected) be directly observed by study personnel. The actual method of observation will be at the discretion of the investigator and may require the subject to attend the clinic for dosing or may require study personnel or a home healthcare provider to visit the subject at their home to observe the dosing.

Logistical Considerations

Site personnel will contact each subject's parent/guardian 3-4 days prior to each of the Week 2, 8, 12, 16, 24, 36, and 48 visits, and at the visits every 12 weeks thereafter, to remind them to record the doses, dates, and times of the three FPV/RTV doses administered prior to attending the study site. Site personnel will need to schedule each subject's visits so that the plasma PK trough sample is collected within 10-14 hours following a dose of FPV/RTV. All subject's parents/guardians will be provided with a "dosing card" as a tool to help them record doses for the 3 doses prior to plasma PK steady-state sampling. The dates and times of the 3 doses administered prior to collection of each plasma PK sample and the doses of FPV and RTV that were administered at each of these times will be recorded in the CRF. Information will also be collected on whether or not the subject spit up or vomited these three doses. If the "dosing card" is missing, blank or incomplete, then the corresponding PK CRF pages "Prior Dosing GW433908 and "Prior Dosing Ritonavir" may be completed by oral interview at the site at the discretion of the investigator. The investigator should document the reason in the investigator comments log.

Information regarding partial dosing and subsequent re-dosing, if required, due to subjects either spitting up or vomiting their FPV oral suspension and/or RTV oral solution doses will be collected for the 3 doses prior to any PK sampling and for the dose administered immediately following the pre-dose (0 hour) PK sample on the SDV and Week 2 PK.

It is strongly advised that subject compliance should be carefully reviewed prior to all PK sampling. If a significant deviation affecting kinetic sampling is noted, the investigator is advised to counsel the parent/caregiver as to the importance of compliance and reschedule the sampling until the specific issue is resolved.

For details on collection, processing and shipping of samples consult the Study Reference Manual.

5.8. Safety

The following safety evaluations will be performed during the study (see Section 10 for schedule of events).

- Hematology: including hemoglobin, white blood cell (WBC) count with differential, mean corpuscular volume (MCV) and platelet count to be performed at the Screen visit, Day 1 and Weeks 4, 12, 24, 36, 48, every 12 weeks thereafter, and Withdrawal.
- Clinical chemistry: including sodium, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, albumin, glucose, alkaline phosphatase and creatine phosphokinase (CPK) to be performed at the Screen visit, Day 1 and Weeks 4, 12, 24, 36, 48, every 12 weeks thereafter, and Withdrawal.
- Lipid measures to include triglycerides, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) to be collected at Day 1 and Weeks 24 and 48, every 12 weeks thereafter, and Withdrawal.
- Clinical adverse events to be collected at the Screen visit, the Single Dose Visit, Day 1 and Weeks 2, 4, 8, 12, 16, 24, 36, 48, every 12 weeks thereafter, and Withdrawal: Refer to Section 7 for details.
- Concurrent medications/blood products and background antiretroviral medication to be collected at the Single Dose Visit, Day 1 and Weeks 2, 4, 8, 12, 16, 24, 36, 48, every 12 weeks thereafter, and Withdrawal.

Scheduled laboratory evaluations within the study will be undertaken by a central laboratory nominated by GSK. However, evaluation of hematology and clinical chemistry may be undertaken at a local accredited laboratory with the approval of GSK.

Refer to the central laboratory manual for specific instructions on sample collection, processing, storage and shipping for each laboratory test. Hematology and clinical chemistry undertaken at a local laboratory should be handled according the standard local procedures.

5.9. Premature Discontinuation

5.9.1. Premature Discontinuation from the Study

A subject will be said to have completed the study if the subject does not permanently stop study drug dosing prior to end of the study and completes all scheduled study visits.

Subjects may be prematurely discontinued from the study for any of the following reasons:

- Subject, subject's parent/guardian or investigator non-compliance.
- At the request of the subject's parent/guardian, investigator or GSK.
- Progression of any medical condition which, in the opinion of the principal investigator, should preclude further participation.
- If the subject requires treatment with any of the medications listed in the Exclusion Criteria (Section 3.2.2).
- If the subject requires cytotoxic chemotherapy or radiation therapy (with the exception of local treatment for Kaposi's sarcoma).
- If the subject requires another investigational drug which when combined with the study drug would, in the opinion of the investigator or GSK, jeopardize the validity of the subject's continued participation.

Subjects who prematurely discontinue from the study will not be replaced unless <8 subjects from each treatment regimen in each cohort have completed PK analysis after 2 weeks on their selected regimen. In this case, additional subjects will be added to the cohorts as replacement subjects.

Withdrawal

Subjects who prematurely discontinue from the study, whether voluntarily or not, should have the Withdrawal visit assessments performed (refer to Section 10). Once a subject's weight has increased to 39 kg or more, they should be withdrawn from the study (refer to Section 3.1). A Follow-up visit will be performed 4 weeks after the Withdrawal visit.

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time. If a subject is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform the following evaluations listed below. These data should be recorded, as they comprise an essential evaluation that should be done prior to discharging any subject from the study.

Clinical Evaluations

- Body weight and height
- Head circumference
- Vital Signs
- Concurrent medications/blood products
- Background ART
- HIV-associated conditions
- Adverse events
- Questionnaires for humanistic outcomes

Laboratory Evaluations

- Hematology (hemoglobin, WBC with differential, MCV and platelet count).
- Lymphocyte subsets by flow cytometry (total lymphocytes and absolute and percentage CD4+ and CD8+ lymphocyte counts).
- Clinical chemistry panel and transaminase levels (sodium, potassium, AST, ALT, total bilirubin, creatinine, albumin, glucose, alkaline phosphatase, and CPK).
- Lipid measures including triglycerides, and total cholesterol, HDL, and LDL cholesterol.
- Quantitative plasma HIV-1 RNA PCR.
- Plasma for storage where permitted by blood volume restrictions. This sample may be used for HIV-1 genotype and phenotype testing.

In the event that a subject is prematurely discontinued from the study at any time due to an AE (as defined in Section 7.1, "Definition of an AE") or SAE (as defined in Section 7.2, "Definition of a SAE"), the procedures stated in Section 7, ("AEs and SAEs") must be followed.

5.10. Follow Up

All study subjects should have a follow up study visit 4 weeks following permanent discontinuation of study drug. The follow up assessments required are detailed below and in Section 10.

Clinical Evaluations

- Concurrent medications/blood products
- Current ART
- HIV-associated conditions
- Adverse events
- Serious adverse events

Laboratory Evaluations

- Hematology (hemoglobin, WBC with differential, MCV and platelet count).
- Clinical chemistry panel and transaminase levels (sodium, potassium, AST, ALT, total bilirubin, creatinine, albumin, glucose, alkaline phosphatase, and CPK).

6. DATA ANALYSIS METHODS

6.1. Sample Size Determination

The sample size of 48 subjects was selected as an appropriate number to allow an accurate description of plasma APV PK, safety and tolerability of FPV BID, Arm B (N=24 for PK and safety; enrolment closed per Amendment 10) and FPV/RTV BID, Arm A (N=24 for PK and safety). Safety and tolerability assessment of the FPV/RTV BID regimen (Arm A) will be for the duration of the study or until a subject permanently discontinues study drug. If less than 8 subjects in a cohort and dosage regimen complete the steady-state PK analysis on Week 2, additional subjects may be enrolled as replacement subjects. Additionally, if dose modification to the cohort dose is warranted, a further 8 subjects in each arm may be recruited to provide steady-state PK data on the revised dose.

Based on plasma APV PK data from previous studies, the highest variability was observed for the FPV oral suspension formulation in APV10008. The inter-subject standard deviation of $\log_e$ (AUC) was 0.42. Assuming 12 subjects provide plasma APV PK data for the each regimen, the width of the 95% CI for plasma APV $AUC_{\tau,ss}$ will be 54% of the geometric mean; therefore, the 95% CI for a FPV/RTV BID regimen geometric mean of 33.8μg*h/mL (the value estimated in adults) will be 25.9-44.2μg*h/mL, and the 95% CI for a FPV BID geometric mean of 16.5μg*h/mL (the value estimated in adults) will be 12.6-21.5μg*h/mL.

6.2. General Considerations

Only descriptive methods will be used in the analysis of the data obtained from this study. No statistical hypothesis testing will be performed.

Data will be summarized by treatment (FPV and FPV/RTV) and may be further summarized by cohort and ART-experience.

6.2.1. Analysis Populations

All subjects receiving FPV or FPV/RTV at any dose will be included in the safety population. This will be the primary population for any efficacy and safety analyses.

Other populations, such as “per-protocol” population may also be considered as secondary populations for efficacy analysis. Per-protocol analyses will only include subject data collected during treatment with FPV or FPV/RTV and will exclude data following major protocol deviations (these will be defined in the data analysis plan).

Pharmacokinetic Population

All subjects for whom a plasma PK sample has been analyzed will be included in the listing of plasma APV, FPV and RTV concentration-time data.

Pharmacokinetic Summary Population

All subjects for whom a plasma APV, RTV and/or FPV PK parameter value is estimated will be included in the listings and summaries of derived plasma APV, FPV and RTV PK parameters and the summaries of plasma APV and FPV concentration-time data.

Pharmacokinetic/Pharmacodynamic Population

The pharmacokinetic/pharmacodynamic population will consist of all subjects with Baseline factors including age, body weight, height, sex, race, CD4+ cell percentage, plasma HIV-1 RNA concentration, and viral susceptibility data and who have at least one evaluable plasma APV trough concentration.

6.2.2. Interim Analysis

For the first 6-10 subjects enrolled in each cohort, rapid turn-around plasma APV, RTV and FPV PK analysis will occur in order to provide individual dosage regimen recommendations to investigators. In addition, expedited analysis of plasma APV, RTV and FPV may be undertaken on a case-by-case basis on PK trough samples collected to allow for dose regimen adjustment due to the physiological development with age.

Interim analyses of safety, antiviral activity, and plasma APV, FPV and RTV PK data will be performed as required for regulatory submissions. No stopping rules will be applied.

6.2.3. Other Issues

For any analyses which use HIV-1 RNA levels as a continuous measure (e.g., change from Baseline) the values will be logged to the base 10. HIV-1 RNA values recorded as <400copies/mL (using the Roche HIV-1 Monitor test, version 1.5, standard assay LOD = 400copies/mL) will be given a value of 399copies/mL. Similarly, HIV-1 RNA values recorded as <50copies/mL will be given a value of 49copies/mL. For plasma HIV-1 RNA, lymphocyte subsets and other clinical laboratory parameters, the Baseline value will be defined as the value observed on Day 1 (or, if this value is missing, the last value observed before the start of multiple dosing with FPV or FPV/RTV).

Response to treatment within various subgroups (e.g. age, gender, background antiretroviral therapy) may be investigated descriptively by the presentation of summary statistics by subgroup.

6.3. Efficacy

No formal inferential analyses are planned. Data will be presented in summary or graphical form.

6.3.1. Efficacy Measurements

- Proportions of subjects with plasma HIV-1 RNA levels <400 copies/mL at each study visit
- Change from Baseline in plasma HIV-1 RNA at each study visit (absolute values and time-averaged)
- Proportion of subjects with ≥1.0 log10 decrease in HIV-1 RNA at each study visit
- Change from Baseline in CD4+ % at each study visit (absolute values and time-averaged)

These efficacy measures will be summarized by treatment (FPV and FPV/RTV) and visit, and may be further summarized by cohort and ART-experience.

6.4. Viral Resistance Testing

Viral resistance testing may be performed for subjects at Screening at the investigator's discretion if needed to guide selection of background ART.

Where permitted by blood volume restrictions, viral resistance testing may also be performed on samples collected at Baseline/Day 1, Weeks 12, 24, 36, 48, every 12 weeks thereafter, and Withdrawal (time of premature discontinuation). In addition, where blood volumes permit, viral resistance testing may be performed if the subject meets one of the criterion described in Section 3.3.8.

Analysis of viral resistance data, including an investigation of any potential correlations between clinical response and genotype/phenotype data, will be performed in at least a subset of subjects. Viral resistance testing will evaluate pre-existing or emerging viral resistance in both the PI and RT coding regions of the pol gene and in the cleavage site coding region of the gag gene. Viral mutations at codons associated with drug resistance will be evaluated with the HIV RNA response. In addition, any difference in emerging resistance patterns between FPV alone or FPV enhanced with RTV will be assessed.

6.5. Health Outcomes

6.5.1. Humanistic Outcomes

Adherence Questionnaire

Items 1-4 of the Adherence Questionnaire measure adherence behavior during the last 3 days for each medication prescribed to the subject. The subject's parent/guardian will respond "yes/no" to questions 1-4, assessing whether the subjects were adherent with

FPV or FPV/RTV. The frequency of yes/no responses will be summarized per treatment group for questions 1-4, by visit. Item 5 asks about the number of doses of FPV or FPV/RTV missed since the subject's last study visit. Number of doses missed will be summarized per treatment group, by visit.

Perfect adherence: Answering "no" to items 1-4 (must respond "no" to all four items) and answering "0" to item 5 will result in a perfect adherence score. The number of subjects per treatment group with perfect adherence scores will be calculated by visit and across all visits. Depending on the data, perfect adherence may be further analyzed, looking at the number of subjects per treatment group who were perfectly adherent across all visits and relationship to viral load and C_{min}.

Parent/Guardian Perception of Study Medication

Parent/guardian's attitude or perceptions of medications can impact on the acceptability of a medication to a child, affecting adherence and the subsequent drug efficacy in the pediatric population. Parent/guardian perceptions of FPV BID and FPV/RTV BID will be assessed using a Parent/Guardian Perception of Study Medication assessment administered during Weeks 2, 24 and 48/premature study discontinuation. Data from the Parent/Guardian Perception of Study Medication questionnaire will be summarized by visit for each question. Between treatment group comparisons will be made, adjusting for country if the data permit.

6.6. Pharmacokinetics

6.6.1. Bioanalysis

Plasma PK samples will be analyzed for APV, RTV and where plasma volumes allow FPV concentrations using a validated analytical method.

6.6.2. Pharmacokinetic Parameters

The GSK division of Clinical Pharmacology will conduct noncompartmental PK analysis of plasma APV and RTV concentration-time data using Winnonlin Professional, Version 3.0 (or higher), computer software (Pharsight Corporation, Mountain View, CA.)

Values for the following single-dose plasma APV PK parameters will be estimated:

- The maximum plasma concentration (Cmax) and the first time to reach Cmax (tmax) will be the actual observed values.
- The apparent terminal plasma elimination rate-constant (λz) will be estimated from log-linear regression analysis of the terminal phase of the plasma concentration-time profile. The associated apparent terminal elimination half-life (t1/2) will be calculated as $t1/2=\ln 2/\lambda z$.

- The area under the plasma concentration-time curve to the last sample time (AUClast) and to infinity (AUC0-∞) will be calculated by the log-linear trapezoidal method.
- The apparent plasma clearance (CL/F) will be calculated as Dose/AUC∞.

Values for the following steady-state plasma APV and RTV PK parameters will be estimated:

- The maximum concentration at steady-state (Cmax,ss), the first time to reach Cmax,ss (tmax,ss), the minimum concentration during a dosing interval (Cmin,ss), and the time that Cmin,ss occurs (tmin,ss) will be the actual observed values.
- The concentration at the end of a dosing interval, τ, at steady-state (Cτ,ss) will be calculated as the mean of the pre-dose and 12-hour plasma APV concentrations.
- The area under the concentration-time curve during a dosing interval, τ, at steady-state (AUCτ,ss) will be calculated by the log-linear trapezoidal method.
- The average concentration during a dosing interval, τ, at steady-state (Cavg,ss) will be calculated as AUCτ,ss/τ.
- The apparent plasma clearance at steady-state (CLss/F) will be calculated as Dose/ AUCτ,ss.

PK analysis of plasma FPV concentrations will not be conducted because were few quantifiable FPV concentrations are expected based on data in adults and older children.

Plasma APV and RTV concentration data may be also analyzed using population PK methods.

6.6.3. Statistical Analysis

6.6.3.1. Descriptive Statistics

Plasma APV, FPV and RTV concentrations will be listed by subject and planned sampling time and summarized by treatment regimen, dose (mg/kg), cohort, and planned sampling time. Plasma APV, FPV and RTV concentrations may also be summarized by treatment regimen, dose (mg/kg) and planned sampling time (combined cohorts). Plasma APV and RTV PK parameter values will be listed by subject and summarized by treatment regimen, dose (mg/kg) and cohort and may be plotted. Plasma APV and RTV PK values may also be summarized by treatment (combined cohorts). Plasma APV PK parameters collected for this study will be plotted with plasma APV PK data collected in adult subjects in FPV studies.

6.6.3.2. Assessment of Variables Correlated with Plasma APV PK

The relationship between age, body weight, sex, height, race, Baseline CD4+ percentage, Baseline plasma HIV-1 RNA concentration, treatment and steady- state plasma APV PK parameters will be examined.

6.7. Pharmacokinetics/Pharmacodynamics

The pharmacokinetic/pharmacodynamic population will consist of all subjects with baseline factors including age, body weight, height, sex, race, CD4+ cell percentage, plasma HIV-1 RNA concentration, and viral resistance data and who have at least one evaluable plasma APV trough concentration.

The association of the above mentioned baseline factors, treatment, plasma APV trough concentration, and the ratio of plasma APV trough concentration to baseline viral resistance with changes in HIV-1 RNA concentrations, CD4+ cell counts and adverse events may be explored to determine which factors are important for predicting virological response, immunologic response and the occurrence of adverse events. Categorical analysis and stepwise logistic regression analysis may be used to estimate these relationships.

6.8. Safety

No formal inferential analyses are planned. Data will be presented in summary or graphical form.

6.8.1. Adverse Events

Adverse events (AEs) will be coded and assigned system organ classifications, which will be used when summarizing the data. The verbatim text will be used in listings together with the preferred and group terms.

Summaries of treatment-emergent AEs by treatment group will be produced for all AEs, drug-related AEs, serious AEs, AEs leading to permanent discontinuation of study drug, and Grade 3/4 AEs. An adverse event is considered treatment emergent if it has onset date on or after the date of the first dose of study drug, and on or before the date of the final dose of study drug.

6.8.2. Laboratory Test Results

Summary statistics of measured results and changes from Baseline for each hematology and clinical chemistry parameter will be presented. Quartile plots for selected parameters will also be presented.

Treatment-emergent toxicity grades will be presented for each graded laboratory parameter by treatment group. A toxicity is considered treatment emergent if it is greater than the Baseline grade and if it is observed on or after the date of the first dose of study drug, and on or before the date of the final dose of study drug.

7. AEs AND SAEs

The investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol. During each treatment period, when there is a safety evaluation, the investigator or study site personnel will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol. In order to fulfill international safety reporting obligations, the investigator will include in his or her assessment any SAEs resulting from study participation (e.g., complications resulting from the taking of a blood sample).

7.1. Definition of an AE

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE **does** include a/an:

- exacerbation of a pre-existing illness.
- increase in frequency or intensity of a pre-existing episodic event or condition.
- condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- continuous persistent disease or symptoms present at Baseline that worsen following the start of the study.

An AE **does not** include a/an:

- medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social and/or convenience admissions).
- the disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the subject's condition.
- overdose of either study drug or concurrent medication without any signs or symptoms.

For ViiV Healthcare clinical trials, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

Information on managing an overdose, including drug and non-drug therapies, is described in Section 3.3.7, "Overdose and Toxicity Management".

7.2. Definition of a SAE

An SAE is any adverse event occurring at any dose that results in any of the following outcomes:

a. Death

b. A life-threatening adverse event

c. Inpatient hospitalization or prolongation of existing hospitalization

d. A disability/incapacity

e. A congenital anomaly in the offspring of a subject who received drug

f. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

g. All presumed hypersensitivity reactions to abacavir should be reported as SAEs.

Clarifications:

- "Occurring at any dose" does not imply that the subject is receiving study drug.
- Life-threatening means that the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form, might have caused death.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE.
- Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.
- "Inpatient" hospitalization means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room.
- With regard to criteria "f" above, medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

7.2.1. Events or Outcomes Not Qualifying as SAEs

The events or outcomes listed in Section 11.1, Appendix 1 will be recorded in the "Disease-Related Events" CRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes, **are not reported** to GSK as SAEs even though such event or outcome may meet the definition of SAE, **unless the following conditions apply**:

- the investigator determines that the event or outcome qualifies as an SAE under part "f" of the SAE definition (see Section 7.2, "Definition of a SAE"), or
- the event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual subject, or
- death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV related.

7.3. Lack of Efficacy as an AE or SAE

"Lack of efficacy" per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

7.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., electrocardiogram [ECGs], X-rays, vital signs) that are judged by the investigator as **clinically significant** must be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 7.1, ("Definition of an AE"), or SAE, as defined in Section 7.2, ("Definition of a SAE"). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected after study drug administration or that are present at Baseline and worsen following the start of the study are included as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study that do not worsen, are **not** included as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

7.5. Method, Frequency, and Time Period for Detecting AEs and SAEs

One of the aims of this study is to assess the safety and tolerability of FPV and the combination of FPV/RTV. The investigator (or his/her designee) should record all adverse events and serious adverse events as defined above. At each visit, after the subject's parent/guardian has had an opportunity to spontaneously mention any problems, the investigator should inquire about the occurrence of adverse events through open-ended verbal questioning of the parent/guardian. Appropriate open-ended verbal questions include:

- "How is the subject feeling?"
- "Has the subject had any (other) medical problems since his/her last visit/assessment?"
- "Has the subject taken any new medicines, other than those provided for him/her in this study, since his/her last visit/assessment?"

Care must be taken in any instance not to introduce bias when detecting AEs and/or SAEs. For this reason, the use of checklists for soliciting AEs and SAEs should be avoided.

All adverse event and serious adverse event information will be collected at each visit starting from SDV/Day 1 through to the Follow-up visit. Only serious adverse events relating to study participation will be collected by the investigator, starting from the Screening visit (Screening will be within approximately 21 days prior to Baseline/Day 1 for all subjects.) through to the initial dosing visit (SDV/Day 1 visit).

7.6. Documenting AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator must then record all relevant information regarding an AE/SAE on the CRF.

Any AE occurring during the study must be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the AE page of the CRF. SAEs that occur during the study must be documented in the subject's medical record and on the "SAE" page of the CRF.

A separate set of "SAE" pages should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same "SAE" page.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE or SAE, then the AE CRF page or "SAE" CRF page must be completed, as appropriate. A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the clinically significant abnormal laboratory finding, should be completed on AE or "SAE" CRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded. The laboratory data should either be recorded in Section 1 of the "SAE" form with the reference range and Baseline value(s) or copies of the laboratory reports and reference ranges should be sent with the "SAE" CRF pages.

The "SAE" pages of the CRF should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to GSK. It is **very important** that the investigator provide his/her assessment of causality to study drug at the time of the initial SAE report.

AEs and subject-completed questionnaires are independent components of the study. Responses to each question in the questionnaires will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

7.7. Follow-up of AEs and SAEs

All AEs and SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, GSK will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed "SAE" CRF with all changes signed and dated by the investigator.

7.8. Regulatory Reporting Requirements For SAEs

The investigator must promptly report all SAEs to GSK in accordance with the procedures detailed in Section 7.9, "Prompt Reporting of SAEs to GSK". GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, must comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

This protocol has been filed under an Investigational New Drug (IND) application with the US Food and Drug Administration (FDA). A given SAE may qualify as an IND Safety Report if the SAE is both attributable to the investigational product and unexpected. In this case, all investigators filed to the IND (and associated INDs for the same compound) will receive an Expedited Investigator Safety Report (EISR), identical in content to the IND Safety Report submitted to the FDA.

EISRs are prepared according to GSK policy and are forwarded to investigators as necessary. An EISR is prepared for a SAE that is both attributable to the investigational product and unexpected. The purpose of the EISR is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

When a site receives from GSK an Initial or Follow-up EISR or other safety information (e.g., Investigator's Brochure Supplement and local product information or the International Product Information), the responsible person according to local requirements is required to promptly notify his or her IRB or IEC.

7.9. Prompt Reporting of SAEs to GSK

SAEs must be reported promptly to GSK as described in the following table once the investigator determines that the event meets the protocol definition of an SAE.

7.9.1. Timeframes for Submitting SAE Reports to GSK

	Initial SAE Reports		**Additional Information on a Previously Reported SAE**	
Type of SAE	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hrs	"SAE" CRF pages	24 hrs	Updated "SAE" CRF pages

7.9.2. Transmission of the SAE Reports

Facsimile transmission of the "SAE" CRF is the preferred method to transmit this information to the project contact for SAE receipt. In the absence of facsimile equipment, notification by telephone is acceptable for deaths and life-threatening events, with a copy of the "SAE" CRF sent by overnight mail. For SAEs that are not deaths or life-threatening events, telephone notification, in the absence of facsimile equipment, is not acceptable. Instead, a copy of the "SAE" CRF will be sent by overnight mail. GSK will provide separately a list of project contacts for SAE receipt, fax numbers, and mailing addresses.

7.10. Post-study AEs and SAEs

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and such event(s) is (are) reasonably related to the study drug, the investigator will promptly notify GSK.

7.11. SAEs Related to Study Participation

An SAE considered related to study participation (e.g., procedures, invasive tests), even if it occurs during the pre- or post-treatment period, will be reported promptly to GSK (see Section 7.9, "Prompt Reporting of SAEs to GSK").

7.12. SAEs Involving a Non-ViiV Healthcare Product

In those instances where an SAE has occurred in a subject receiving a non-ViiV Healthcare product as a comparator or concurrent medication, the report must be sent to the appropriate project contact for SAE receipt in the same time frames as if it were a ViiV Healthcare product (see Section 7.9, "Prompt Reporting of SAEs to GSK").

8. STUDY ADMINISTRATION

8.1. Data Collection

All subjects who are screened for the trial must be documented. The screening pages of the CRF will be used for this purpose. Additionally, each site will keep a log of subjects who are screened and not registered. Further information on the use of this log can be found in the Study Reference Manual.

GSK will provide full CRFs for each subject. At site - all data on the CRFs must be entered legibly in black ink or typed, in English. Amendments and errors on the CRFs should **NOT** be erased, covered with correction fluid or white-out, or completely crossed out. Instead, a single line should be drawn through the error and the correction initialed and dated by the investigator or his/her authorized designee. In those countries where the Committee for Proprietary Medicinal Products (CPMP) guidelines are accepted by law, an explanatory note for the change should also be written on the CRF. The CRF must be currently maintained and should never bear the study participant's name. Subjects will be identified by subject number and treatment number only.

The investigator or designee must record all required subject data using the previously specified data collection method defined by GSK. An explanation must be documented for any missing data. Entering 'ND', 'UNK' or 'NA' should identify any requested information, which is not obtained or unanswerable. The investigator must sign and date a declaration on the CRF attesting to his/her responsibility for the quality of all data recorded and that the data represents a complete and accurate record of each subject's participation in the study. Details and procedures for the completion of the CRFs are specified in the Study Procedures Manual.

Pages will be reviewed by the monitor and clarified in accordance with the GSK protocol specific Review and Data handling guidelines. Original CRFs will be returned to Data Management for processing and copies will be retained by the investigator.

CRF data will be converted to electronic form via a data entry application and loaded into a quality controlled database.

Validation checks will be performed on the database. Data failing any check will be flagged for output on an approved hard copy form: Data query (DQ) form or via the electronic data query system (eDQ). If the query cannot be resolved in house (ie: is not subject to a standard clarification agreement (SCA) or a data processing error), the original query form is sent to the GSK monitor and/or study site investigator for query resolution. In such cases the investigator is requested to sign and date any explanation or correction. This signed copy is the original DQ. On return, the database will be updated appropriately and the original DQ stored (and eventually archived) with the original CRF. The database will be subject to agreed Quality Control checks before authorization and database lock.

Data management should ensure the completion of the protocol data specifications, which are supplied to an approved central laboratory. A data manager will receive laboratory study files upon an agreed method of transfer (ie: electronically or via diskette) as noted in the specification package from the central laboratory. The central laboratory is responsible for resolving and documenting validation discrepancies with study site personnel and/or project team members. Discrepancies identified during data management validation will be communicated to the central lab.

All data requiring analysis retrieved from the site and confirmed will be entered into a quality controlled database. The data will subsequently be analyzed according to the methods outlined in Section 6, "Data Analysis Methods."

8.2. Regulatory and Ethical Considerations

8.2.1. Notification of Primary Care Physician

If agreed by the subject's parent/guardian, the investigator should notify the subject's primary care physician (if applicable) of the subject's participation in the study. The primary care physician may contact the investigator for any further information regarding the subject's participation in the study.

8.2.2. Regulatory Authority Approval

GSK will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulations prior to a site initiating the study in that country.

8.2.3. Ethical Conduct of the Study and Ethics Approval

The study will be conducted in accordance with "good clinical practice" (GCP) and all applicable regulations, including, where applicable, the Declaration of Helsinki.

It is the investigator's responsibility to ensure that this protocol, the site's informed consent form, and any other information (e.g., advertisements or information that supports or supplements the informed consent) is reviewed and approved by the appropriate IEC or IRB. GSK must receive copies of the IEC or IRB approval and the approved informed consent materials before shipment of study drug.

If, during the study, it is necessary to amend either the protocol or the informed consent form, the investigator is responsible for ensuring the IEC or IRB reviews and approves these amended documents. IEC or IRB approval of the amended informed consent form must be obtained before new subjects consent to take part in the study using this version of the form. Copies of the IEC or IRB approval of the amended informed consent form and the approved amended informed consent form must be forwarded to GSK as soon as available.

8.2.4. Subject Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

If the informed consent form is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended informed consent form by the IEC or IRB and use of the amended form.

Per protocol amendment 12: Assent forms will also be obtained from subjects still enrolled in the study as of Nov 1, 2019.

8.2.5. Investigator Reporting Requirements

In accordance with applicable local regulatory requirements, the investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her site and notification of study closure to the IRB or IEC. Such periodic safety updates and notifications are the responsibility of the investigator and not of GSK.

8.3. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov.

8.4. Study Monitoring

In accordance with applicable regulations, GCP, and GSK procedures, monitors will periodically contact the site, including conducting on-site visits. The extent, nature and

frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrolment rate.

During these contacts, the monitor will:

- check and assess the progress of the study
- review study data collected
- conduct Source Document Verification
- identify any issues and address their resolution

This will be done in order to verify that the:

- data are authentic, accurate, and complete
- safety and rights of subjects are being protected
- study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the monitor will also contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel.

At study closure, monitors will also conduct all activities as indicated in Section 8.6, "Study and Site Closure".

The monitor is also responsible for reviewing parent/guardian-completed health outcome questionnaires. The monitor will review the parent/guardian-completed health outcome questionnaires for extraneous written comments that could indicate possible AEs. Information collected in the CRF and in the parent/guardian-completed health outcome questionnaires are independent components of this study. Except for header section information (e.g., subject number, treatment number, visit date), and other information as defined in the standard clarification agreement (SCA), neither the monitor nor the investigator will reconcile data recorded on the parent/guardian-completed health outcome questionnaire with data recorded in the CRFs. Parent/guardian-completed health outcome questionnaires generally serve as the source document; therefore, unless otherwise specified in the source document verification agreement, no other source document is available for data validation.

8.5. Quality Assurance

At its discretion, GSK may conduct a quality assurance audit of this study. If such an audit occurs, the investigator agrees to allow the auditor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor to discuss findings and any relevant issues.

In addition, regulatory agencies may conduct a regulatory inspection of this study. If such an inspection occurs, the investigator agrees to allow the inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the inspector to discuss findings and any relevant issues.

8.6. Study and Site Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator, as appropriate:

- Return of all study data to GSK.
- Data clarifications and/or resolutions.
- Accountability, reconciliation, and arrangements for unused study drugs.
- Review of site study records for completeness.
- Return of treatment codes to GSK.
- Shipment of pharmacokinetic and/or pharmacodynamic samples to assay laboratory

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time and for reasons including, but are not limited to, safety or ethical issues or severe non-compliance. If such action is taken, GSK will discuss this with the investigator (including the reasons for taking such action) at that time. GSK will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB or IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused study drugs in accordance with GSK procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and GSK.

8.7. Records Retention

In accordance with applicable regulatory requirements, following closure of the study, the investigator will maintain a copy of all site study records in a safe and secure location. GSK will inform the investigator of the time period for retaining these records in order to comply with applicable regulatory requirements.

8.8. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

GSK will provide the investigator with a copy of the CRF data collected from the site. When a clinical study report is completed, GSK will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subject.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

8.9. Information Disclosure and Inventions

Ownership:

All data and records provided by GSK or generated during the study (other than a subject's medical records) and all inventions discovered in the course of conducting the study are the property of ViiV Healthcare. If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:

The investigator and other study site personnel will keep confidential any information provided by GSK (including this protocol) related to this study and all data and records generated in the course of conducting the study, and will not use the information, data, or records for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or study site personnel; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject, or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with

this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:

For multi-center studies, the first publication or disclosure shall be a complete, joint multi-center publication or disclosure that GSK will coordinate. Thereafter, any secondary publications will reference the original publication(s).

The investigator shall inform GSK of any publication plans. Prior to submitting for publication, presenting, using for instructional purposes or otherwise disclosing the results of the study, the investigator shall allow GSK a period of at least thirty (30) days or, for abstracts, at least five (5) working days, to review the proposed publication or disclosure prior to its submission for publication or other disclosure. Publications or disclosures of study results shall not include other, confidential information of GSK's. If the proposed publication/disclosure risks GSK's ability to patent any invention related to the study, the publication or disclosure will be modified or delayed, at the investigator's option, a sufficient time to allow GSK to seek patent protection of the invention. This statement does not give GSK any editorial rights over the content of a publication or disclosure, other than to restrict the disclosure of GSK's confidential information. If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

8.10. External Review Committee

As per Amendment 9, an External Review Committee (ERC) will be established and utilized in this study. The ERC will provide external oversight of study conduct and medical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for ERC review is described in the charter, which is available upon request.

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10. TABLES

Revised Flow Chart of Clinical Scheduled Assessments (Per Amendments 5 and 7)

CLINCAL EVALUATION	Screening Visit [1]	Single Dose Visit [2]	Day 1 (Baseline) [3]	Week										
				2	4	8	12	16	24	36	48	Every 12 weeks thereafter	With-drawal	Follow-up [4]
Written Informed Consent	✓													
Inclusion/Exclusion Criteria	✓													
Demography (date of birth, sex, and race)	✓													
HIV Risk Factors	✓													
CDC HIV-1 Classification	✓		✓											
Current Medical Conditions			✓											
Body Weight , Height and Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Head Circumference	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior Antiretroviral Therapy History		✓	✓											
Background Antiretroviral Therapy		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concurrent Medications/Blood Products		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HIV-associated Conditions			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Experience Surveillance	✓ [5]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adherence Questionnaire			✓	✓			✓		✓		✓		✓	
Parent/Guardian Perception of Study Medication				✓					✓		✓		✓	

1. Screening will be within approximately 21 days prior to Baseline/Day 1 for all subjects. At screening only, the evaluation of the hematology, clinical chemistry and liver function tests may be undertaken at a local accredited laboratory at the discretion of the investigator and with approval of GlaxoSmithKline.
2. **SDVs are no longer needed for Cohort 1 Arm A and Cohort 2 Arm A.**.
3. Subjects will initiate multiple dosing on Day 1 (Baseline)
4. 4 weeks after permanent study drug discontinuation
5. Record serious adverse events related to study participation only during screening.

Revised Flow Chart of Laboratory Scheduled Assessments (Per Amendments 5 and 7)

LABORATORY EVALUATION[2]	Screening Visit[1]	Single Dose Visit	Day 1 (Baseline)	Week										
				2	4	8	12	16	24	36	48	Every 12 weeks thereafter[12]	Withdrawal	Follow-up
Lipids [3]			✓						✓		✓	✓	✓	
Hematology [4]	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓
Clinical Chemistry and Liver Function Tests [5]	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓
Lymphocyte subsets	✓		✓		✓		✓		✓	✓	✓	✓	✓	
Quanatitative plasma HIV-1 RNA PCR	✓		✓		✓		✓		✓	✓	✓	✓	✓	
Plasma for storage [6]			✓				✓		✓	✓	✓	✓	✓	
Pharmacokinetic Sampling[10, 11]		✓[7]		✓[8]		✓[9]	✓	✓	✓	✓	✓	✓		
HIV-1 resistance testing[13]	✓													

1. Screening will be within approximately 21 days prior to Baseline/Day 1 for all subjects.
2. Laboratory assessments for all cohorts are prioritized as follows: hematology, chemistry, PK, plasma HIV-1 RNA PCR, lymphocyte subsets, HIV-1 RNA resistance testing, lipids, and plasma for storage.
3. Lipid measures include: triglycerides and total, high density lipoprotein (HDL), and LDL cholesterol.
4. Hematology includes: hemoglobin, WBC with differential, MCV and platelet count.
5. Clinical chemistry panel and transaminase levels (sodium, potassium, AST, ALT, total bilirubin, creatinine, albumin, glucose, alkaline phosphatase, and CPK).
6. Plasma collected for storage where permitted by blood volume restrictions at Day 1 and Week 12, 24, 36, 48, every 12 weeks thereafter and Withdrawal. This sample may be used for HIV-1 resistance testing in subjects experiencing virologic failure.
7. SDV plasma PK sampling no longer required for Cohort 1 Arm A and Cohort 2 Arm A.
8. Week 2: Plasma PK sampling over 8-12 hours (at 0 [pre-dose], 1, 2, 4, 6, 8, and 12 hours (12 hour sample optional) post-dosing for Cohort 2 Arm A subjects and over 4 hours (at 0 [pre-dose], 2 and 4 hours) post-dosing for subjects in Cohort 1 Arm A
9. Week 8: Plasma PK sampling over 8-12 hours (at 0 [pre-dose], 1, 2, 4, 6, 8, and 12 hours (12 hour sample optional) post-dosing for subjects in Cohort 1 Arm A.
10. Samples for APV/RTV trough concentration determination collected 12 hours after the last dose at Week 8 (Cohort 2 Arm A only) and Weeks 12, 16, 24, 36, 48, and every 12 weeks thereafter (both cohorts). In consultation with the investigator, GSK may discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis once a subject has reached and exceeded 2 years and has initiated the 23/3 mg/kg BID dosing regimen after Week 48. Any further dosing changes would follow the approved dosing recommendations without PK sampling, including a transition to FPV/RTV 18/3 mg/kg BID at 6 years.
11. Samples for unbound APV concentration evaluation should be collected 12 hours after the last dose at Week 2 (Cohort 1 Arm A), Week 8 (Cohort 2 Arm A), Week 16 (both cohorts), and Week 36 (Cohort 1 Arm A).
12. After Protocol Amendment 11 became effective and after the last enrolled subject had completed their 48 week visit, PK sample collection was discontinued.
13. A sample for HIV-1 RNA resistance testing may be collected at Screening at the investigator's discretion if needed to guide selection of background ART.

11. APPENDICES

11.1. Appendix 1: 1994 CDC Revised Classification System for HIV Infection in Children < 13 years of Age

Reference – 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994: 43 (No. RR-12): 1-10.

Pediatric Human Immunodeficiency Virus (HIV) Classification[1]

Immunologic Categories	Clinical Categories			
	N: No signs/symptoms	A: Mild signs/symptoms	B:[2] Moderate signs/symptoms	C:[2] Severe signs/symptoms
1. No evidence of suppression	N1	A1	B1	C1
2. Evidence of moderate suppression	N2	A2	B2	C2
3. Severe suppression	N3	A3	B3	C3

1. Children whose HIV infection status is not confirmed are classified by using the above grid with a letter E (for perinatally exposed) placed before the appropriate classification code (e.g., EN2).
2. Both Category C and lymphoid interstitial pneumonitis in Category B are reportable to state and local health departments as acquired immunodeficiency syndrome.

Immunologic Categories Based on Age-Specific CD4+ T-Lymphocyte Counts and Percent of Total Lymphocytes

	Age of Child					
	< 12 Months		1-5 Years		6-12 Years	
Immunologic Categories	µl	(%)	µl	(%)	µl	(%)
1. No evidence of suppression	≥1,500	(≥ 25)	≥1,000	(≥ 25)	≥500	(≥ 25)
2. Evidence of moderate suppression	750-1,499	(15-24)	500-999	(15-24)	200-499	(15-24)
3. Severe suppression	< 750	(< 15)	< 500	(< 15)	< 200	(< 15)

Box 2. Clinical Categories for Children with Human Immunodeficiency Virus (HIV) Infection

CATEGORY N: NOT SYMPTOMATIC

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

CATEGORY A: MILDLY SYMPTOMATIC

Children with two or more of the conditions listed below but none of the conditions listed in Categories B and C.

- Lymphadenopathy (0.5 cm at more than two sites: bilateral - one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

CATEGORY B: MODERATELY SYMPTOMATIC

Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include but are not limited to:

- Anemia (< 8gm/dl), neutropenia (< 1,000/mm^3) or thrombocytopenia (< 100,000/mm^3) persisting $\geq$30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children >6 months of age
- Cardiomyopathy
- Cytomegalovirus infection with onset before one month of age
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (more than two episodes within one year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before one month of age
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before 1 month of age
- Varicella, disseminated (complicated chickenpox)

CATEGORY C: SEVERELY SYMPTOMATIC

Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome (10), with the exception of LIP (Box 3).

Box 3. Conditions Included in Clinical Category C for Children Infected with Human Immunodeficiency Virus (HIV)
CATEGORY C: SEVERELY SYMPTOMATIC
• Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a two-year period) of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
• Candidiasis, esophageal or pulmonary (bronch, trachea, lungs)
• Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
• Cryptococcosis, extrapulmonary
• Cryptosporidiosis or isosporiasis with diarrhea persisting greater than one month
• Cytomegalovirus disease with onset of symptoms at age greater than one month (at a site other than liver, spleen, or lymph nodes)
• Encephalopathy (at least one of the following progressive findings present for at least two months in the absence of a concurrent illness other than HIV infection that could explain the findings): A. Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; B. Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children < two years of age); C. Acquired symmetric motor deficit manifested by two or more of the following: 1. Paresis 2. Pathologic reflexes 3. Ataxia 4. Gait disturbance
• Herpes simplex virus infection causing a mucocutaneous ulcer that persists for greater than one month, or bronchitis, pneumonitis, or esophagitis for any duration affecting a child greater than one month of age
• Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
• Kaposi's sarcoma
• Lymphoma, primary, in brain
• Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of b-cell or unknown immunologic phenotype
• Mycobacterium tuberculosis, disseminated or extrapulmonary
• Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
• Mycobacterium avium complex or Mycobacterium kansasii, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
• Pneumocystis carinii pneumonia
• Progressive multifocal leukoencephalopathy

• Salmonella (nontyphoid) septicemia, recurrent
• Toxoplasmosis of the brain with onset at greater than one month of age
• Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: A. Persistent weight loss greater than 10% of baseline , or B. Downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child greater than or equal to one year of age ; or C. Less than 5th percentile on weight-for-height chart on two consecutive measurements. Greater than or equal to 30 days apart PLUS (1) chronic diarrhea (i.e., at least two loose stools per day for greater than or equal to 30 days; OR (2) documented fever (for greater than or equal to 30 days, intermittent or constant)

11.2. Appendix 2: Declaration of Helsinki (Only Applicable to European Sites)

Initiated: 1964 17.C Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles
for
Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

A Introduction / I.Basic Principles / II.Medical Research Combined with Medical Care / III. Non-Therapeutic Biomedical Research / Other Options

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words: "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration. Comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interest of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the Patient to participate in the study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I. 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

11.3. Appendix 3: Grading of Laboratory Test Abnormalities - DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant[1,2], 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant[1,2], 1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

Continued

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*
Infant[1,2], 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *1.32 – 1.46 mmol/L*	7.0 – 8.4 g/dL *1.09 – 1.31 mmol/L*	6.0 – 6.9 g/dL *0.93 – 1.08 mmol/L*	< 6.00 g/dL *< 0.93 mmol/L*
Infant[1,2], 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *1.47 – 1.63 mmol/L*	8.0 – 9.4 g/dL *1.24 – 1.46 mmol/L*	7.0 – 7.9 g/dL *1.09 – 1.23 mmol/L*	< 7.00 g/dL *< 1.09 mmol/L*
Infant[1,2], 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *1.86 – 2.02 mmol/L*	10.0 – 11.9 g/dL *1.55 – 1.85 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L*	< 9.0 g/dL *< 1.40 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
				Continued
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/Dl *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN[2]	2.6 – 5.0 x ULN[2]	5.1 – 10.0 x ULN[2]	> 10.0 x ULN[2]
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)				
Adult and Pediatric >14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant[1,2], ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant[1,2], ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant[1,2], < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
				Continued

LABORATORY					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	Infant[1,2], < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)		NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)		NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)					
	Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
	Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase		3.0 – 5.9 x ULN[2]	6.0 – 9.9 x ULN[2]	10.0 – 19.9 x ULN[2]	≥ 20.0 x ULN[2]
Creatinine		1.1 – 1.3 x ULN[2]	1.4 – 1.8 x ULN[2]	1.9 – 3.4 x ULN[2]	≥ 3.5 x ULN[2]
Glucose, serum, high					
	Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
	Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low					
	Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
	Infant[1,2], < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*

Continued

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*

Continued

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random Collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo -< 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

1. Values are for term infants.
2. Use age and sex appropriate values (e.g., bilirubin), including preterm infants

11.4. Appendix 4: Grading of Clinical Adverse Experiences - DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Continued

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Unintentional weight loss		NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION					
Infection (any other than HIV infection)		Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS					
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)		Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)					
	Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
	Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children >10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	> 140 – 159 mmHg systolic OR > 90 – 99 mmHg diastolic	> 160 – 179 mmHg systolic OR > 100 – 109 mmHg diastolic	> 180 mmHg systolic OR > 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay **– Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with <24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without Secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care Functions
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support Indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care Functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, Mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA

Continued

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

1. **Basic Self-care Functions** – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
2. **Basic Self-care Functions** – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
3. **Usual Social & Functional Activities** – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.
4. **Usual Social & Functional Activities** – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

11.5. Appendix 5: Dosing Table for FPV Oral Suspension

FPV 45 mg/kg BID (<2 years old)

Weight (kg)	Dose (mg): 45 mg/kg	Amount of 50 mg/mL suspension (mL) per Dose	No. Bottles (225mL) Needed Per Month
3	135	2.7	**1**
3.5	158	3.2	**1**
4	180	3.6	**1**
4.5	203	4.1	**2**
5	225	4.5	**2**
5.5	248	5.0	**2**
6.0	270	5.4	**2**
6.5	293	5.9	**2**
7.0	315	6.3	**2**
7.5	338	6.8	**2**
8	360	7.2	**2**
8.5	383	7.7	**3**
9	405	8.1	**3**
9.5	428	8.6	**3**
10	450	9.0	**3**
10.5	473	9.5	**3**
11	495	9.9	**3**
11.5	518	10.4	**3**
12	540	10.8	**3**
12.5	563	11.3	**4**
13	585	11.7	**4**

FPV 60 mg/kg BID (<2 years old)

Weight (kg)	Dose (mg): 60 mg/kg	Amount of 50 mg/mL suspension (mL) per Dose	No. Bottles (225mL) Needed Per Month
3	180	3.6	1
3.5	210	4.2	2
4	240	4.8	2
4.5	270	5.4	2
5	300	6	2
5.5	330	6.6	2
6.0	360	7.2	2
6.5	390	7.8	3
7.0	420	8.4	3
7.5	450	9	3
8	480	9.6	3
8.5	510	10.2	3
9	540	10.8	3
9.5	570	11.4	4
10	600	12	4
10.5	630	12.6	4
11	660	13.2	4
11.5	690	13.8	4
12	720	14.4	4
12.5	750	15	5
13	780	15.6	5

As per Section 3.3.5.1, for subjects exceeding 6 years of age, the following weight-based dosing for FPV should be used:

FPV 18 mg/kg BID (>6 years old)

Weight (kg)	Dose (mg): 18 mg/kg	Amount of 50 mg/mL suspension (mL) per Dose	No. Bottles (225mL) Needed Per Month
25	450	9	3
26	468	9.4	3
27	486	9.7	3
28	504	10.1	3
29	522	10.4	3
30	540	10.8	3
31	558	11.2	3
32	576	11.5	4
33	594	11.9	4
34	612	12.2	4
35	630	12.6	4
36	648	13	4

Weight (kg)	Dose (mg): 18 mg/kg	Amount of 50 mg/mL suspension (mL) per Dose	No. Bottles (225mL) Needed Per Month
37	666	13.3	4
38	684	13.7	4

11.6. Appendix 6: Dosing Table for RTV Oral Solution, Powder, Capsules and Tablets

RTV Oral Solution 7 mg/kg BID (<2 years old)

Weight (kg)	Dose (mg): 7 mg/kg	Amount of 80 mg/mL solution (mL) per Dose
3	21	**0.26**
3.5	24.5	**0.31**
4	28	**0.35**
4.5	31.5	**0.39**
5	35	**0.44**
5.5	38.5	**0.48**
6.0	42	**0.53**
6.5	45.5	**0.57**
7.0	49	**0.61**
7.5	52.5	**0.66**
8	56	**0.70**
8.5	59.5	**0.74**
9	63	**0.79**
9.5	66.5	**0.83**
10	70	**0.88**
10.5	73.5	**0.92**
11	77	**0.96**
11.5	80.5	**1.01**
12	84	**1.05**
12.5	87.5	**1.09**
13	91	**1.14**

As per Section 3.3.5.1, for subjects exceeding 6 years of age, the following weight-based dosing for RTV oral solution should be used:

RTV Oral Solution 3 mg/kg BID (>6 years old)

Weight (kg)	Dose (mg): 3 mg/kg	Amount of 80 mg/mL suspension (mL) per Dose
25	75	0.9
26	78	1.0
27	81	1.0
28	84	1.1
29	87	1.1
30	90	1.1
31	93	1.2
32	96	1.2
≥33[a]	99	1.2

Subjects who are ≥33kg and are receiving RTV oral solution at a dose of 3mg/kg should remain at the recommended optimal dose for ≥33kg (99mg BID for 3mg/kg dosing) even as their weight increases above 33kg. The maximum allowed total daily dose for RTV oral solution is 200mg.

The following weight-based dosing for RTV oral powder can be used if RTV oral solution is not available. For doses less than 100 mg or partial doses between 100 mg increments: Mix 1 packet/sachet of oral powder (100 mg) with 9.4 mL of liquid (such as water, chocolate milk, or infant formula) in a mixing cup. Once mixed, use an oral dosing syringe to measure and administer the prescribed volume. Once the powder is mixed, the dosage must be consumed within 2 hours. Discard any mixture remaining in the mixing cup.

RTV Oral Powder (100 mg sachets) 3 mg/kg BID (>6 year old)

Weight (kg)	Dose (mg): 3 mg/kg	Amount of liquid per dose once the sachet with 100 mg powder is dissolved in 9.4 mL of liquid (10 mg/mL)
25	75	7.5 mL
26	78	7.8 mL
27	81	8.1 mL
28	84	8.4 mL
29	87	8.7 mL
30	90	9.0 mL
31	93	9.3 mL
32	96	9.6 mL
≥33[a]	99	10.0 mL

As per Section 3.3.5.1, for subjects exceeding 6 years of age who weigh ≥33kg and can swallow capsules or tablets whole, the following weight-based dosing for RTV oral 100 mg tablets or 100 mg capsules should be used: 1 capsule or tablet (dose of 100 mg) BID. The maximum allowed total daily dose of RTV capsules or tablets is 200 mg.

11.7. Appendix 7: Country Specific Requirements

Country-Specific Requirements

No country-specific requirements exist.

11.8. Appendix 8: Protocol Amendment 1

A summary of protocol changes for Amendment 1 are listed below. These changes were incorporated into the protocol at the time Amendment was issued and are incorporated into Amendment 7.

STUDY DESIGN CHANGES

- To change the lower age limit for subject participation from 6 weeks to 4 weeks.
- To revise the study design.
- To revise the stratification within the two age cohorts.
- To revise the details of the study population in line with the revised study design.
- To describe study measurements and evaluations.
- To revise the study objectives.
- To revise the study endpoints.
- To revise details of subject allocation to treatment groups.
- To add details of screening and enrolment procedures.
- To reschedule the administration of the adherence questionnaire from week 4 to week 2.
- To revise details of scheduled safety assessments and selected safety laboratories.
- To revise details of planned interim analysis.
- To revise details of dose volumes required.
- To revise the flow chart of scheduled assessments.
- To revise the timelines for cohort recruitment and Dosing of Subjects with GW433908 and / or GW433908/RTV.
- To revise the rash management table.

ADDITION OF NEW DATA FROM OTHER FPV STUDIES

- To update information pertaining the phase III pivotal adult studies.
- To update study background and rationale.
- To update the FPV neonatal toxicology section.

CHANGES RELATING TO DOSE SELECTION AND PHARMACOKINETIC ASSESSMENTS

- To revise the dose selection for FPV and RTV.
- To describe the revised starting and maximum doses of FPV and RTV.
- To describe study drug dose adjustment criteria.

- To revise the definition of a study drug overdose.
- To revise the details of PK sampling and bioanalysis.
- To change details of analytes for PK samples to allow for analysis and RTV concentrations and to clarify the concentrations of FPV will only be measured where plasma volumes allow.
- To update the analysis plan for PK samples collected.
- To revise the target plasma APV exposures.

OTHER CHANGES

- To revise subject management options.
- To include details of additional references.
- To add additional items the List of Abbreviations.
- To update the list of concurrent medications and non drug therapies.

11.9. Appendix 9: Protocol Amendment 2

There was one change to the protocol as a result of Protocol Amendment 2. Exclusion criteria number 8 was modified as follows:

Original Wording:

Any acute laboratory abnormality at screen which, in the opinion of the investigator, should preclude the subject's participation in the study of an investigational compound. Any Grade 4 laboratory abnormality at screen will exclude a subject from study participation.

Revised Wording:

Any acute laboratory abnormality at screen which, in the opinion of the investigator, should preclude the subject's participation in the study of an investigational compound. Any Grade 3 or higher laboratory abnormality at screen will exclude a subject from study participation.

This change is incorporated into Amendment 7.

11.10. Appendix 10: Protocol Amendment 3

A summary of protocol changes for Amendment 3 are listed below. These changes were incorporated into the protocol at the time Amendment 3 was issued and are thus incorporated into Amendment 7.

1. To add the revised dose recommendation for Cohort 1A (PI-naïve or PI-experienced subjects 6 months to < 2 years of age receiving boosted GW433908 (908) + RTV). The revised dose recommendation is 908 45 mg/kg BID + RTV 7 mg/kg BID, which represents a 25% increase from the original dose of 908 30 mg/kg BID and 16% increase from the original RTV 6 mg/kg BID dose. Consequently, screening was re-opened to PI- naïve and PI-experienced subjects to enrol within Arm A2 of Cohort 1A. Any further subjects randomized into Cohorts 1A Arm A2 and receiving 908 oral suspension + RTV should be placed on the revised dosing recommendation listed above. It is recommended that subjects already randomized should remain on their current 908+RTV BID dosing regimen.
2. Reason for change: Following PK analysis of the first 9 subjects from Cohort 1A1, a revised dose recommendation was determined and communicated to the sites. It is now being added to the protocol for completeness.
3. To update information regarding closing of the unboosted GW433908 Arm B for Cohort 1 pending discussions with regulatory authorities around dosing volumes.
4. Reason for change: In the original study design, Cohort 1 Arm B would open to enrolment following determination of the revised dose for Cohort 1 Arm A. Due to concerns regarding dosing volumes, Cohort 1 Arm B remains closed until discussions with regulators have been completed.
5. To amend the current study design to allow the simultaneous enrolment of Cohort 2 Arms A and B.
6. Reason for change: Due to the increasing non-availability of RTV OS in several participating countries, we are allowing the parallel enrolment of Arm A and Arm B of Cohort 2 to facilitate enrolment in countries where the RTV solution is no longer available. Consequently, two SDVs will occur for subjects now enrolling into Arm B to ensure an appropriate starting unboosted FPV dose at Day 1, and to determine a boosted dose should the subject elect to switch to the boosted regimen after Week 2. Additionally, the SDV visits for Cohort 2 Arm A have been amended to only collect boosted FPV serial PK samples.
7. To clarify the statement that subjects enrolled in Cohort 1B or Cohort 2B may have their treatment switched from the 908 BID regimen to the 908/RTV BID regimen at any time after the Week 2 visit by adding the caveat “only in countries where RTV solution is locally available for long-term use”.
8. Reason for change: After the study started RTV oral solution became unavailable in some participating countries.
9. To update the Study Drugs and Dosages and Dosage Regimen Adjustment Criteria
10. Reason for change: To provide updated information per protocol amendment No 3.

11. To add information regarding continuation of subjects in APV20002 past Week 48.
12. Reason for change: To provide details surrounding the continuation of study visits and laboratory assessments past Week 48. Subjects may remain in the study until 908 oral suspension is locally available, or until the subject is no longer deriving any clinical benefit from 908.
13. To provide clarification regarding the maximum age allowed for each cohort.
14. Reason for change: The existing inclusion criteria number 1 was unclear as to which study visit the age criteria applied. Inclusion criteria 1 has been revised to state that Cohort 1 (6 months - <2 years) subjects must be <2 years of age at the Week 2 visit therefore the maximum age at screening is 22 months, and Cohort 2 (4 weeks - <6 months) subjects must be <6 months of age at the Week 2 visit, therefore the maximum age at screening is 4 months.
15. To update the protocol with current information and to correct minor inconsistencies.

11.11. Appendix 11: Protocol Amendment 4

Protocol Amendment 4 was sent to the FDA for review and comment but because of the outcome of discussions with FDA, this amendment was not sent to the sites for implementation. The change suggested in Amendment 4 is also incorporated into Amendment 5.

This amendment consisted of the following changes:

1. To add information regarding removal of the unboosted GW433908 Arm B for Cohort 1.

   Reason for change: Due to the required increase in 908 dose in Cohort 1A (6 months to 2 years of age) to 45 mg/kg BID, the unboosted dose would have also increased from 15 mg/kg BID to 22.5 mg/kg BID and resulted in unacceptable dosing volumes for these children. Based on the weight range of the currently enrolled subjects in Cohort 1A (6 kg to 12.6 kg, range 9 months to 2 years of age) and using the CDC weight for age percentile growth charts (6 kg to 13.4 kg), the required dosing volumes for the unboosted 908 dose(s) is estimated to be in the range of 10.8 mls to 24.1 mls per dose for Cohort 1B. Physician feedback has indicated that these dosing volumes would lead to unacceptably low levels of adherence in this age group.

11.12. Appendix 12: Protocol Amendment 5

Title: A 48 Week Phase II, Open-label, 2-cohort, Multicentre Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of GW433908 and GW433908/RTV When Administered to HIV-1 Infected Protease Inhibitor (PI) Naïve and PI-Experienced Pediatric Subjects aged 4 weeks to <2 years.

This format 2 protocol amendment will apply to all study sites.

This amendment is considered substantial since the changes may impact the safety of the subjects and the conduct/management of the study.

This amendment is being implemented to defer the enrolment of subjects in the unboosted FPV cohorts (Cohort 1 Arm B and Cohort 2 Arm B), to increase the dose of FPV at the Week 2 visit and revise the PK visits and sampling times for subjects in Cohort 1 Arm A (FPV/RTV BID), to include trough PK samples to determine the concentration of unbound APV, to revise the doses given to Cohort 2 Arm A at the single dose visit, to revise the list of excluded concurrent medications to remove rifabutin and phenytoin, and to update the DAIDS toxicity grading tables (2004), information on rash, abacavir hypersensitivity reaction, background information, and to correct minor inconsistencies in the protocol. As all new sites will be receiving this protocol and amendments for the first time, the content and organization of the protocol were also updated and revised to simplify and improve clarity.

This amendment consists of the following changes:

1. Defer the enrolment of subjects in the unboosted FPV cohorts (Cohort 1 Arm B and Cohort 2 Arm B)
2. Reason for change: Enrolment into Cohort 1 Arm B and Cohort 2 Arm B is deferred until serial PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.
3. Increasing the FPV dose to 60 mg/kg at the Week 2 visit for subjects in Cohort 1 Arm A only.
4. Reason for change: Data from five 6 months to <2 year old subjects who received the revised dose of FPV 45 mg/kg BID + RTV 7 mg/kg BID were compared with the historical adult population (based on a FPV 700 mg BID + RTV 100 mg BID regimen and an average weight of 77kg). Despite an approximate 5-fold increase in FPV and RTV doses, plasma APV AUC(0-τ) was approximately 48% lower, Cmax 26% lower, and Cτ 29% lower in the pediatric subjects. In addition, high APV and RTV CL/F values were observed in these 5 pediatric subjects suggesting that children 6 months to <2 years old may require higher doses of FPV and RTV. Therefore new subjects will increase the FPV dose from 45 mg/kg BID to 60 mg/kg BID with RTV 7 mg/kg BID after the PK evaluations at the Week 2 visit.

5. Revision to the PK visits and sampling times for subjects in Cohort 1 Arm A and the addition of trough PK samples to determine the concentration of unbound APV for all subjects.
6. Reason for change: Subjects in Cohort 1 will start at baseline receiving FPV 45 mg/kg BID + RTV 7 mg/kg BID, and a "mini" PK profile will be conducted over 4 hours at Week 2 to confirm adequate exposure after attaining steady-state. The dose of FPV will be then be increased to 60 mg/kg BID + RTV 7 mg/kg BID after the Week 2 PK, and serial PK sampling will be conducted over 8-12 hours at Week 8 to confirm the target exposure after attaining steady-state.
7. Current PK data from children <2 years old in APV20002 is highly variable. Since subjects who are <2 years old may have reduced protein binding, it is possible that these pediatric subjects may achieve therapeutic plasma unbound APV concentrations even if plasma total APV concentrations are below target when compared to adult exposure. Therefore, measuring plasma unbound APV concentrations may help to determine dosing recommendations at acceptable dosing volumes.
8. The single doses administered in Cohort 2 Arm A SDV changed from FPV 30 mg/kg and RTV 6mg/kg to FPV 45 mg/kg and RTV 7 mg/kg to be aligned with dosing in Cohort 1 Arm A.
9. Revisions to the concurrent medications, specifically removing rifabutin and phenytoin from the list of excluded medications.
10. Updated information on rash and abacavir hypersensitivity reaction
11. Updated DAIDS table for the grading of adult and pediatric adverse events to the 2004 version.
12. Updated background information, removal of redundant wording, and correction of minor inconsistencies throughout the protocol.

Summary of Primary Changes for Amendment 5

Section 1 Introduction

- Section 1.1 Backgrond and Section 1.2 Rationale were updated with current information, reorganized, and condensed.
- Section 1.3 Fosamprenavir was condensed, Section 1.3.1 FPV Neonatal Toxicology was revised with current information and condensed, and Section 1.3.2 FPV Pediatric Clinical Data was added.
- Section 1.4 Ritonavir, Section 1.5 Abacavir, and Section 1.6 Lamivudine were updated and condensed.

Section 2 Study Objectives and Endpoints

- Section 2.1 Study Objectives and Section 2.2 Study Endpoints were revised to indicate which of the objectives and endpoints are deferred as a result of the deferral of the unboosted FPV Arm B cohorts. One new primary study endpoint was added: Plasma unbound APV $C_{\tau,ss}$ and percent protein binding

Section 3 Investigational Plan

- Section 3.1 Study Design
  - Study center regions revised to include Africa.
  - Statement about subjects continuing on study until commercial supplies of FPV are available locally was updated to include a statement about continued FPV according to agreements between GSK and participating study sites.
  - Updated with text and a revised table to state approximately how many additional subjects are required.
  - Schematics were revised according to the changes in this amendment, moved to follow the Overview section and renamed Figure 1 and Figure 2.
  - Overview: Updated to explain the terminology of Arm A SDV and Arm A.
    - Cohort 1 Arm A SDV- original wording deleted as it is no longer applicable; wording added to clarify that no additional subjects in this Cohort are required to undergo SDV assessments.
    - Cohort 2 Arm A SDV- Single doses changed from FPV 30 mg/kg and RTV 6mg/kg to FPV 45 mg/kg and RTV 7 mg/kg. Wording added to explain that the 12 hour sample may be omitted with prior agreement of the sponsor.
    - Cohort 1 Arm A- dosing updated as follows: All new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit. After the Week 2 PK samples have been collected (sampling over 4 hours), these subjects will receive FPV 60 mg/kg BID + RTV 7 mg/kg BID and will undergo plasma PK serial sampling at Week 8 (over 8-12 hours).

  - Cohort 1 Arm B and Cohort 2 Arm B- wording added to explain these cohorts are deferred and the rationale for deferment.
  - Figure 1 and Figure 2 were revised
- Section 3.2 Study Population clarifies the approximate number of additional subjects to be enrolled.
- Section 3.2.2 Exclusion Criteria
  - #3 revised to state that the exclusion of subjects receiving PI therapy within 5 days prior to study drug administration is applicable only for subjects undergoing single dose visits
  - #5 CDC Class C event criteria revised
  - #7 revised to include clinically relevant pancreatitis
  - #8 lab abnormality criteria revised
  - former #9 criteria about serum lipase removed
- Section 3.3.2 Background NRTI options, the manufacturing sites of abacavir oral solution and lamivudine oral solution were changed from Speke, UK to Mississauga, Ontario, Canada. Section 3.3.3 was revised to Background ART Not Provided by GSK, and new wording added to state that GSK will not provide or reimburse background ART other than ABC or 3TC.
- Section 3.3.4 was updated with current information and condensed. Previous sections Original Dose Selection and Revised Dose Selection were removed as the data was no longer applicable.
- Section 3.3.5 Study Drugs and Dosages- condensed and redundant text removed; instructions added for sites in case of vomiting after administration of study drug. Section 3.3.5.1 Dosage Regimen Adjustment Criteria- text updated and condensed.
- Section 3.3.7.3 Rash and Section 3.3.7.4 Abacavir Hypersensitivity Reaction sections updated to provide the most current information and guidance to investigators.
- Section 3.3.8 Subject Management Options were revised to allow for greater flexibility according to local guidelines and local standard of care.
- Section 3.3.10 Concurrent Medications- rifabutin and phenytoin were removed as excluded medications. Additional guidance added for co-administration of rifabutin.

Section 4 Study Drug Management- No changes

Section 5 Measurements and Evaluations

- Section 5.5 Efficacy- Collection of plasma samples at screening for reistance testing, formerly required, was revised per this amendment to state collection of this sample is left to the investigator's discretion if needed to guide selection of background ART.

- Section 5.7 Bioanalysis and Pharmacokinetic Samples- section extensively revised to reflect the new dosing and new PK sample schedule implemented with this amendment; paragraph added regarding directly observed therapy
- Section 5.8 Safety- collection of samples for serum lipase testing and serum α1-Acid Glycoprotein (AAG) concentrations removed as these parameters will no longer be tested. Lipid measures will no longer be collected at the Screening visit.

Section 6 Data Analysis Methods- No changes

Section 7 AEs and SAEs- No changes

Section 8 Study Administration- No changes

Section 9 References - updated

Section 10 Tables- The time and events tables were updated to reflect the changes per the current amendment

Section 11 Appendices

- Appendix 3 -The previous DAIDS table for the grading of adult and pediatric adverse events was replaced with the more current DAIDS 2004 version.
- Appendix 5 and Appendix 6- The dosing tables were revised according to the updated dosing schedule.

11.13. Appendix 13: Protocol Amendment 6

Title: APV20002: A 48 Week Phase II, Open-label, 2-cohort, Multicentre Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of GW433908 and GW433908/RTV When Administered to HIV-1 Infected Protease Inhibitor (PI) Naïve and PI-Experienced Pediatric Subjects aged 4 weeks to <2 years

This format 2 protocol amendment will apply to all study sites.

This amendment is considered non-substantial since the changes to the FPV and RTV dosing tables and exclusion criteria No. 9 did not impact the safety of the subjects or the conduct/management of the study. The inaccurate RTV dosing table was provided in amendment 5 of the protocol but since this amendment had not been implemented at the sites, no subjects were at risk of any RTV dosing issues.

This amendment is being implemented to correct inaccuracies in the FPV and RTV dosing tables and in exclusion criteria No 9 (per amendment 5).

1. In the FPV 45 mg/kg BID dosing table, revisions were made to the number of bottles of FPV OS required by the subject per month based on their weight. In the RTV 7 mg/kg BID dosing table, corrections were made to the amount of RTV oral solution administered per dose to each subject based on their weight.
2. In exclusion criteria No. 9 (per amendment 5), the ULN (>10x ULN) stated for a Grade 3 ALT and/or AST was changed to (>5x ULN) to correctly represent a Grade 3.

Change 1: To update the FPV 45 mg/kg BID dosing table to reflect the correct supply of FPV OS required per month and to correct the dose of RTV oral solution to be administered per dose to each subject based on their weight.

Amend:

11.15, Appendix 5: Dosing Table for FPV Oral Suspension, FPV 45 mg/kg BID

Original Table:

Dosing Table for FPV Oral Suspension

FPV 45 mg/kg BID

Weight (kg)	Dose (mg): 45 mg/kg	Amount of 50 mg/mL suspension (mL) per Dose	No. Bottles (225mL) Needed Per Month
3	135	2.7	1
3.5	158	3.2	1
4	180	3.6	1
4.5	203	4.1	2
5	225	4.5	2
5.5	248	5.0	2
6.0	270	5.4	2
6.5	293	5.9	2
7.0	315	6.3	2
7.5	338	6.8	2
8	360	7.2	2
8.5	383	7.7	2
9	405	8.1	2
9.5	428	8.6	2
10	450	9.0	2
10.5	473	9.5	3
11	495	9.9	3
11.5	518	10.4	3
12	540	10.8	3
12.5	563	11.3	3
13	585	11.7	3

Revised Table:

FPV 45 mg/kg BID

Weight (kg)	Dose (mg): 45 mg/kg	Amount of 50 mg/mL suspension (mL) per Dose	No. Bottles (225mL) Needed Per Month
3	135	2.7	**1**
3.5	158	3.2	**1**
4	180	3.6	**1**
4.5	203	4.1	**2**
5	225	4.5	**2**
5.5	248	5.0	**2**
6.0	270	5.4	**2**
6.5	293	5.9	**2**
7.0	315	6.3	**2**
7.5	338	6.8	**2**
8	360	7.2	**2**
8.5	383	7.7	**3**
9	405	8.1	**3**
9.5	428	8.6	**3**
10	450	9.0	**3**
10.5	473	9.5	**3**
11	495	9.9	**3**
11.5	518	10.4	**3**
12	540	10.8	**3**
12.5	563	11.3	**4**
13	585	11.7	**4**

Amend:

11.16, Appendix 6: Dosing Table for RTV Oral Solution, RTV 7 mg/kg BID

Original Table:

Dosing Table for RTV Oral Solution

RTV 7 mg/kg BID

Weight (kg)	Dose (mg): 7 mg/kg	Amount of 80 mg/mL solution (mL) per Dose
3	21	0.42
3.5	24.5	0.49
4	28	0.56
4.5	31.5	0.63
5	35	0.70
5.5	38.5	0.77
6.0	42	0.84
6.5	45.5	0.91
7.0	49	0.98
7.5	52.5	1.05
8	56	1.12
8.5	59.5	1.19
9	63	1.26
9.5	66.5	1.33
10	70	1.40
10.5	73.5	1.47
11	77	1.54
11.5	80.5	1.61
12	84	1.68
12.5	87.5	1.75
13	91	1.82

Revised Table:

RTV 7 mg/kg BID

Weight (kg)	Dose (mg): 7 mg/kg	Amount of 80 mg/mL solution (mL) per Dose
3	21	**0.26**
3.5	24.5	**0.31**
4	28	**0.35**
4.5	31.5	**0.39**
5	35	**0.44**
5.5	38.5	**0.48**
6.0	42	**0.53**
6.5	45.5	**0.57**
7.0	49	**0.61**
7.5	52.5	**0.66**
8	56	**0.70**
8.5	59.5	**0.74**
9	63	**0.79**
9.5	66.5	**0.83**
10	70	**0.88**
10.5	73.5	**0.92**
11	77	**0.96**
11.5	80.5	**1.01**
12	84	**1.05**
12.5	87.5	**1.09**
13	91	**1.14**

Change 2: To correct the ULN for Grade 3 ALT and /or AST to (>5x ULN)

Amend:

Section 3.1.2, Exclusion Criteria, bullet # 9 (per amendment 5)

Original Text:

9. Grade 3 or higher (>10x ULN) serum aminotransferase levels (alanine aminotransferase, ALT and/or aspartate aminotransferase, AST) within 28 days prior to study drug administration and / or clinically relevant hepatitis within the previous 6 months.

Revised Text:

9. Grade 3 or higher (**>5x ULN**) serum aminotransferase levels (alanine aminotransferase, ALT and/or aspartate aminotransferase, AST) within 28 days prior to study drug administration and / or clinically relevant hepatitis within the previous 6 months.

11.14. Appendix 14: Protocol Amendment 7

Title: APV20002 - A 48 week phase II, open-label, 2-cohort, multicentre study to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of GW433908 and GW433908/RTV when administered to HIV-1 infected protease inhibitor (PI) naïve and PI-experienced pediatric subjects aged 4 weeks to <2 years.

This protocol amendment will apply to all study sites.

This amendment is being implemented to provide the dose recommendation for new subjects enrolled in Cohort 2 Arm A, to remove the Single Dose Visit (SDV) for subjects enrolled into this cohort and to increase the overall number of subjects to be enrolled into Cohort 2 Arm A. This amendment also allows for the option to use local accredited laboratories for hematology and clinical chemistry on approval from GSK.

This amendment is considered substantial since the changes impact the conduct of the study.

This amendment consists of the following changes:

1. Add a dose recommendation for subjects recruited into Cohort 2 Arm A.

   Reason for change: Following the analysis of available PK data from the first 12 subjects enrolled in Cohort 2 Arm A (4 weeks to <6 months), a FPV/RTV dose regiment of 45/10 mg/kg BID is being recommended for all new subjects enrolled into this cohort.

   Dose rationale: Plasma APV PK data are available from the first 12 subjects enrolled in Cohort 2 Arm 1 (4 week to <6 month age group). On both single dose and repeat dose administration of FPV/RTV, pediatric subjects 4 weeks to <6 month old had higher plasma APV Cmax and AUC values, but similar C12 (single dose) and lower Cτ (repeat dose) values than historically observed for adults. Repeat dose plasma RTV Cmax and AUC values were similar to historical adult data, but plasma RTV Cτ values were lower in the pediatric subjects. Because plasma APV Cτ is important for long-term efficacy and minimization of resistance development, it is important to try to achieve plasma APV Cτ values in pediatric subjects similar to those achieved with the FPV/RTV 700/100 mg BID regimen that has demonstrated efficacy in adults. It is possible that the lower plasma RTV Cτ values are responsible for the lower plasma APV Cτ values; therefore, an increase in the RTV dose for all subsequently enrolled subjects is being recommended. Therefore, the recommended dosage regimen for 4 weeks to <6 month old subjects enrolled into Study APV20002 is FPV/RTV 45/10 mg/kg BID. Newly enrolled subjects will not undergo the SDV, but will have serial PK sampling on Week 2 and trough sampling on subsequent visits.

2. Single Dose Visit is deleted from the assessments, and Flow Chart of Clinical Scheduled Assessments for subjects recruited into Cohort 2 Arm A.

Reason for change: As per Section 3.3.4 of the protocol, sufficient PK data is now available to inform on the dose recommendation for subjects enrolled into Cohort 2 Arm A and therefore this visit is no longer required.

3. Update to the number of subjects to be recruited into Cohort 2 Arm A.

   Reason for change: Additional subjects need to be enrolled into Cohort 2 Arm A to provide sufficient data on the FPV/RTV 45/10 mg/kg BID dose.

4. Include the option to use a local accredited laboratory for hematology and clinical chemistry at the discretion of the investigator and with approval of GSK.

   Reason for change: To add the option to use local accredited laboratories for hematology and clinical chemistry to aid subject management.

5. Correction of some typographical errors.

Individual Changes:

Change 1:

Amend:

Sponsor Information Page

Original Text:

Sponsor Medical Representatives:

PPD, MD
GlaxoSmithKline
891-995 Greenford Road
Greenford, Middlesex, UB6 0HE, UK
Telephone: PPD

PPD, MD
GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

Revised Text:

PPD, MD
GlaxoSmithKline
891-995 Greenford Road
Greenford, Middlesex, UB6 0HE, UK
Telephone: PPD

Change 2:

Amend:

Protocol Summary, Dose Rationale, 5th paragraph

Original Text:

Plasma APV PK data are not available for the 4 week to <6 month age group (Cohort 2). Based on the higher doses required in the 6 month to <2 year age group (Cohort 1), a single dose of FPV/RTV 45/7 mg/kg will be administered at the SDV for Cohort 2 Arm A SDV. Further dose modification is described in Section 3.1 and Section 3.3.5.1. When sufficient data are available to provide a dose recommendation for Cohort 2 Arm A, the information will be communicated to the sites through a letter, followed by a formal protocol amendment.

Revised Text:

Plasma APV PK data are available from the first 12 subjects enrolled in Cohort 2 Arm 1 (4 week to <6 month age group). All 12 subjects received FPV/RTV 45/7 mg/kg as a single dose, and 11 subjects underwent repeat administration of FPV/RTV BID at individualized dosage regimens ranging from FPV 30-60 mg/kg and RTV 7-10 mg/kg based on each subject's single dose PK data. On both single dose and repeat dose administration of FPV/RTV, pediatric subjects 4 week to <6 month old had higher plasma APV Cmax and AUC values, but similar C12 (single dose) and lower Cτ (repeat dose) values compared with that historically observed for adults. Repeat dose plasma RTV Cmax and AUC values were similar to historical adult data, but plasma RTV Cτ values were lower in the pediatric subjects. As plasma APV Cτ is important for long-term efficacy and minimization of resistance development, it is important to try to achieve plasma APV Cτ values in pediatric subjects similar to those achieved with the approved FPV/RTV 700/100 mg BID regimen in adults. It is possible that the lower plasma RTV Cτ values are responsible for the lower plasma APV Cτ values; therefore, an increase in the RTV dose for all subsequently enrolled subjects is recommended.

Per Protocol Amendment 7, a SDV is no longer required for newly enrolled 4 week to <6 month age subjects (Cohort 2 Arm A). These subjects will initiate dosing with FPV/RTV 45/10 mg/kg BID and have serial PK sampling at Week 2 and trough sampling on subsequent visits.

Change 3:

Amend:

Protocol Summary, Study Design

Original Text:

As per Amendment 5, the approximate number of subjects required in APV20002 in addition to the 13 previously enrolled is illustrated in the following table.

Approximate Number of Additional Subjects Required in APV20002 (as of Protocol Amendment 05)

		Approximate Number of Additional Subjects Required	
Cohort	**Age**	**Arm A FPV/ RTV BID PI Naïve or Experienced**	**Arm B FPV BID PI Naive**
1	6 months – <2 years	**12**	**NA[1]**
2	4 weeks – <6 months	**12**	**NA[1]**

1. Not Applicable as Arm B enrolment is deferred

Revised Text:

As per Amendments 5 and 7, the approximate number of additional subjects required in APV20002 in addition to the 13 previously enrolled is illustrated in the following table.

Number of Additional Subjects Required in APV20002 (as of Protocol Amendments 5 and 7)

		Approximate Number of Subjects Required		
Cohort	**Age**	**Arm A FPV/ RTV BID PI Naïve or Experienced**		**Arm B FPV BID PI Naive**
		SDV[1]	**Initiate multiple-dosing at baseline**	
1	6 months – <2 years	6-10	**12[2]**	NA[4]
2	4 weeks – <6 months	6-10	**8-12[3]**	NA[4]

1. Recruitment complete for Cohort 1 Arm A SDV and Cohort 2 Arm A SDV
2. Subjects initiate multiple dosing with FPV/RTV 45/7 mg/kg BID from baseline, after Week 2 PK, subjects will receive FPV/RTV 60/7 mg/kg BID (Amendment 5)
3. Subjects initiate multiple dosing with FPV/RTV 45/10 mg/kg BID from baseline (Amendment 7)
4. Not Applicable as Arm B enrolment is deferred

Change 4:

Amend:

Protocol Summary, Study Design, Overview, 2nd paragraph onwards

Original Text:

The initial group of subjects enrolled who undergo single dose visit (SDV) assessments before commencing multiple dosing with for example FPV/RTV at Baseline are referred to as Arm A SDV. The subsequent group of subjects enrolled that do not undertake single dose visit assessments and begin multiple dosing with FPV/RTV at Baseline are simply referred to as Arm A.

Refer to Section 3.1 (Figure 1 and Figure 2) for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

The first 6-10 subjects in Cohort 2 Arm A will undergo one Single Dose Visit (SDV). The SDV will be undertaken a minimum of 15 days prior to the Baseline visit/Day 1. At the SDV, the subject will receive a single dose of FPV 45 mg/kg and a single dose of RTV 7 mg/kg administered simultaneously and undergo serial plasma PK sampling over 8-12 hours. With prior agreement of the sponsor, the 12-hour sample may be omitted if logistical reasons do not allow collection of this sample. The SDV plasma PK samples will be analyzed for APV, RTV and where plasma volumes allow, FPV concentrations in order to construct an individualized dosing regimen prior to initiation of multiple dosing at Baseline/Day 1 (See Section 3.3.4). Every effort will be made to ensure that the investigator is advised, within 14 days after completion of the SDV evaluations of the individualized dose regimen selected. Multiple dosing with FPV/RTV may not be initiated until the subject's single dose PK data are available.

The first 6-10 subjects in Cohort 2 Arm A will also undertake further plasma PK sampling over 8-12 hours (12 hour sample optional) after attaining steady-state at the Week 2 visit. Following the Week 2 evaluations, the plasma PK samples will be analyzed for APV, RTV and where plasma volumes allow FPV concentrations and every effort will be made to ensure that the investigator is advised, within 14 days, whether the subject should remain on the current regimen or undergo a dosage regimen adjustment at the Week 4 visit. The Week 4 visit should not be undertaken until Week 2 PK data are available.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit. After the Week 2 PK samples have been collected (sampling over 4 hours), these subjects will receive FPV 60 mg/kg BID + RTV 7 mg/kg BID and will undergo plasma PK serial sampling at Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Approximately 12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 1 Arm A to receive this dosing regimen.

Cohort 2 (4 weeks to <6 months)

Additional PI-experienced or PI-naïve subjects will subsequently be recruited into Cohort 2 Arm A and will commence multiple dosing with FPV/RTV BID on study Day 1 without undertaking a SDV. The dose will be based on the Week 2 plasma PK data from the initial 6-10 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo plasma PK serial sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit.

Revised Text:

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments. Refer to Section 3.1 (Figure 1 and Figure 2) for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit. After the Week 2 PK samples have been collected (sampling over 4 hours), these subjects will receive FPV 60 mg/kg BID + RTV 7 mg/kg BID and will undergo plasma PK serial sampling at Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Approximately 12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 1 Arm A to receive this dosing regimen.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence multiple dosing with FPV 45 mg/kg BID + RTV 10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is based on the Week 2 plasma PK data from the initial 12

subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo plasma PK serial sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit. Approximately 8-12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 2 Arm A to receive this dosing regimen.

Change 5:

Amend:

Protocol Summary, Study Population, 2nd paragraph

Original Text:

As of Amendment 5, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 12 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 12 subjects to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Revised Text:

As per Amendments 5 and 7, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 12 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 20-24 subjects to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Change 6:

Amend:

Protocol Summary, Measurements and Evaluations

Original Text:

Schedules showing the timing of study procedures and laboratory evaluations for all subjects are shown in Section 10. Subjects will attend the clinic at Screening (within approximately 21 days prior to Baseline/Day 1), the Single Dose Visit (first 6-10 subjects, Cohort 2 Arm A SDV only), Day 1 (Baseline), and Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART. A follow-up visit will be performed 4 weeks after the permanent discontinuation of study drug.

Cohort 1 (6 months to <2 years) Arm A: Plasma samples for evaluation of PK parameters will be collected over 4 hours at Week 2 and over 8-12 hours (12 hour sample optional) at Week 8. Plasma trough PK samples will be collected at Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter.

Cohort 2 (4 weeks to <6 months) Arm A SDV/ Arm A: Plasma samples for evaluation of PK parameters will be collected at the Single Dose Visit for the first 6-10 subjects (Arm A SDV). For all subjects in Cohort 2 Arm A, plasma PK samples will be collected over 8-12 hours (12 hour sample optional) at Week 2. Plasma trough PK samples will be collected at Weeks 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.

Revised Text:

Schedules showing the timing of study procedures and laboratory evaluations for all subjects are shown in Section 10. Subjects will attend the clinic at Screening (within approximately 21 days prior to Baseline/Day 1), Day 1 (Baseline), and Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART. A follow-up visit will be performed 4 weeks after the permanent discontinuation of study drug.

Cohort 1 (6 months to <2 years) Arm A: Plasma samples for evaluation of PK parameters will be collected over 4 hours at Week 2 and over 8-12 hours (12 hour sample optional) at Week 8. Plasma trough PK samples will be collected at Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter.

Cohort 2 (4 weeks to <6 months) Arm A: Plasma PK samples will be collected over 8-12 hours (12 hour sample optional) at Week 2. Plasma trough PK samples will be collected at Weeks 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.

Change 7:

Amend:

Section 3.1 Study Design, 2nd paragraph onwards

Original Text:

As per Amendment 5, the approximate number of subjects required in APV20002 in addition to the 13 previously enrolled is illustrated in Table 1.

Table 1. Approximate Number of Additional Subjects Required in APV20002 (as of Protocol Amendment 05)

		Approximate Number of Additional Subjects Required	
Cohort	**Age**	**Arm A FPV/ RTV BID PI Naïve or Experienced**	**Arm B FPV BID PI Naive**
1	6 months – <2 years	**12**	**NA[1]**
2	4 weeks – <6 months	**12**	**NA[1]**

1. Not Applicable as Arm B enrolment is deferred

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

The initial group of subjects enrolled who undergo single dose visit (SDV) assessments before commencing multiple dosing with for example FPV/RTV at Baseline are referred to as Arm A SDV. The subsequent group of subjects enrolled that do not undertake single dose visit assessments and begin multiple dosing with FPV/RTV at Baseline are simply referred to as Arm A.

Refer to Figure 1 and Figure 2 for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

The first 6-10 subjects in Cohort 2 Arm A will undergo one Single Dose Visit (SDV). The SDV will be undertaken a minimum of 15 days prior to the Baseline visit/Day 1. At the SDV, the subject will receive a single dose of FPV 45 mg/kg and a single dose of RTV 7 mg/kg administered simultaneously and undergo serial plasma PK sampling post-dosing over 8-12 hours. With prior agreement of the sponsor, the 12-hour sample may be omitted if logistical reasons do not allow collection of this sample. The SDV plasma PK samples will be analyzed for APV, RTV and where plasma volumes allow, FPV concentrations in order to construct an individualized dosing regimen prior to initiation of multiple dosing at Baseline/Day 1. (See Section 3.3.4) Every effort will be made to ensure that the investigator is advised, within 14 days after completion of the SDV assessments, of the individualized dose regimen selected. Multiple dosing with FPV/RTV may not be initiated until the subject's single dose PK data are available.

The first 6-10 subjects in Cohort 2 Arm A will also undertake further plasma PK sampling over 8-12 hours (12-hour sample optional) after attaining steady-state at the Week 2 visit. Following the Week 2 evaluations, the plasma PK samples will be analyzed for APV, RTV and where plasma volumes allow FPV concentrations and every effort will be made to ensure that the investigator is advised, within 14 days, whether the subject should remain on the current regimen or undergo a dosage regimen adjustment at the Week 4 visit. The Week 4 visit should not be undertaken until Week 2 PK data are available.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit. After the Week 2 PK samples have been collected (sampling over 4 hours), these subjects will receive FPV 60 mg/kg BID + RTV 7 mg/kg BID and will undergo serial plasma PK sampling at Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Approximately 12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 1 Arm A to receive this dosing regimen**.**

Cohort 2 (4 weeks to <6 months)

Additional PI-experienced or PI-naïve subjects will subsequently be recruited into Cohort 2 Arm A and will commence appropriate multiple dosing with FPV/RTV BID on study Day 1 without undertaking a SDV. The dose will be based on the Week 2 plasma PK data from the initial 6-10 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo serial plasma PK sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit.

Revised Text:

As per Amendments 5 and 7, the approximate number of additional subjects required in APV20002 in addition to the 13 previously enrolled is illustrated in Table 1**.**

Table 1 Number of Additional Subjects Required in APV20002 (as of Protocol Amendments 5 and 7)

		Approximate Number of Subjects Required		
Cohort	**Age**	**Arm A FPV/ RTV BID PI Naïve or Experienced**		**Arm B FPV BID PI Naive**
		SDV[1]	**Initiate multiple-dosing at baseline**	
1	6 months – <2 years	6-10	**12[2]**	NA[4]
2	4 weeks – <6 months	6-10	**8-12[3]**	NA[4]

1. Recruitment complete for Cohort 1 Arm A SDV and Cohort 2 Arm A SDV
2. Subjects initiate multiple dosing with FPV/RTV 45/7 mg/kg BID from baseline, after Week 2 PK, subjects will receive FPV/RTV 60/7 mg/kg BID (Amendment 5)
3. Subjects initiate multiple dosing with FPV/RTV 45/10 mg/kg BID from baseline (Amendment 7)
4. Not Applicable as Arm B enrolment is deferred

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments.

Refer to Figure 1 and Figure 2 for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit. After the Week 2 PK samples have been collected (sampling over 4 hours), these subjects will receive FPV 60 mg/kg BID + RTV 7 mg/kg BID and will undergo serial plasma PK sampling at Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Approximately 12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 1 Arm A to receive this dosing regimen**.**

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence multiple dosing with FPV 45 mg/kg BID + RTV10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is be based on the Week 2 plasma PK data from the initial 12 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo serial plasma PK sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit. Approximately 8-12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 2 Arm A to receive this dosing regimen.

Change 8:

Amend:

Section 3.3.4, 6th paragraph

Original Text:

Plasma APV PK data are not yet available for the 4 week to <6 month age group (Cohort 2). Based on the higher doses required in the 6 month to <2 year age group, a single dose of FPV/RTV 45/7 mg/kg will be administered at the SDV for Cohort 2 Arm A SDV (4 weeks to <6 months). Further dose modification is described in Section 3.1 and Section 3.3.5.1. When sufficient data are available to provide a dose recommendation for Cohort 2 Arm A, the information will be communicated to the sites through a letter, followed by a formal protocol amendment.

Revised Text:

Plasma APV PK data are available from the first 12 subjects enrolled in Cohort 2 Arm 1 (4 week to <6 month age group). Overall, pediatric subjects 4 week to <6 month old had higher plasma APV Cmax and AUC values, but similar C12 (single dose, Table 2) and lower Cτ (repeat dose, Table 3) values than historically observed for adults. Repeat dose plasma RTV Cmax and AUC values were similar to historical adult data, but plasma RTV Cτ values were lower in the pediatric subjects overall (Table 4). Because plasma APV Cτ is important for long-term efficacy and minimization of resistance development, it is important to try to achieve plasma APV Cτ values in pediatric subjects similar to those achieved with the FPV/RTV 700/100 mg BID regimen that has demonstrated

efficacy in adults. Although FPV/RTV 60/10 mg/kg exhibited APV Cτ,ss most similar to adults (Figure 3), the APV Cmax for this regimen was considered unnecessarily high (Figure 4). The RTV 10 mg/kg in the FPV/RTV 60/10 mg/kg regimen provided the most consistently high RTV Cτ,ss values as compared to 30/7 and 45/7 mg/kg (Figure 5). It is possible that the lower plasma RTV Cτ values resulted in the lower plasma APV Cτ values for the lower two regimens. Therefore, all subjects <6 months in age subsequently enrolled in the study will receive FPV/RTV 45/10 mg/kg to maximize RTV Cτ while maintaining APV Cmax values that are not excessively high.

Per Protocol Amendment 7, newly enrolled 4 week to <6 month age subjects (Cohort 2 Arm A) will initiate dosing with FPV/RTV 45/10 mg/kg BID. Newly enrolled subjects will not undergo the SDV, but will have serial PK sampling on Week 2 and trough sampling on subsequent visits.

Table 2 Summary of Single Dose Plasma APV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma APV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV 45/7 mg/kg (N=11)[1]	Adult Subjects FPV/RTV 700/100 mg (N=17)
Cmax (μg/mL)	9.74 (5.67, 16.2)	3.65 (2.54, 6.76)
AUC(0-∞) (μg.h/mL)	57.5 (20.2, 111)	35.2 (20.8, 114)
C8h (μg/mL)	2.64 (0.819, 5.86)	1.10 (0.451, 2.20)
C12h (μg/mL)[2]	1.13 (0.41, 3.76)	1.19 (0.659, 1.92)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10013
3. Data for pediatric Subject PPD was excluded because exposures were very high: Cmax: 30.9μg/mL, AUC(0-∞): 335μg.h/mL, C8hr: 16.9μg/mL.
4. C12h is extrapolated value for pediatric subjects and observed value for adult subjects

Table 3 Summary of Repeat Dose Plasma APV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma APV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV BID[1] (N=9)[2]	Adult Subjects FPV/RTV 700/100 mg (N=14)
Cmax (μg/mL)	8.90 (2.07, 12.1)	4.76 (2.47, 7.68)
AUC(0-τ) (μg.h/mL)	41.0 (16.2, 70.4)	28.3 (17.9, 43.1)
C8h (μg/mL)	2.05 (1.10, 3.25)	1.58 (0.816, 2.64)
Cτ (μg/mL)[3]	0.970 (0.438, 1.95)	1.46 (1.06, 2.20)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10013
3. Pediatric FPV/RTV dosage regimens included: 30/7 mg/kg BID (N=2), 45/7 mg/kg BID (N=4), 45/10 mg/kg BID (N=1), and 60/10 mg/kg BID (N=4).
4. Data for pediatric Subject PPD was excluded because pre-dose APV concentration was non-quantifiable (NQ).
5. Cτ calculated as the mean of the pre-dose and C12h (extrapolated) values.

Table 4 Summary of Repeat Dose Plasma RTV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma RTV PK Parameter		Pediatric Subjects 1 to <6 months FPV/RTV BID[1]		Adult Subjects FPV/RTV 700/100 mg BID
		(N=9)[2]	(N=8)[2,3]	(N=24)
Cmax (μg/mL)		1.28 (0.228, 7.70)	0.999 (0.228, 2.11)	1.24 (0.520, 3.84)
AUC(0-τ) (μg.h/mL)		6.66 (0.922, 28.8)	4.67 (0.922, 14.30)	5.59 (2.88, 14.4)
C8h (μg/mL)		0.270 (0.021, 1.05)	0.239 (0.021, 1.05)	0.260 (0.068, 0.614)
Cτ (μg/mL)[3]		0.075 (NQ, 0.496)	0.069 (NQ, 0.496)	0.165 (0.010, 0.610)

1.
2. Pediatric data from Study APV20002
3. Adult data from Study APV10010
4. Pediatric FPV/RTV dosage regimens included: 30/7 mg/kg BID (N=2), 45/7 mg/kg BID (N=4), 45/10 mg/kg BID (N=1), and 60/10 mg/kg BID (N=4).
5. Data for pediatric Subject PPD was excluded because pre-dose APV concentration was non-quantifiable (NQ).
6. Data summarized excluding Subject PPD who had high RTV Cmax and AUC values.
7. Cτ calculated as the mean of the pre-dose and C12h (extrapolated) values.

Figure 3 Week 2 Plasma APV Ctau,ss Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)

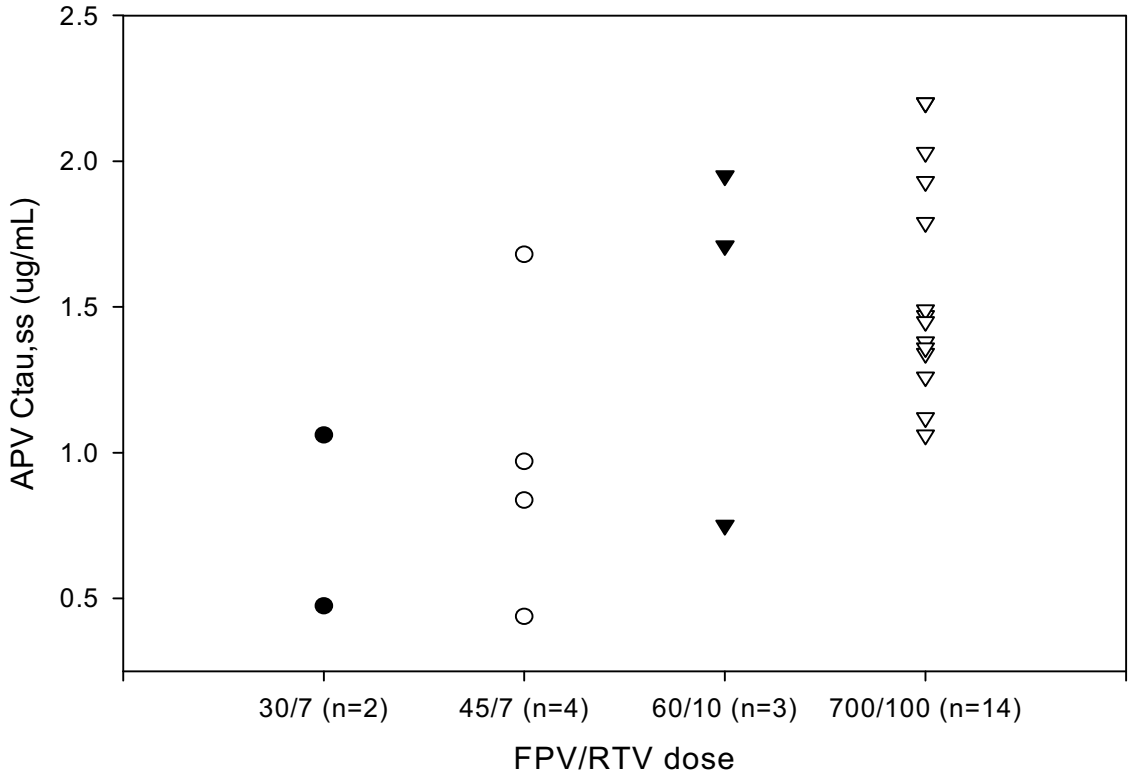


Figure 4 **Week 2 Plasma APV Cmax Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)**

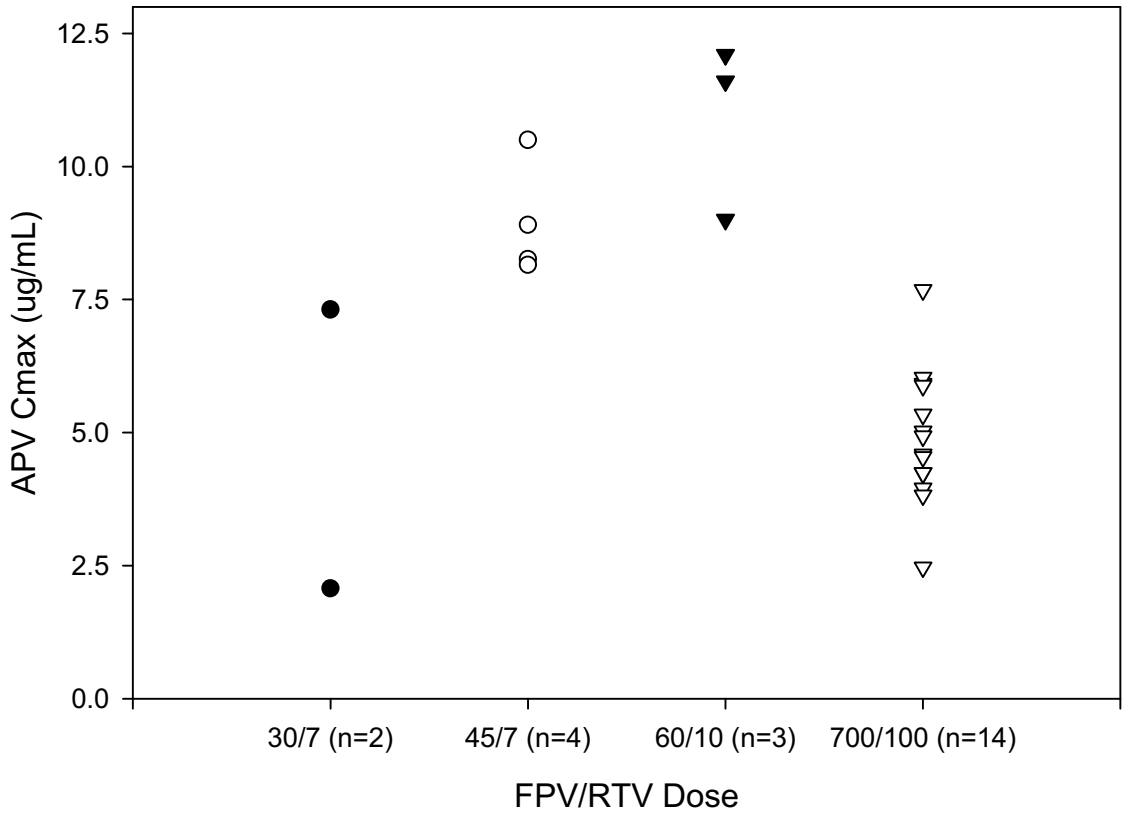
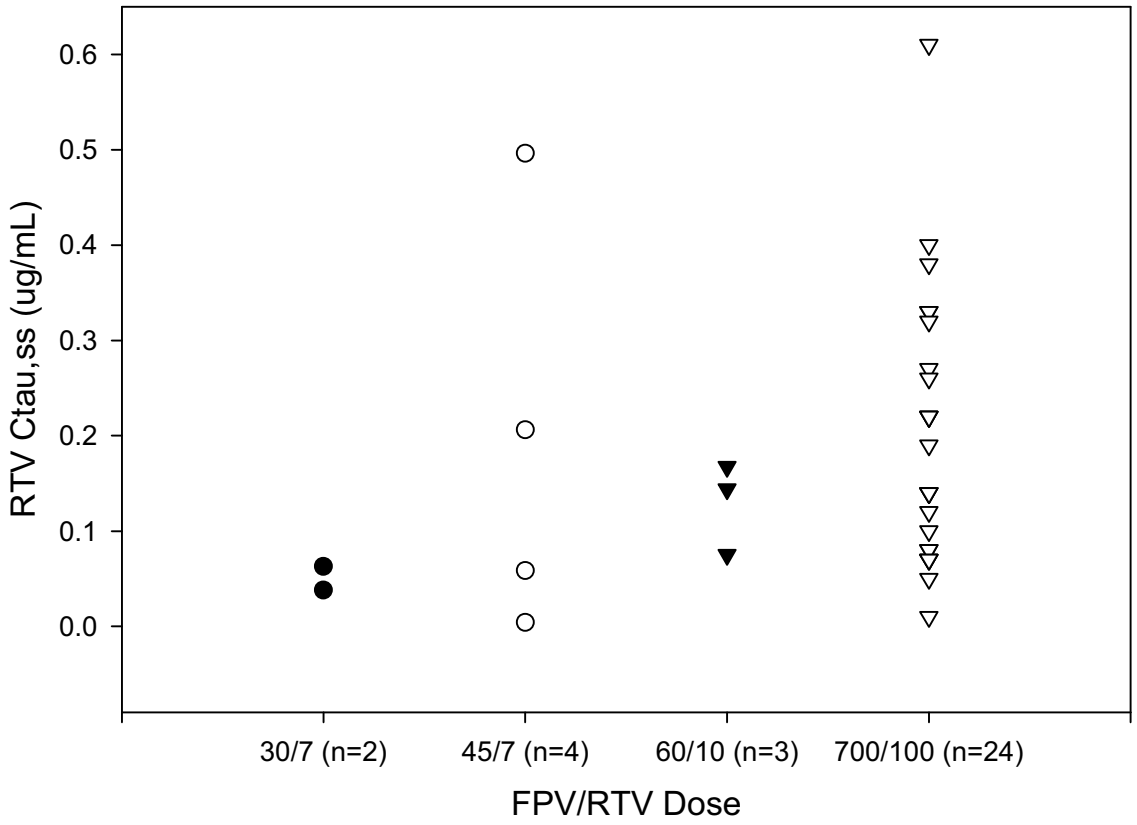


Figure 5 Week 2 Plasma RTV Ctau,ss Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)



Change 9:

Amend:

Section 5.1 Time and Events Schedule, 1st to 3rd paragraphs

Original Text:

Schedules showing the timing of study procedures and laboratory evaluations for all subjects are shown in Section 10.

After determining that a subject is potentially eligible for enrolment, written informed consent from each subject's parent/guardian must be obtained before any investigations are performed which are for the sole purposes of this study.

Subjects will attend the clinic at Screening, the Single Dose Visit (first 6-10 subjects, Cohort 2 Arm A only), Day 1 (Baseline), and Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical

benefit or according to prior agreements between GSK and participating study sites for provision of ART. A follow-up visit will be performed 4 weeks after the permanent discontinuation of study drug.

Revised Text:

Schedules showing the timing of study procedures and laboratory evaluations for all subjects are shown in Section 10.

After determining that a subject is potentially eligible for enrolment, written informed consent from each subject's parent/guardian must be obtained before any investigations are performed which are for the sole purposes of this study.

Subjects will attend the clinic at Screening, Day 1 (Baseline), and Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART. A follow-up visit will be performed 4 weeks after the permanent discontinuation of study drug.

Change 10:

Amend:

Section 5.2 Screening and Enrolment

Original Text:

Subjects will undertake the procedures listed in the schedules in Section 1 Screening will be within approximately 21 days of Baseline/Day 1 for all subjects. The Single Dose Visits to be undertaken by the first 6-10 subjects in Cohort 2 Arm A SDV may be scheduled as soon as screening hematology, clinical chemistry and liver function tests confirming subject eligibility are available.

Reports of screening assessments of lymphocyte subsets, HIV-1 RNA PCR and HIV-1 resistance testing (if performed) should be reviewed prior to Baseline/Day 1 to confirm that the subject meets the full eligibility criteria. Subjects who undertake the Single Dose Visit but whose subsequently reported screening assessments of lymphocyte subsets, HIV-1 RNA PCR and HIV-1 resistance testing (if performed) do not meet with the eligibility criteria may not initiate multiple dosing with FPV.

Revised Text:

Subjects will undertake the procedures listed in the schedules in Section 10. Screening will be within approximately 21 days of Baseline/Day 1 for all subjects. As per amendments 5 and 7, SDV assessments are no longer required for Cohort 1 Arm A and Cohort 2 Arm A.

Reports of screening assessments of lymphocyte subsets, HIV-1 RNA PCR and HIV-1 resistance testing (if performed) should be reviewed prior to Baseline/Day 1 to confirm that the subject meets the full eligibility criteria.

Change 11:

Amend:

Section 5.7 Bioanalysis and Pharmacokinetic Samples, 2nd paragraph

Original Text:

Cohort 2 (4 weeks to <6 months) Arm A: Plasma samples for evaluation of PK parameters will be collected at the Single Dose Visits for the first 6-10 subjects (Arm A SDV). For all subjects in Cohort 2 Arm A, plasma PK samples will be collected over 8-12 hours (12 hour sample optional) at Week 2. Plasma trough PK samples will be collected at Weeks 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.

To measure the unbound concentration of APV, additional plasma trough PK samples will be collected prior to FPV/RTV BID dosing at Weeks 2, 16 and 36 for Cohort 1 Arm A subjects and at Weeks 8 and 16 for Cohort 2 Arm A subjects.

A maximum of 7mL/kg of blood for PK, safety, and virological assessments will be collected during any 56-day period for all subjects. A maximum of 3mL/kg of blood will be collected at any one study visit for subjects 4 weeks to <6 months old.

Single Dose Visit (SDV)

Cohort 1 (6 months - <2 years)

Per protocol amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks - <6 months)

The first 6-10 subjects in Arm A, who may be either PI-experienced or PI-naïve, will undergo one Single Dose Visit (SDV). The SDV will be undertaken a minimum of 15 days prior to the Baseline visit/Day 1. At the SDV, the subject will receive a single 45 mg/kg dose of FPV and a single 7 mg/kg dose of RTV and undergo plasma PK sampling over 8-12 hours (seven whole blood samples of 0.5mL each will be collected at 0, 1, 2, 4, 6, 8, and 12 hours post-dosing). With prior agreement of the sponsor, the 12-hour sample may be omitted if logistical reasons do not allow collection of this sample.

Revised Text:

Cohort 2 (4 weeks to <6 months) Arm A: Plasma PK samples will be collected over 8-12 hours (12 hour sample optional) at Week 2. Plasma trough PK samples will be collected at Weeks 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.

To measure the unbound concentration of APV, additional plasma trough PK samples will be collected prior to FPV/RTV BID dosing at Weeks 2, 16 and 36 for Cohort 1 Arm A subjects and at Weeks 8 and 16 for Cohort 2 Arm A subjects.

A maximum of 7mL/kg of blood for PK, safety, and virological assessments will be collected during any 56-day period for all subjects. A maximum of 3mL/kg of blood will be collected at any one study visit for subjects 4 weeks to <6 months old.

Single Dose Visit (SDV)

Cohort 1 (6 months - <2 years)

Per protocol amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks - <6 months)

Per protocol amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Change 12:

Amend:

Section 5.7 Bioanalysis and Pharmacokinetic Samples, Logistical Considerations, 4th paragraph

Original Text:

Where expedited analysis of PK samples is required to construct individualized dose regimens or undertake individualized dose adjustments (see Section 3.3.4), every effort will be made to ensure that the investigator is advised, within 14 days after completion of the Single Dose Visit evaluations of the individualized dose regimen selected. (On receipt of samples at the nominated bioanalytical laboratory, GSK has contracted that preliminary APV, RTV and where plasma volumes allow FPV concentrations will be made available within 5 working days. It is anticipated that GSK evaluation of the preliminary PK data will be complete and released to the investigator following a further 2 working days.)

Revised Text:

Paragraph deleted

Change 13:

Amend:

Section 5.8 Safety, 2nd and 3rd paragraphs

Original Text:

All routine scheduled laboratory evaluations within the study will be undertaken by a central laboratory nominated by the sponsor. However, evaluation of hematology, clinical chemistry and liver function tests at screening only may be undertaken at a local accredited laboratory at the discretion of the investigator and with the approval of GSK.

Refer to the central laboratory manual for specific instructions on sample collection, processing, storage and shipping for each laboratory test. Screening hematology, clinical chemistry and liver function tests undertaken at a local laboratory should be handled according the standard local procedures.

Revised Text:

Scheduled laboratory evaluations within the study will be undertaken by a central laboratory nominated by the sponsor. However, evaluation of hematology and clinical chemistry may be undertaken at a local accredited laboratory with the approval of GSK.

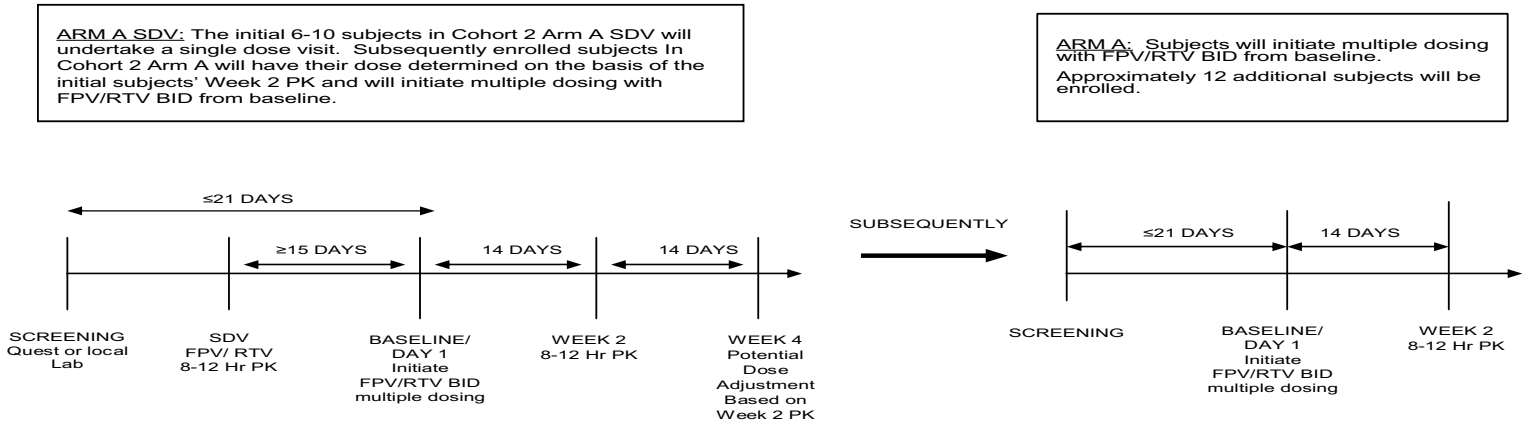
Refer to the central laboratory manual for specific instructions on sample collection, processing, storage and shipping for each laboratory test. Hematology and clinical chemistry undertaken at a local laboratory should be handled according the standard local procedures.

Change 14:

Amend

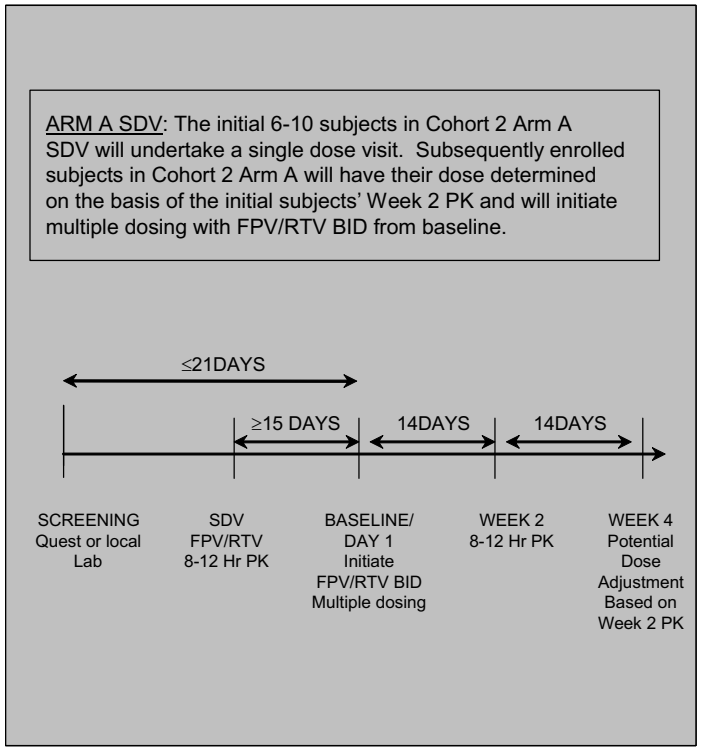
Figure 2: Study Design for Cohort 2 Arm A: PI-naïve or PI-experienced subjects 4 weeks to <6 months of age

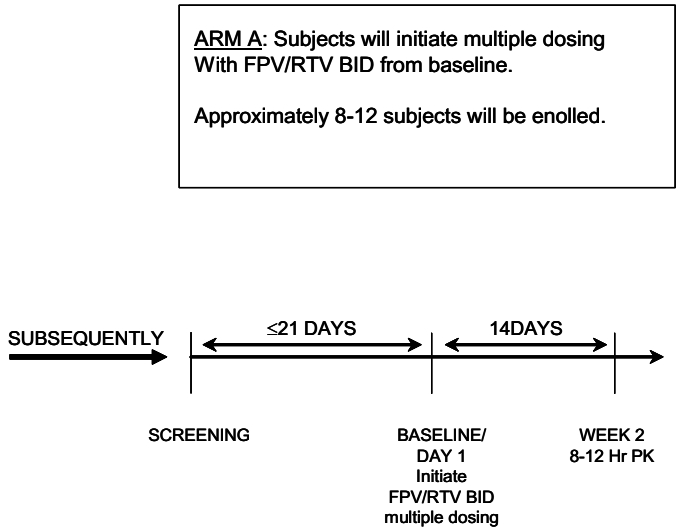
Original Figure:



Revised Figure:

Note: Cohort 2 Arm A SDV is complete.
Further subjects will enroll in Cohort 2 Arm A and initiate multiple dosing with FPV/RTV BID from Baseline





Change 15:

Amend:

Section 10, *Original Chart*

Revised Flow Chart of Clinical Scheduled Assessments (Per Amendment 5)

CLINCAL EVALUATION	Screening Visit [1]	Single Dose Visit [2]	Day 1 (Baseline) [3]	Week										
				2	4	8	12	16	24	36	48	Every 12 weeks thereafter	With-drawal	Follow-up [4]
Written Informed Consent	✓													
Inclusion/Exclusion Criteria	✓													
Demography (date of birth, sex, and race)	✓													
HIV Risk Factors	✓													
CDC HIV-1 Classification	✓		✓											
Current Medical Conditions			✓											
Body Weight , Height and Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Head Circumference	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior Antiretroviral Therapy History		✓	✓											
Background Antiretroviral Therapy		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concurrent Medications/Blood Products		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HIV-associated Conditions			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Experience Surveillance	✓ [5]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adherence Questionnaire			✓	✓			✓		✓		✓		✓	
Parent/Guardian Perception of Study Medication				✓					✓		✓		✓	

1. Screening will be within approximately 21 days prior to Baseline/Day 1 for all subjects. At screening only, the evaluation of the hematology, clinical chemistry and liver function tests may be undertaken at a local accredited laboratory at the discretion of the investigator and with approval of GlaxoSmithKline.
2. **The first 6-10 subjects in Cohort 2 Arm A will undergo a Single Dose Visit (SDV). The SDV will be undertaken a minimum of 15 days prior to Baseline/Day 1. Note: SDVs are no longer needed for Cohort 1 Arm A**.
3. Subjects will initiate multiple dosing on Day 1 (Baseline)
4. 4 weeks after permanent study drug discontinuation
5. Record serious adverse events related to study participation only during screening.

Revised Flow Chart of Laboratory Scheduled Assessments (Per Amendment 5)

LABORATORY EVALUATION[2]	**Screening Visit**[1]	**Single Dose Visit**	**Day 1 (Baseline)**	**Week**										
				2	**4**	**8**	**12**	**16**	**24**	**36**	**48**	**Every 12 weeks thereafter**	**Withdrawal**	**Follow-up**
Lipids [3]			✓						✓		✓	✓	✓	
Hematology [4]	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓
Clinical Chemistry and Liver Function Tests [5]	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓
Lymphocyte subsets	✓		✓		✓		✓		✓	✓	✓	✓	✓	
Quanatitative plasma HIV-1 RNA PCR	✓		✓		✓		✓		✓	✓	✓	✓	✓	
Plasma for storage [6]			✓				✓		✓	✓	✓	✓	✓	
Pharmacokinetic Sampling[10, 11]		✓[7]		✓[8]		✓[9]	✓	✓	✓	✓	✓	✓		
HIV-1 resistance testing[12]	✓													

1. Screening will be within approximately 21 days prior to Baseline/Day 1 for all subjects.
2. Laboratory assessments for all cohorts are prioritized as follows: hematology, chemistry, PK, plasma HIV-1 RNA PCR, lymphocyte subsets, HIV-1 RNA resistance testing, lipids, and plasma for storage.
3. Lipid measures include: triglycerides and total, high density lipoprotein (HDL), and LDL cholesterol.
4. Hematology includes: hemoglobin, WBC with differential, MCV and platelet count.
5. Clinical chemistry panel and transaminase levels (sodium, potassium, AST, ALT, total bilirubin, creatinine, albumin, glucose, alkaline phosphatase, and CPK).
6. Plasma collected for storage where permitted by blood volume restrictions at Day 1 and Week 12, 24, 36, 48, every 12 weeks thereafter and Withdrawal. This sample may be used for HIV-1 resistance testing in subjects experiencing virologic failure.
7. **SDV: Plasma PK sampling over 8-12 hours (at 0 [pre dose], 1, 2, 4, 6, 8, and 12 hours (12 hour sample optional) post-dosing following a single dose of FPV and RTV administered simultaneously for the first 6-10 subjects in Cohort 2 Arm A SDV.**
8. **Week 2: Plasma PK sampling over 8-12 hours (at 0 [pre-dose], 1, 2, 4, 6, 8, and 12 hours (12 hour sample optional) post-dosing for Cohort 2 Arm A subjects and over 4 hours (at 0 [pre-dose], 2 and 4 hours) post-dosing for subjects in Cohort 1 Arm A**
9. **Week 8: Plasma PK sampling over 8-12 hours (at 0 [pre-dose], 1, 2, 4, 6, 8, and 12 hours (12 hour sample optional) post-dosing for subjects in Cohort 1 Arm A.**
10. **Samples for APV/RTV trough concentration determination collected 12 hours after the last dose at Week 8 (Cohort 2 Arm A only) and Weeks 12, 16, 24, 36, 48, and every 12 weeks thereafter (both cohorts).**
11. **Samples for unbound APV concentration evaluation should be collected 12 hours after the last dose at Week 2 (Cohort 1 Arm A), Week 8 (Cohort 2 Arm A), Week 16 (both cohorts), and Week 36 (Cohort 1 Arm A).**
12. **A sample for HIV-1 RNA resistance testing may be collected at Screening at the investigator's discretion if needed to guide selection of background ART.**

Revised Chart:

Revised Flow Chart of Clinical Scheduled Assessments (Per Amendments 5 and 7)

CLINCAL EVALUATION	Screening Visit [1]	Single Dose Visit [2]	Day 1 (Baseline) [3]	Week										
				2	4	8	12	16	24	36	48	Every 12 weeks thereafter	With-drawal	Follow-up [4]
Written Informed Consent	✓													
Inclusion/Exclusion Criteria	✓													
Demography (date of birth, sex, and race)	✓													
HIV Risk Factors	✓													
CDC HIV-1 Classification	✓		✓											
Current Medical Conditions			✓											
Body Weight , Height and Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Head Circumference	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior Antiretroviral Therapy History		✓	✓											
Background Antiretroviral Therapy		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concurrent Medications/Blood Products		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HIV-associated Conditions			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Experience Surveillance	✓ [5]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adherence Questionnaire			✓	✓			✓		✓		✓		✓	
Parent/Guardian Perception of Study Medication				✓					✓		✓		✓	

1. Screening will be within approximately 21 days prior to Baseline/Day 1 for all subjects. At screening only, the evaluation of the hematology, clinical chemistry and liver function tests may be undertaken at a local accredited laboratory at the discretion of the investigator and with approval of GlaxoSmithKline.
2. **SDVs are no longer needed for Cohort 1 Arm A and Cohort 2 Arm A** .
3. Subjects will initiate multiple dosing on Day 1 (Baseline)
4. 4 weeks after permanent study drug discontinuation
5. Record serious adverse events related to study participation only during screening.

Revised Flow Chart of Laboratory Scheduled Assessments (Per Amendments 5 and 7)

LABORATORY EVALUATION[2]	**Screening Visit[1]**	**Single Dose Visit**	**Day 1 (Baseline)**	**Week**										
				2	**4**	**8**	**12**	**16**	**24**	**36**	**48**	**Every 12 weeks thereafter**	**Withdrawal**	**Follow-up**
Lipids [3]			✓						✓		✓	✓	✓	
Hematology [4]	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓
Clinical Chemistry and Liver Function Tests [5]	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓
Lymphocyte subsets	✓		✓		✓		✓		✓	✓	✓	✓	✓	
Quanatitative plasma HIV-1 RNA PCR	✓		✓		✓		✓		✓	✓	✓	✓	✓	
Plasma for storage [6]			✓				✓		✓	✓	✓	✓	✓	
Pharmacokinetic Sampling[10, 11]		✓[7]		✓[8]		✓[9]	✓	✓	✓	✓	✓	✓		
HIV-1 resistance testing[12]	✓													

1. Screening will be within approximately 21 days prior to Baseline/Day 1 for all subjects.
2. Laboratory assessments for all cohorts are prioritized as follows: hematology, chemistry, PK, plasma HIV-1 RNA PCR, lymphocyte subsets, HIV-1 RNA resistance testing, lipids, and plasma for storage.
3. Lipid measures include: triglycerides and total, high density lipoprotein (HDL), and LDL cholesterol.
4. Hematology includes: hemoglobin, WBC with differential, MCV and platelet count.
5. Clinical chemistry panel and transaminase levels (sodium, potassium, AST, ALT, total bilirubin, creatinine, albumin, glucose, alkaline phosphatase, and CPK).
6. Plasma collected for storage where permitted by blood volume restrictions at Day 1 and Week 12, 24, 36, 48, every 12 weeks thereafter and Withdrawal. This sample may be used for HIV-1 resistance testing in subjects experiencing virologic failure.
7. **SDV plasma PK sampling no longer required for Cohort 1 Arm A and Cohort 2 Arm A..**
8. **Week 2: Plasma PK sampling over 8-12 hours (at 0 [pre-dose], 1, 2, 4, 6, 8, and 12 hours (12 hour sample optional) post-dosing for Cohort 2 Arm A subjects and over 4 hours (at 0 [pre-dose], 2 and 4 hours) post-dosing for subjects in Cohort 1 Arm A**
9. **Week 8: Plasma PK sampling over 8-12 hours (at 0 [pre-dose], 1, 2, 4, 6, 8, and 12 hours (12 hour sample optional) post-dosing for subjects in Cohort 1 Arm A.**
10. **Samples for APV/RTV trough concentration determination collected 12 hours after the last dose at Week 8 (Cohort 2 Arm A only) and Weeks 12, 16, 24, 36, 48, and every 12 weeks thereafter (both cohorts).**
11. **Samples for unbound APV concentration evaluation should be collected 12 hours after the last dose at Week 2 (Cohort 1 Arm A), Week 8 (Cohort 2 Arm A), Week 16 (both cohorts), and Week 36 (Cohort 1 Arm A).**
12. **A sample for HIV-1 RNA resistance testing may be collected at Screening at the investigator's discretion if needed to guide selection of background ART.**

Change 16:

Amend:

Appendix 6: Dosing Table for RTV Oral Solution

Change:

Add a dosing

table for RTV 10 mg/kg BID

RTV 10 mg/kg BID

Weight (kg)	Dose (mg): 10 mg/kg	Amount of 80 mg/mL solution (mL) per Dose
3	30	**0.38**
3.5	35	**0.44**
4	40	**0.50**
4.5	45	**0.56**
5	50	**0.63**
5.5	55	**0.69**
6.0	60	**0.75**
6.5	65	**0.81**
7.0	70	**0.88**
7.5	75	**0.94**
8	80	**1.00**
8.5	85	**1.06**
9	90	**1.13**
9.5	95	**1.19**
10	100	**1.25**

11.15. Appendix 15: Protocol Amendment 8

Title: APV20002 - A 48 week phase II, open-label, 2-cohort, multicentre study to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of GW433908 and GW433908/RTV when administered to HIV-1 infected protease inhibitor (PI) naïve and PI-experienced pediatric subjects aged 4 weeks to <2 years.

This protocol amendment will apply to all study sites.

This amendment is considered substantial since the changes impact the dosing regime in Cohort 1A.

This amendment is being implemented to provide the dose recommendation for new subjects enrolled in Cohort 1 Arm A, to provide guidance for the dosing of subjects already in Cohort 1 Arm A, and how dosing should be managed for subjects who reach 2 years of age during the conduct of the study.

This amendment consists of the following changes:

a. Revision of the dose recommendation for new subjects enrolled into Cohort 1, Arm A to FPV/RTV 45/7 mg/kg with no increase to 60/7 mg/kg at week 2 and up date the number of subjects to be recruited into Cohort 1, Arm A.

   Reason for change: An analysis of available PK data in 2009 from the first *five* subjects enrolled in Cohort 1 Arm A (6 months to 2 years) and from 11 newly enrolled subjects indicated that exposure in this age group was closer to adult target exposure with a dose of 45/7 mg/kg BID than 60/7 mg/kg BID. Therefore, it is recommended that for all new subjects enrolled into this cohort, the dose of FPV remains 45 mg/kg BID at week 2.

b. Additional dosing advice for existing subjects in Cohort 1 Arm A, receiving FPV/RTV 60/7 mg/kg .

   Reason for change: Following the analysis of available PK data from the first *five* subjects enrolled in Cohort 1 Arm A (6 months to <2 years) and 11 newly enrolled subjects, guidance is provided to allow individual dose adjustments , based on viral load, pharmacokinetic and safety assessments

c. Guidance on dosing for subjects when reaching 2 and 6 years of age during the study

   Reason for change: Dosing recommendations for patients reaching 2 years of age and 6 years of age to allow staged dose reductions to the recommended doses for these ages.

d. Guidance to allow individual dose adjustments

   Reason for change: To allow flexibility to make individual dose adjustments based on results and review of available PK data from Cohort 1 and 2.

e. Provision for a single repeat testing for liver enzymes in the event of grade 3 or higher within 28 days prior to study drug administration to determine eligibility

Reason for change: To allow retesting of eligible patients with an unexpected acute sporadic raised liver enzyme result at screening.

Individual Changes:

Change 1:

Amend:

SPONSOR INFORMATION PAGE

Original Text:

Sponsor Medical Representatives:

PPD, MD
GlaxoSmithKline
891-995 Greenford Road
Greenford, Middlesex, UB6 0HE, UK
Telephone: PPD

Revised Text:

Sponsor Medical Representatives:

PPD, MD
GlaxoSmithKline
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD

Mobile: PPD

Change 2:

Amend:

INVESTIGATOR AGREEMENT PAGE

Original Text:

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

Investigator Name: _____

Investigator Signature Date

Revised Text:

For protocol number APV20002

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature Date

Change 3:

Amend:

ABBREVIATIONS

Original Text:

FPV	fosamprenavir, GW433908, 908

Revised Text:

FPV	fosamprenavir, GW433908, 908, Telzir, Lexiva

Change 4:

Amend:

PROTOCOL SUMMARY, Dose Rationale

Original Text:

Given the young age of the children enrolled into this study, subjects will receive the FPV oral suspension formulation. In children, the FPV oral suspension is recommended to be administered with food.

Per protocol amendment 5, the FPV/RTV doses being studied are based on data from previously enrolled subjects in APV20002. All 13 previously enrolled subjects underwent PK sampling during the study and 12 subjects provided evaluable PK data. Only two subjects below the age of 6 months provided PK data. Ten subjects between the ages of 6 months to <2 years provided PK data.

Plasma APV PK parameter values were highly variable (CVb ranging from 113 to 165% across the PK parameters) for the subjects 6 months to <2 years of age (Cohort 1). Nine of these subjects 6 months to <2 years of age receiving FPV/RTV BID regimens ranging from 29.4/5.6 to 51.1/8.2mg/kg BID had steady-state plasma APV CL/F values approximately 7-fold and RTV CL/F values approximately 4.2-fold higher than those observed in the historical adult population. Compared to the historical adult population, a subset of five pediatric subjects ages 6 months to <2 years receiving FPV/RTV 45/7 mg/kg BID demonstrated that despite an approximate 5-fold increase in FPV and RTV doses on a mg/kg basis, plasma APV AUC(0-τ) was approximately 48% lower, Cmax 26% lower, and Cτ 29% lower in the pediatric subjects. This data suggest that children 6 months to <2 years of age old require higher doses of FPV and RTV than were previously explored in this study.

Per Protocol Amendment 5, newly enrolled 6 month to <2 year old subjects (Cohort 1 Arm A) will initiate dosing with FPV/RTV 45/7 mg/kg BID for two weeks and then increase to FPV/RTV 60/7 mg/kg BID. This will allow additional PK data for the FPV/RTV 45/7 mg/kg BID regimen and also for an increased dosage regimen. However, further dose increases could be problematic because they would require high volumes of the FPV oral suspension. Thus, plasma unbound APV concentrations (free drug) are being measured in order to determine if these concentrations are similar to historical adult values even if plasma total concentrations are lower.

Plasma APV PK data are available from the first 12 subjects enrolled in Cohort 2 Arm 1 (4 week to <6 month age group). All 12 subjects received FPV/RTV 45/7 mg/kg as a single dose, and 11 subjects underwent repeat administration of FPV/RTV BID at individualized dosage regimens ranging from FPV 30-60 mg/kg and RTV 7-10 mg/kg based on each subject's single dose PK data. On both single dose and repeat dose administration of FPV/RTV, pediatric subjects 4 week to <6 month old had higher plasma APV Cmax and AUC values, but similar C12 (single dose) and lower Cτ (repeat dose) values compared with that historically observed for adults. Repeat dose plasma RTV Cmax and AUC values were similar to historical adult data, but plasma RTV Cτ

values were lower in the pediatric subjects. As plasma APV Cτ is important for long-term efficacy and minimization of resistance development, it is important to try to achieve plasma APV Cτ values in pediatric subjects similar to those achieved with the approved FPV/RTV 700/100 mg BID regimen in adults. It is possible that the lower plasma RTV Cτ values are responsible for the lower plasma APV Cτ values; therefore, an increase in the RTV dose for all subsequently enrolled subjects is recommended.

Per Protocol Amendment 7, a SDV is no longer required for newly enrolled 4 week to <6 month age subjects (Cohort 2 Arm A). These subjects will initiate dosing with FPV/RTV 45/10 mg/kg BID and have serial PK sampling at Week 2 and trough sampling on subsequent visits.

Per Protocol Amendment 5, enrolment in the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is deferred until serial PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Revised Text:

Given the young age of the children enrolled into this study, subjects will receive the FPV oral suspension formulation. In children, the FPV oral suspension is recommended to be administered with food.

APV20002 was designed to determine FPV/RTV regimens for pediatric subjects 4 weeks to <2 years of age that would deliver plasma APV exposures proven to be safe and effective in adults.

In a small subset of five subjects aged 6 months to <2 years (Cohort 1, Arm A) who received FPV/RTV 45/7 mg/kg BID, plasma APV AUC(0-τ) was approximately 48% lower, Cmax 26% lower, and Cτ 29% lower than the adult target values. Conversely, RTV levels appeared to be similar between these pediatric subjects and adult comparators. Based on these results, Amendment 5 (05-Jul-2007) was undertaken to initiate dosing with FPV/RTV 45/7 mg/kg BID for two weeks (to allow collection of additional data on this regimen) and then increase the dose to FPV/RTV 60/7 mg/kg BID (to collect data on a higher dose regimen) for the duration of the study.

Subsequent to Amendment 5, eleven additional subjects have been enrolled in Cohort 1, Arm A. APV PK was evaluated at Week 2 (sampling predose, 2h, and 4h post dose) for the FPV/RTV 45/7 mg/kg BID regimen and at Week 8 (sampling predose, 1, 2, 4, 6, 8h post dose) for the FPV/RTV 60/7 mg/kg BID regimen. Plasma APV Cτ values were collected at all subsequent visits. APV PK parameters for newly enrolled subjects in Cohort 1A (6 months to <2 years) are compared to those for the subjects of this age group previously report as well as adult counterparts.

APV Cmax and Cτ following FPV/RTV 45/7 mg/kg BID were higher in the eleven newly enrolled subjects than in the original five subjects who received the same dose. However, upon re-evaluation of data for the original subjects who received 45/7 mg/kg BID, one subject (PPD) had extremely low PK parameter values at Week 2 that appear to

have affected the statistical point estimate of each parameter. Excluding that one subject from the originally enrolled group,the geometric mean Cmax for the remaining 4 subjects is increased from 4.16μg/mL to 6.07μg/mL, more consistent with adult values and more similar to the geometric mean Cmax at 7.5ug.mL of the newly enrolled subjects receiving 45/7 mg/kg BID at Week 2. Geometric mean AUC(0-τ) is increased from 19.3μg*h/mL (n=5) to 31.2μg*h/mL (n=4), again much closer to the adult target values; AUC(0-τ) following 45/7 mg/kg BID could not be determined at Week 2 for newly enrolled subjects due to limited sampling scheme. Overall geometric mean (95% CI) Cτ was increased from 1.54μg/mL (1.13, 2.09μg/mL, n=5) to 1.81μg/mL (1.40, 2.33μg/mL n=4), also closer to adult targets and newly enrolled subjects.

APV parameters following FPV/RTV 60/7 mg/kg BID in subjects 6 months to <2 years were significantly higher than adult target parameters. Geometric mean APV AUC(0-τ) and Cmax following FPV/RTV 60/7 mg/kg BID were 1.8-fold and 2.6-fold higher than the geometric mean values in adults.

Per protocol amendment 8, since APV parameters following FPV/RTV 45/7 mg/kg BID were closer to adult targets in the newly enrolled subjects and in the original 6 month to 24 month olds upon exclusion of the one low outlier and since APV parameters following FPV/RTV 60/7 mg/kg BID were significantly higher than adult targets, subjects enrolled in the future will receive FPV/RTV 45/7 mg/kg BID continuously without an increase to FPV/RTV 60/7 mg/kg BID at Week 2. Some subjects with consistently high Cτ values following FPV/RTV 60/7 mg/kg BID have had their dose reduced to FPV/RTV 45/7 mg/kg BID. Other subjects previously enrolled and currently receiving FPV/RTV 60/7 mg/kg may have their dose modified at the discretion of the investigator and Sponsor.

Plasma APV PK data are available from the first 12 subjects enrolled in Cohort 2 Arm A (4 week to <6 month age group) All 12 subjects received FPV/RTV 45/7 mg/kg as a single dose, and 11 subjects underwent repeat administration of FPV/RTV BID at individualized dosage regimens ranging from FPV 30-60 mg/kg and RTV 7-10 mg/kg based on each subject's single dose PK data. On both single dose and repeat dose administration of FPV/RTV, pediatric subjects 4 weeks to <6 months of age had higher plasma APV Cmax and AUC values, but similar C12 (single dose) and lower Cτ (repeat dose) values compared with those historically observed for adults. Repeat dose plasma RTV Cmax and AUC values were similar to historical adult data, but plasma RTV Cτ values were lower in the pediatric subjects. As plasma APV Cτ is important for long-term efficacy and minimization of resistance development, it is important to try to achieve plasma APV Cτ values in pediatric subjects similar to those achieved with the approved FPV/RTV 700/100 mg BID regimen in adults. It is possible that the lower plasma RTV Cτ values are responsible for the lower plasma APV Cτ values; therefore per Protocol Amendment 7, an increase in the RTV dose from 7 mg/kg BID to 10 mg/kg BID for all subsequently enrolled subjects was recommended. These subjects will initiate dosing with FPV/RTV 45/10 mg/kg BID and have serial PK sampling at Week 2 and trough sampling on subsequent visits. Additionally a SDV is no longer required for newly enrolled 4 week to <6 month age subjects (Cohort 2 Arm A).

Per Protocol Amendment 5, enrolment in the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is deferred until serial PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Change 5:

Amend:

PROTOCOL SUMMARY, STUDY DESIGN

Original Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

As per Amendments 5 and 7, the approximate number of additional subjects required in APV20002 in addition to the 13 previously enrolled is illustrated in the following table.

Number of Additional Subjects Required in APV20002 (as of Protocol Amendments 5 and 7)

		Approximate Number of Subjects Required		
Cohort	**Age**	**Arm A FPV/ RTV BID PI Naïve or Experienced**		**Arm B FPV BID PI Naive**
		SDV[1]	**Initiate multiple-dosing at baseline**	
1	6 months – <2 years	6-10	**12[2]**	NA[4]
2	4 weeks – <6 months	6-10	**8-12[3]**	NA[4]

1. Recruitment complete for Cohort 1 Arm A SDV and Cohort 2 Arm A SDV
2. Subjects initiate multiple dosing with FPV/RTV 45/7 mg/kg BID from baseline, after Week 2 PK, subjects will receive FPV/RTV 60/7 mg/kg BID (Amendment 5)
3. Subjects initiate multiple dosing with FPV/RTV 45/10 mg/kg BID from baseline (Amendment 7)
4. Not Applicable as Arm B enrolment is deferred

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments.

Refer to Section 3.1 (Figure 1 and Figure 2) for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit. After the Week 2 PK samples have been collected (sampling over 4 hours), these subjects will receive FPV 60 mg/kg BID + RTV 7 mg/kg BID and will undergo plasma PK serial sampling at Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Approximately 12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 1 Arm A to receive this dosing regimen.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence multiple dosing with FPV 45 mg/kg BID + RTV 10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is based on the Week 2 plasma PK data from the initial 12 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo plasma PK serial sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit. Approximately 8-12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 2 Arm A to receive this dosing regimen.

Enrolment of Arm B (FPV BID)

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 5, the decision to open the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) will be deferred until the Week 2 PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Revised Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

As per Amendments 7 and 8, the approximate number of additional subjects required in APV20002 is illustrated in the following table.

Single dose PK data for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in this and previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Enrolment into Arm B (unboosted FPV cohorts 1 and 2) as per amendment 5 has been deferred.

Recruitment Status for APV20002 – from (FSFV) Oct 03 to 21 Sep. 09

Age (yrs) Cohorts	**No. of Subjects originally planned**	**Cumulative enrolment and current status**	**No. still to be recruited to receive latest dose as per current protocol**
1A 6 months - <2yr PI-naïve/exp FPV/RTV (boosted)	**12**	21[1] enrolled 12 ongoing	Approx 4 more subjects
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	**12**	**25[1] enrolled** 22 Ongoing	Approx 4 more subjects

1. Current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments.

Refer to Section 3.1 (Figure 1 and Figure 2) for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 8, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit and will undergo plasma PK serial sampling at Week 2 (over 4 hours) and Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Per Amendment 8, approximately 4 new subjects will be enrolled at this dose regimen (45/7 mg/kg BID) .

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence multiple dosing with FPV 45 mg/kg BID + RTV 10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is based on the Week 2 plasma PK data from the initial 12 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo plasma PK serial sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit. Approximately 8-12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 2 Arm A to receive this dosing regimen.

Enrolment of Arm B (FPV BID)

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 5, the decision to open the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) will be deferred until the Week 2 PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Change 6:

Amend:

PROTOCOL SUMMARY, PLANNED SAMPLE SIZE, Additional 2nd Paragraph

Revised Text:

Revisions to the planned sample size have been made following dose adjustments as specified in previous amendments.

Change 7:

Amend:

PROTOCOL SUMMARY, STUDY POPULATION, 2nd Paragraph

Original Text:

As per Amendments 5 and 7, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 12 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 20-24 subjects to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Revised Text:

Following Amendments 5 and 8, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 25 subjects in total to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 29 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Change 8:

Amend:

3.1 Study Design

Original Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

As per Amendments 5 and 7, the approximate number of additional subjects required in APV20002 in addition to the 13 previously enrolled is illustrated in Table 1**.**

Table 1 Number of Additional Subjects Required in APV20002 (as of Protocol Amendments 5 and 7)

		Approximate Number of Subjects Required		
Cohort	**Age**	**Arm A FPV/ RTV BID PI Naïve or Experienced**		**Arm B FPV BID PI Naive**
		SDV[1]	**Initiate multiple-dosing at baseline**	
1	6 months – <2 years	6-10	**12[2]**	NA[4]
2	4 weeks – <6 months	6-10	**8-12[3]**	NA[4]

1. Recruitment complete for Cohort 1 Arm A SDV and Cohort 2 Arm A SDV
2. Subjects initiate multiple dosing with FPV/RTV 45/7 mg/kg BID from baseline, after Week 2 PK, subjects will receive FPV/RTV 60/7 mg/kg BID (Amendment 5)
3. Subjects initiate multiple dosing with FPV/RTV 45/10 mg/kg BID from baseline (Amendment 7)
4. Not Applicable as Arm B enrolment is deferred

Revised Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric

dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

As per Amendments 7 and 8, the approximate number of additional subjects required in APV20002 is illustrated in Table 1.

SDV for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in this and previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Arm B (unboosted FPV cohorts 1 and 2) as per amendment 5 has been deferred.

Table 1 Recruitment Status for APV20002 – from (FSFV) Oct 03 to 21 Sep. 09

Age (yrs) Cohorts	**No. of Subjects originally planned**	**Cumulative enrolment and current status**	**No. still to be recruited to receive latest dose as per current protocol**
1A 6 months - <2yr PI-naïve/exp FPV/RTV (boosted)	**12**	21[1] enrolled 12 ongoing	Approx 4 more subjects
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	**12**	**25[1] enrolled** 22 Ongoing	Approx 4 more subjects

Notes
1. Current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments
2. Approximately 8 more subjects required to complete the study

Table 2 Number of Additional Subjects Required in APV20002 (as of Protocol Amendments 5 and 7)

		Approximate Number of Subjects Required		
Cohort	**Age**	**Arm A FPV/ RTV BID PI Naïve or Experienced**		**Arm B FPV BID PI Naive**
		SDV[1]	**Initiate multiple-dosing at baseline**	
1	6 months – <2 years	6-10	**12[2]**	NA[4]
2	4 weeks – <6 months	6-10	**8-12[3]**	NA[4]

1. Recruitment complete for Cohort 1 Arm A SDV and Cohort 2 Arm A SDV
2. Subjects initiate multiple dosing with FPV/RTV 45/7 mg/kg BID from baseline, after Week 2 PK, subjects will receive FPV/RTV 60/7 mg/kg BID (Amendment 5)
3. Subjects initiate multiple dosing with FPV/RTV 45/10 mg/kg BID from baseline (Amendment 7)
4. Not Applicable as Arm B enrolment is deferred

Change 9:

Amend:

3.1 Study Design, Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Original Text:

Cohort 1 (6 months to <2 years)

Per Amendment 5, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit. After the Week 2 PK samples have been collected (sampling over 4 hours), these subjects will receive FPV 60 mg/kg BID + RTV 7 mg/kg BID and will undergo serial plasma PK sampling at Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Approximately 12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 1 Arm A to receive this dosing regimen**.**

Revised Text:

Cohort 1 (6 months to <2 years)

Per Amendment 8, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit and will undergo plasma PK serial sampling at Week 2 (over 4 hours) and Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Approximately 4 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 1 Arm A to receive this dosing regimen following amendment 8**.** Existing subjects in Cohort 1 Arm A whose dose of FPV was increased to 60 mg/kg BID at Week 2 as per amendment 5 may have their dose adjusted based on ongoing viral load, pharmacokinetic and safety assessments.

Change 10:

Amend:

3.2 Study Population, 1st Paragraph

Original Text:

HIV-1 infected pediatric subjects 4 weeks to <2 years of age with screening plasma HIV-RNA ≥400copies/mL and who meet the eligibility criteria will be recruited into the study. As of Amendment 5, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 12 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 12 subjects to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Revised Text:

HIV-1 infected pediatric subjects 4 weeks to <2 years of age with screening plasma HIV-RNA ≥400copies/mL and who meet the eligibility criteria will be recruited into the study. As of Amendment 8, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 4 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 20-25 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Change 11:

Amend:

3.2.2 Exclusion Criteria, 9th Criterium

Original Text:

9. Grade 3 or higher (>5x ULN) serum aminotransferase levels (alanine aminotransferase, ALT and/or aspartate aminotransferase, AST) within 28 days prior to study drug administration and / or clinically relevant hepatitis within the previous 6 months.

Revised Text:

9. Grade 3 or higher (>5x ULN) serum aminotransferase levels (alanine aminotransferase, ALT and/or aspartate aminotransferase, AST) within 28 days prior to study drug administration and / or clinically relevant hepatitis within the previous 6 months. A single repeat test is allowed to determine eligibility.

Change 12:

Amend:

3.3.4 Rationale for Study Drug Dose Selection

Original Text:

Given the young age of the children enrolled into this study, subjects will receive the FPV oral suspension formulation. In children, the FPV oral suspension is recommended to be administered with food due to the following considerations:

- Children tend to eat frequently throughout the day
- Parents may wish to enhance adherence, medication intake and mask taste by offering medication with food
- FPV will be co-administered with ritonavir, which is recommended to be administered with food.

In adults, the FPV oral suspension formulation delivered an equivalent plasma APV AUC(0-∞) and 14.5% higher Cmax compared to the FPV tablet formulation [GlaxoSmithKline Document Number RM2006/00240/00, Study APV10024] Administration of the FPV suspension with food reduced plasma APV AUC(0-∞) by 29% and C_{max} by 46% [GlaxoSmithKline Document Number RM2002/00048/00, Study APV10016].

Per protocol amendment 5, the FPV/RTV doses being studied are based on data from previously enrolled subjects in APV20002 [GlaxoSmithKline Document Number RM2006/00360/00, Study APV20002]. All 13 previously enrolled subjects underwent PK sampling during the study and 12 subjects provided evaluable PK data. Only two subjects below the age of 6 months provided PK data; one subject was 3 months and the other was 4 months of age at study entry. Ten subjects between the ages of 6 months to <2 years of age provided PK data. Of these 10 subjects, study entry ages ranged from 8 to 23 months, weights from 6 to 12kg, and heights from 65 to 87cm. All 10 subjects were Hispanic and 5 (50%) were female and 5 (50%) were male.

Plasma APV PK parameter values were highly variable (CVb ranging from 113 to 165% across the PK parameters) for the pediatric subjects 6 months to <2 years of age. Nine of these subjects ages 6 month to <2 years receiving FPV/RTV BID regimens ranging from 29.4/5.6 to 51.1/8.2mg/kg BID had steady-state plasma APV CL/F values approximately 7-fold and RTV CL/F values approximately 4.2-fold higher than those observed in the historical adult population. Compared to the historical adult population, a subset of five pediatric subjects ages 6 months to <2 years of age receiving FPV/RTV 45/7 mg/kg BID demonstrated that despite an approximate 5-fold increase in FPV and RTV doses on a mg/kg basis, plasma APV AUC(0-τ) was approximately 48% lower, Cmax 26% lower, and Cτ 29% lower in the pediatric subjects. This data suggest that children 6 months to <2 years of age require higher doses of FPV and RTV than were previously explored in this study. Refer to the local product information and subsequent APV20002 study

publications for safety and antiviral response data in this initial group of subjects from APV20002 [Cotton, 2014].

Per Protocol Amendment 5, newly enrolled subjects in Cohort 1 Arm A (6 months to <2 years) will initiate dosing with FPV/RTV 45/7 mg/kg BID for two weeks and then increase to FPV/RTV 60/7 mg/kg BID. This will allow additional PK data for the FPV/RTV 45/7 mg/kg BID regimen and also for an increased dosage regimen. However, further dose increases could be problematic because they would require high volumes of the FPV oral suspension. Thus, plasma unbound APV concentrations (free drug) are being measured in order to determine if these concentrations are similar to historical adult values even if plasma total concentrations are lower.

Plasma APV PK data are available from the first 12 subjects enrolled in Cohort 2 Arm 1 (4 week to <6 month age group). Overall, pediatric subjects 4 week to <6 month old had higher plasma APV Cmax and AUC values, but similar C12 (single dose, Table 2 and lower $C\tau$ (repeat dose, Table 5) values than historically observed for adults. Repeat dose plasma RTV Cmax and AUC values were similar to historical adult data, but plasma RTV $C\tau$ values were lower in the pediatric subjects overall (Table 4). Because plasma APV $C\tau$ is important for long-term efficacy and minimization of resistance development, it is important to try to achieve plasma APV $C\tau$ values in pediatric subjects similar to those achieved with the FPV/RTV 700/100 mg BID regimen that has demonstrated efficacy in adults. Although FPV/RTV 60/10 mg/kg exhibited APV $C\tau$,ss most similar to adults (Figure 3), the APV Cmax for this regimen was considered unnecessarily high (Figure 4). The RTV 10 mg/kg in the FPV/RTV 60/10 mg/kg regimen provided the most consistently high RTV $C\tau$,ss values as compared to 30/7 and 45/7 mg/kg (Figure 5). It is possible that the lower plasma RTV $C\tau$ values resulted in the lower plasma APV $C\tau$ values for the lower two regimens. Therefore, all subjects <6 months in age subsequently enrolled in the study will receive FPV/RTV 45/10 mg/kg to maximize RTV $C\tau$ while maintaining APV Cmax values that are not excessively high.

Per Protocol Amendment 7, newly enrolled 4 week to <6 month age subjects (Cohort 2 Arm A) will initiate dosing with FPV/RTV 45/10 mg/kg BID. Newly enrolled subjects will not undergo the SDV, but will have serial PK sampling on Week 2 and trough sampling on subsequent visits.

Table 2 Summary of Single Dose Plasma APV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma APV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV 45/7 mg/kg (N=11)[1]	Adult Subjects FPV/RTV 700/100 mg (N=17)
Cmax (μg/mL)	9.74 (5.67, 16.2)	3.65 (2.54, 6.76)
AUC(0-∞) (μg.h/mL)	57.5 (20.2, 111)	35.2 (20.8, 114)
C8h (μg/mL)	2.64 (0.819, 5.86)	1.10 (0.451, 2.20)
C12h (μg/mL)[2]	1.13 (0.41, 3.76)	1.19 (0.659, 1.92)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10013
3. Data for pediatric Subject PPD was excluded because exposures were very high: Cmax: 30.9μg/mL, AUC(0-∞): 335μg.h/mL, C8hr: 16.9μg/mL.
4. C12h is extrapolated value for pediatric subjects and observed value for adult subjects

Table 3 Summary of Repeat Dose Plasma APV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma APV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV BID[1] (N=9)[2]	Adult Subjects FPV/RTV 700/100 mg (N=14)
Cmax (μg/mL)	8.90 (2.07, 12.1)	4.76 (2.47, 7.68)
AUC(0-τ) (μg.h/mL)	41.0 (16.2, 70.4)	28.3 (17.9, 43.1)
C8h (μg/mL)	2.05 (1.10, 3.25)	1.58 (0.816, 2.64)
Cτ (μg/mL)[3]	0.970 (0.438, 1.95)	1.46 (1.06, 2.20)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10013
3. Pediatric FPV/RTV dosage regimens included: 30/7 mg/kg BID (N=2), 45/7 mg/kg BID (N=4), 45/10 mg/kg BID (N=1), and 60/10 mg/kg BID (N=4).
4. Data for pediatric Subject PPD was excluded because pre-dose APV concentration was non-quantifiable (NQ).
5. Cτ calculated as the mean of the pre-dose and C12h (extrapolated) values.

Table 4 Summary of Repeat Dose Plasma RTV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma RTV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV BID[1]		Adult Subjects FPV/RTV 700/100 mg BID
	(N=9)[2]	(N=8)[2,3]	(N=24)
Cmax (μg/mL)	1.28 (0.228, 7.70)	0.999 (0.228, 2.11)	1.24 (0.520, 3.84)
AUC(0-τ) (μg.h/mL)	6.66 (0.922, 28.8)	4.67 (0.922, 14.30)	5.59 (2.88, 14.4)
C8h (μg/mL)	0.270 (0.021, 1.05)	0.239 (0.021, 1.05)	0.260 (0.068, 0.614)
Cτ (μg/mL)[3]	0.075 (NQ, 0.496)	0.069 (NQ, 0.496)	0.165 (0.010, 0.610)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10010
3. Pediatric FPV/RTV dosage regimens included: 30/7 mg/kg BID (N=2), 45/7 mg/kg BID (N=4), 45/10 mg/kg BID (N=1), and 60/10 mg/kg BID (N=4).
4. Data for pediatric Subject PPD was excluded because pre-dose APV concentration was non-quantifiable (NQ).
5. Data summarized excluding Subject PPD who had high RTV Cmax and AUC values.
6. Cτ calculated as the mean of the pre-dose and C12h (extrapolated) values.

Figure 3 Week 2 Plasma APV Ctau,ss Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)

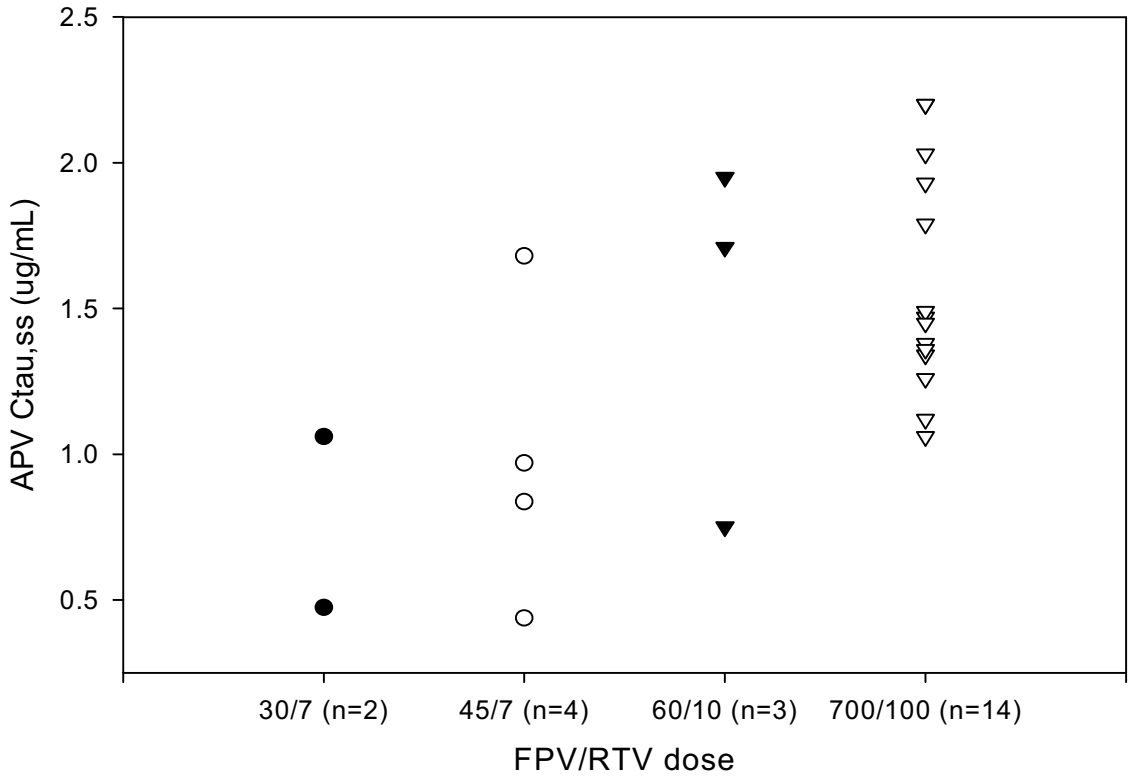


Figure 4 Week 2 Plasma APV Cmax Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)

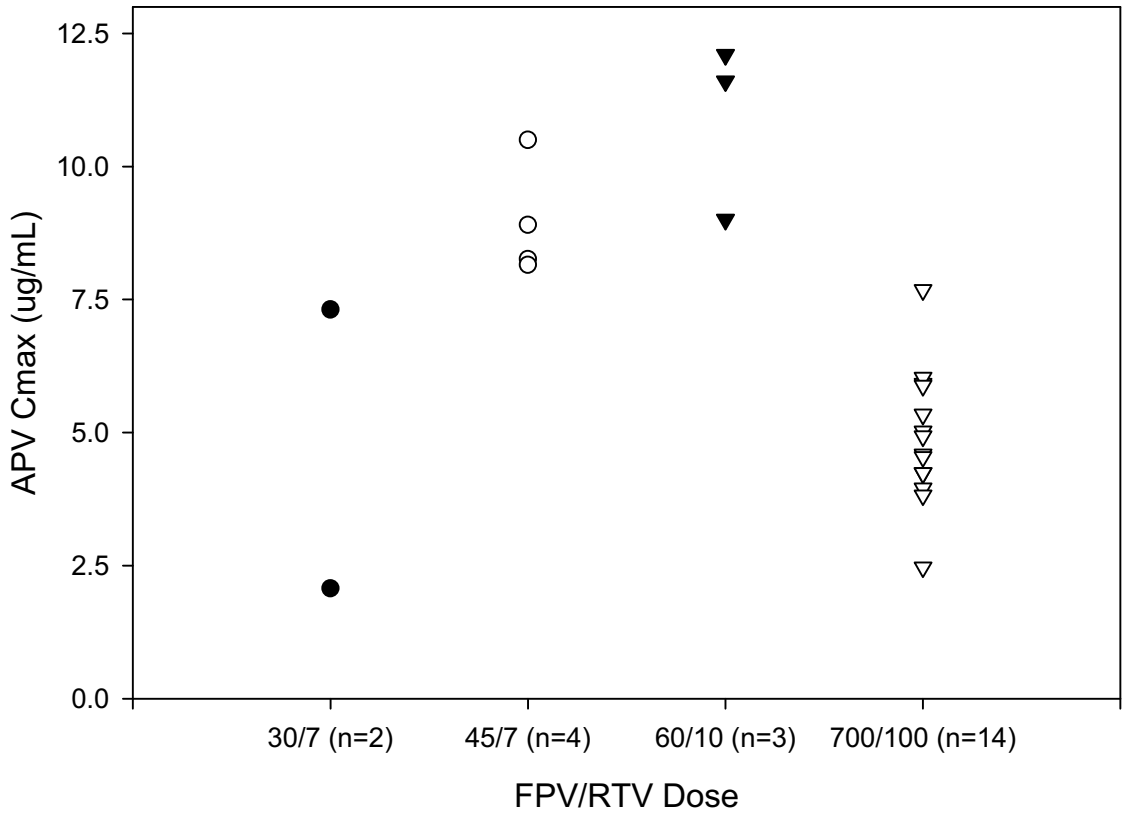
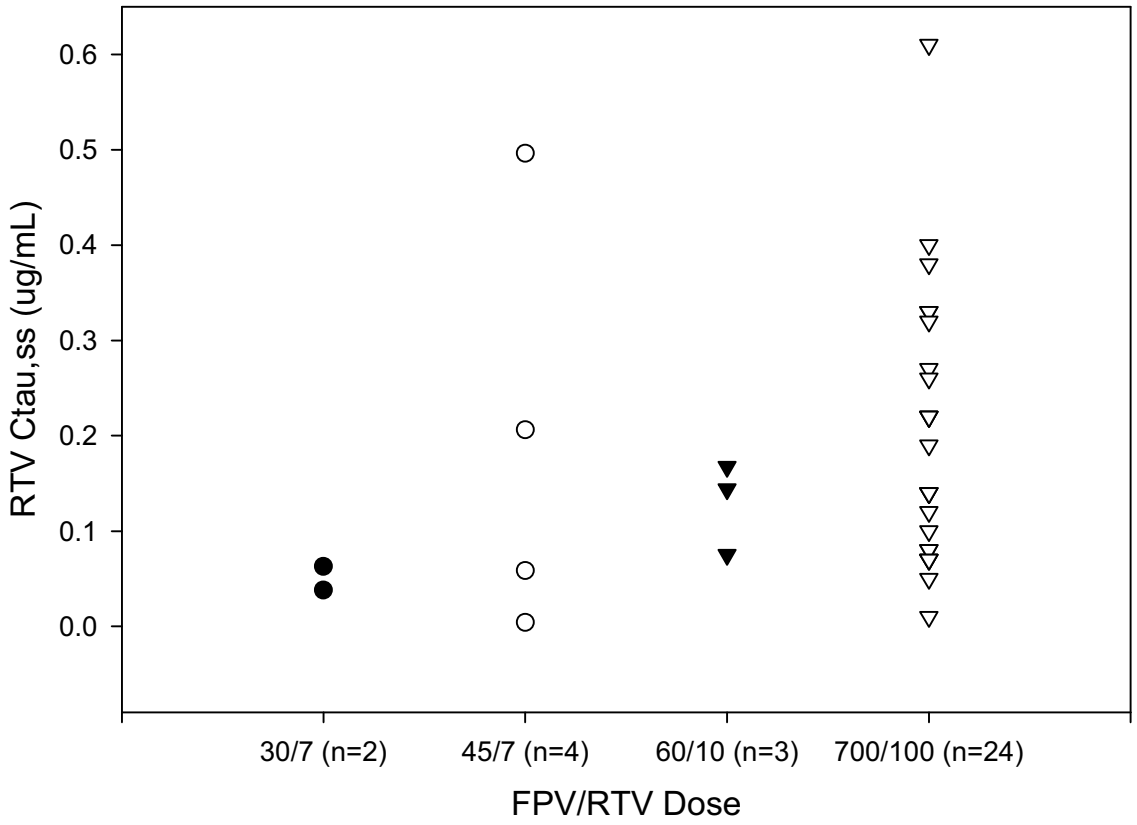


Figure 5 Week 2 Plasma RTV Ctau,ss Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)



Per Protocol Amendment 5, enrolment of the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is deferred until serial PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Revised Text:

Given the young age of the children enrolled into this study, subjects will receive the FPV oral suspension formulation. In children, the FPV oral suspension is recommended to be administered with food due to the following considerations:

- Children tend to eat frequently throughout the day
- Parents may wish to enhance adherence, medication intake and mask taste by offering medication with food
- FPV will be co-administered with ritonavir, which is recommended to be administered with food.

In adults, the FPV oral suspension formulation delivered an equivalent plasma APV AUC(0-∞) and 14.5% higher Cmax compared to the FPV tablet formulation [GlaxoSmithKline Document Number RM2006/00240/00, Study APV10024] Administration of the FPV suspension with food reduced plasma APV AUC(0-∞) by 29% and C_{max} by 46% [GlaxoSmithKline Document Number RM2002/00048/00, Study APV10016].

Rationale for Drug Dose Selection for Cohort 1 (6 months to 2 years)

APV20002 was designed to determine FPV/RTV regimens for pediatric subjects 1 to 24 months of age that would deliver plasma APV exposures proven to be safe and effective in adults.

In a small subset of five subjects aged 6 months to <2 years (Cohort 1, Arm A) who received FPV/RTV 45/7 mg/kg BID, plasma APV AUC(0-τ) was approximately 48% lower, Cmax 26% lower, and Cτ 29% lower than the adult target values. Conversely, RTV levels appeared to be similar between these pediatric subjects and adult comparators. Based on these results, Amendment 5 (05-Jul-2007) was undertaken to initiate dosing with FPV/RTV 45/7 mg/kg BID for two weeks (to allow collection of additional data on this regimen) and then increase the dose to FPV/RTV 60/7 mg/kg BID (to collect data on a higher dose regimen) for the duration of the study.

Subsequent to Amendment 5, eleven additional subjects have been enrolled in Cohort 1, Arm A. APV PK was evaluated at Week 2 (sampling predose, 2h, and 4h post dose) for the FPV/RTV 45/7 mg/kg BID regimen and at Week 8 (sampling predose, 1, 2, 4, 6, 8h post dose) for the FPV/RTV 60/7 mg/kg BID regimen. Plasma APV Cτ values were collected at all subsequent visits. APV PK parameters for newly enrolled subjects in Cohort 1A (6 months to <2 years) are compared to those for the subjects of this age group previously report as well as adult counterparts in Table 3.

Table 3 Summary of Plasma APV PK in pediatric subjects for Cohort 1 (6 months to 2 years)

APV Parameter	Newly enrolled 6 months to <2 years		Original 6 months to <2 years FPV/RTV 45/7 mg/kg BID		Historical Adult FPV/RTV 700/100 mg BID (n=159)[5]
	FPV/RTV 45/7 mg/kg BID (n=11)	FPV/RTV 60/7 mg/kg BID (n=7)[2]	(n=5)[3]	(n=4)[4]	
AUC(0-τ) µg*h/mL	NA	66.9 (31.5, 142) [82] (19.2 – 140)	19.3 (4.64, 79.9) [165] (2.77 – 58.1)	31.2 (15.7, 62.1) [45] (21.8 – 58.1)	37.0 (35.1, 38.9) [33] (15.7 – 95.9)
Cmax µg/mL	7.50 (5.27, 10.7) [56] (4.54 – 28.6)	14.8 (8.09, 27.1) [73.0] (4.79 – 29.6)	4.16 (1.35, 12.8) [113] (0.92 – 9.29)	6.07 (3.27, 11.3) [40] (4.07 – 9.29)	5.62 (5.35, 5.92) [33] (2.47 – 13.3)
Cτ µg/mL	1.92 (1.12, 3.31) [96] (0.48 – 5.28)	3.57 (2.42, 5.25) [99] (1.09 – 16.4)	1.54 (1.13, 2.09) [117] (0.055 – 8.15)	1.81 (1.40, 2.33) [80] (0.246 – 8.15)	2.17 (2.05, 2.30) [38] (0.75 – 5.83)

1. Geometric Mean (95% CI) [CVb%] (min – max)
2. N=6 for AUC(0-τ) and N=20 for Cτ (across Weeks 8 -24)
3. N=38 for Cτ (across Weeks 2 -48)
4. N=32 for Cτ (across Weeks 2 -48)
5. N=158 for AUC(0-τ)

APV Cmax and Cτ following FPV/RTV 45/7 mg/kg BID were higher in the eleven newly enrolled subjects than in the original five subjects who received the same dose. However, upon re-evaluation of data for the original subjects who received 45/7 mg/kg BID, one subject (PPD) had extremely low PK parameter values at Week 2 that appear to have affected the statistical point estimate of each parameter. Excluding that one subject from the originally enrolled group,the geometric mean Cmax for the remaining 4 subjects is increased from 4.16µg/mL to 6.07µg/mL, more consistent with adult values and more similar to the geometric mean Cmax at 7.5ug.mL of the newly enrolled subjects receiving 45/7 mg/kg BID at Week 2. Geometric mean AUC(0-τ) is increased from 19.3µg*h/mL(n=5) to 31.2µg*h/mL(n=4), again much closer to the adult target values; AUC(0-τ) following 45/7 mg/kg BID could not be determined at Week 2 for newly enrolled subjects due to limited sampling scheme. Overall geometric mean (95% CI) Cτ was increased from 1.54µg/mL (1.13, 2.09µg/mL, n=5) to 1.81µg/mL (1.40, 2.33µg/mL, n=4), also closer to adult targets and newly enrolled subjects.

APV parameters following FPV/RTV 60/7 mg/kg BID in subjects 6 months – 2 years old were significantly higher than adult target parameters. Geometric mean APV AUC(0-τ) and Cmax following FPV/RTV 60/7 mg/kg BID were 1.8-fold and 2.6-fold higher than the geometric mean values in adults.

Per protocol amendment 8, since APV parameters following FPV/RTV 45/7 mg/kg BID were closer to adult targets in the newly enrolled subjects and in the original 6 month to 24month olds upon exclusion of the one low outlier and since APV parameters following FPV/RTV 60/7 mg/kg BID were significantly higher than adult targets, subjects enrolled in the future will receive FPV/RTV 45/7 mg/kg BID continuously without an increase to FPV/RTV 60/7 mg/kg BID at Week 2. Some subjects with consistently high Cτ values following FPV/RTV 60/7 mg/kg BID have had their dose reduced to FPV/RTV 45/7 mg/kg BID. Other subjects previously enrolled and currently receiving FPV/RTV 60/7 mg/kg may have their dose modified at the discretion of the investigator and Sponsor.

3.3.4.2 Rationale for Drug Dose Selection for Cohort 2 (4 weeks to 6 months)

Plasma APV PK data are available from the first 12 subjects enrolled in Cohort 2 Arm A (4 week to <6 month age group). All 12 subjects received FPV/RTV 45/7 mg/kg as a single dose, and 11 subjects underwent repeat administration of FPV/RTV BID at individualized dosage regimens ranging from FPV 30-60 mg/kg and RTV 7-10 mg/kg based on each subject's single dose PK data. On both single dose and repeat dose administration of FPV/RTV, pediatric subjects 4 weeks to <6 months of age had higher plasma APV Cmax and AUC values, but similar C12 (single dose, Table 4) and lower Cτ (repeat dose, Table 5) values compared with those historically observed for adults. Repeat dose plasma RTV Cmax and AUC values were similar to historical adult data, but plasma RTV Cτ values were lower in the pediatric subjects (Table 6). As plasma APV Cτ is important for long-term efficacy and minimization of resistance development, it is important to try to achieve plasma APV Cτ values in pediatric subjects similar to those achieved with the approved FPV/RTV 700/100 mg BID regimen in adults. Although FPV/RTV 60/10 mg/kg exhibited APV Cτ,ss, most similar to adults (Figure 3), the APV Cmax for this regimen was considered unnecessarily high (Figure 4). The RTV 10 mg/kg in the FPV/RTV 60/10 mg/kg regimen provided the most consistently high RTV Cτ,ss values as compared to 30/7 and 45/7 mg/kg (Figure 5). It is possible that the lower plasma RTV Cτ values are responsible for the lower plasma APV Cτ values; therefore per Protocol Amendment 7, an increase in the RTV dose from 7 mg/kg BID to 10 mg/kg BID for all subsequently enrolled subjects was recommended. These subjects will initiate dosing with FPV/RTV 45/10 mg/kg BID and have serial PK sampling at Week 2 and trough sampling on subsequent visits. Additionally a SDV is no longer required for newly enrolled 4 week to <6 month age subjects (Cohort 2 Arm A).

Table 4 Summary of Single Dose Plasma APV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma APV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV 45/7 mg/kg (N=11)[1]	Adult Subjects FPV/RTV 700/100 mg (N=17)
Cmax (μg/mL)	9.74 (5.67, 16.2)	3.65 (2.54, 6.76)
AUC(0-∞) (μg.h/mL)	57.5 (20.2, 111)	35.2 (20.8, 114)
C8h (μg/mL)	2.64 (0.819, 5.86)	1.10 (0.451, 2.20)
C12h (μg/mL)[2]	1.13 (0.41, 3.76)	1.19 (0.659, 1.92)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10013
3. Data for pediatric Subject PPD was excluded because exposures were very high: Cmax: 30.9μg/mL, AUC(0-∞): 335μg.h/mL, C8hr: 16.9μg/mL.
4. C12h is extrapolated value for pediatric subjects and observed value for adult subjects

Table 5 Summary of Repeat Dose Plasma APV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma APV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV BID[1] (N=9)[2]	Adult Subjects FPV/RTV 700/100 mg (N=14)
Cmax (μg/mL)	8.90 (2.07, 12.1)	4.76 (2.47, 7.68)
AUC(0-τ) (μg.h/mL)	41.0 (16.2, 70.4)	28.3 (17.9, 43.1)
C8h (μg/mL)	2.05 (1.10, 3.25)	1.58 (0.816, 2.64)
Cτ (μg/mL)[3]	0.970 (0.438, 1.95)	1.46 (1.06, 2.20)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10013
3. Pediatric FPV/RTV dosage regimens included: 30/7 mg/kg BID (N=2), 45/7 mg/kg BID (N=4), 45/10 mg/kg BID (N=1), and 60/10 mg/kg BID (N=4).
4. Data for pediatric Subject PPD was excluded because pre-dose APV concentration was non-quantifiable (NQ).
5. Cτ calculated as the mean of the pre-dose and C12h (extrapolated) values.

Table 6 Summary of Repeat Dose Plasma RTV PK in Pediatric Subjects <6 months old and Adults (median [min, max])

Plasma RTV PK Parameter	Pediatric Subjects 1 to <6 months FPV/RTV BID[1]		Adult Subjects FPV/RTV 700/100 mg BID
	(N=9)[2]	(N=8)[2,3]	(N=24)
Cmax (μg/mL)	1.28 (0.228, 7.70)	0.999 (0.228, 2.11)	1.24 (0.520, 3.84)
AUC(0-τ) (μg.h/mL)	6.66 (0.922, 28.8)	4.67 (0.922, 14.30)	5.59 (2.88, 14.4)
C8h (μg/mL)	0.270 (0.021, 1.05)	0.239 (0.021, 1.05)	0.260 (0.068, 0.614)
Cτ (μg/mL)[3]	0.075 (NQ, 0.496)	0.069 (NQ, 0.496)	0.165 (0.010, 0.610)

1. Pediatric data from Study APV20002
2. Adult data from Study APV10010
3. Pediatric FPV/RTV dosage regimens included: 30/7 mg/kg BID (N=2), 45/7 mg/kg BID (N=4), 45/10 mg/kg BID (N=1), and 60/10 mg/kg BID (N=4).
4. Data for pediatric Subject PPD was excluded because pre-dose APV concentration was non-quantifiable (NQ).
5. Data summarized excluding Subject PPD who had high RTV Cmax and AUC values.
6. Cτ calculated as the mean of the pre-dose and C12h (extrapolated) values.

Figure 3 Week 2 Plasma APV Ctau,ss Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)

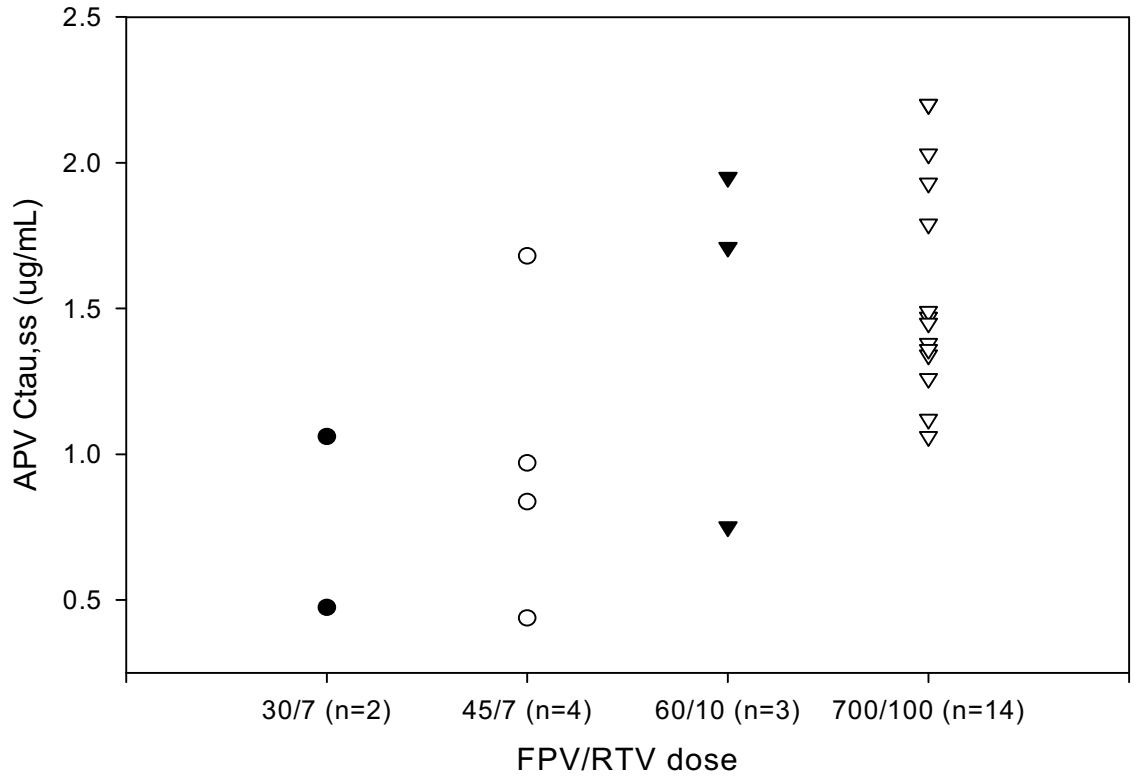


Figure 4 Week 2 Plasma APV Cmax Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)

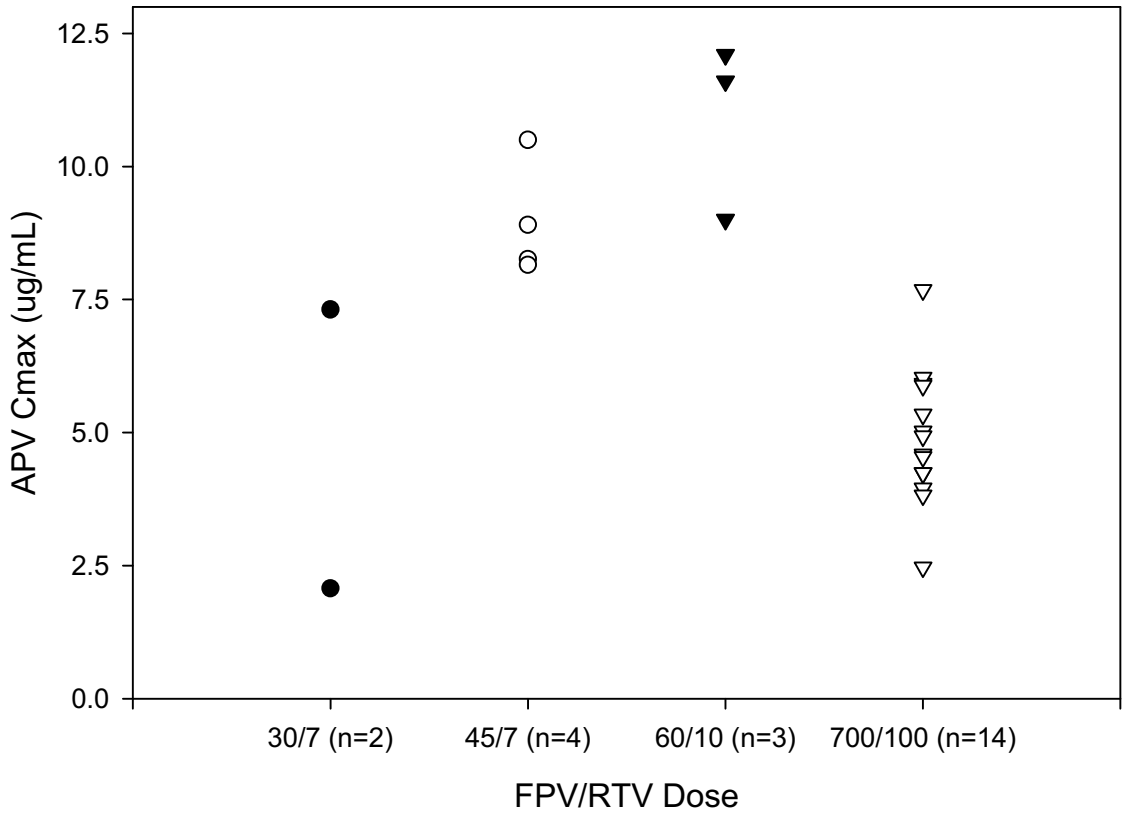
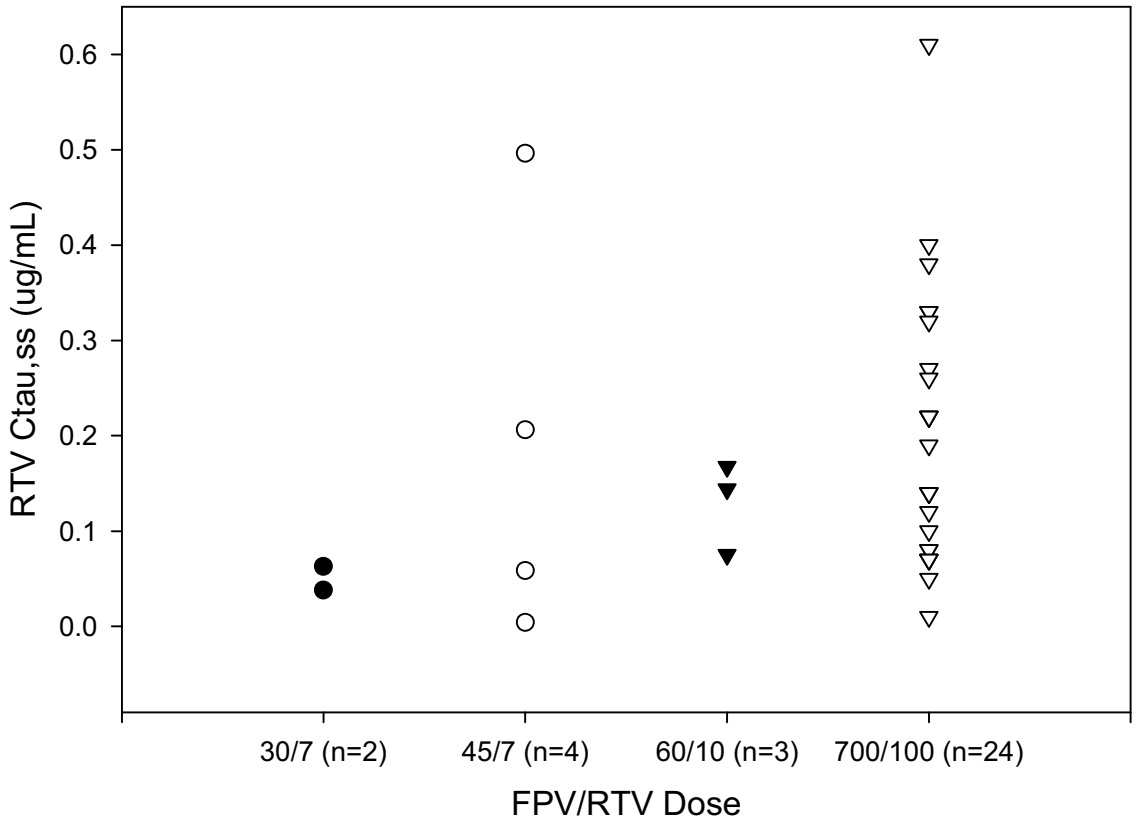


Figure 5 Week 2 Plasma RTV Ctau,ss Following Repeat Administration in Pediatric Subjects <6 months (30/7, 45/7 and 60/10 mg/kg) Compared to Adults (700/100 mg)



Per Protocol Amendment 5, enrolment of the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is deferred until serial PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Following receipt and review of PK results from subjects in Cohorts 1 or 2, individual dose adjustment may be made on a subject by subject basis.

Change 13:

Amend:

3.3.5.1 Dosage Regimen Adjustment Criteria, additional paragraphs

Original Text:

Dose Adjustment Due to Subject Weight

Due to subjects' growth throughout the duration of the study, the dose of all drugs administered must be recalculated at each visit and the total daily dose adjusted according to the child's weight and the recommended dosage regimen. Dose adjustments should occur when the dose would change by ≥10% from the subject's prior calculated dose.

Dose adjustments due to weight change should be delayed until after completion of the PK sampling to ensure that sampling is conducted at steady-state.

Dose Adjustment Due to Subject Physiological Development

Subjects will not automatically change dosage regimens as they increase in age and grow out of their age assigned cohort. However, because subjects may require dose adjustments as they grow and develop, plasma PK samples collected throughout the study will be assayed on an ongoing basis, and if individualized dose adjustments are needed to maintain target concentrations, data will be provided to the investigators.

Revised Text:

Dose Adjustment Due to Subject Weight

Due to subjects' growth throughout the duration of the study, the dose of all drugs administered must be recalculated at each visit and the total daily dose adjusted according to the child's weight and the recommended dosage regimen. Dose adjustments should occur when the dose would change by ≥10% from the subject's prior calculated dose.

Dose adjustments due to weight change should be delayed until after completion of the PK sampling to ensure that sampling is conducted at steady-state.

Dose Adjustment Due to Subject Physiological Development

Subjects will not automatically change dosage regimens as they increase in age and grow out of their age assigned cohort. However, because subjects may require dose adjustments as they grow and develop, plasma PK samples collected throughout the study will be assayed on an ongoing basis, and if individualized dose adjustments are needed to maintain target concentrations, data will be provided to the investigators.

Dose Adjustment Due to Subject Age

Subjects reaching and exceeding 2 years of age during the study in Cohort 1 should transition to the lower dose of FPV and RTV to 23 mg/kg and 3 mg/kg BID respectively, in accordance with the dosage regimen recommended for this age group in protocol APV29005. The change in dosage can be staged gradually over multiple visits and will be based on ongoing viral load, pharmacokinetic and safety assessments, at the investigator's discretion.

Subjects reaching and exceeding 6 years of age in Cohort 2 may transition to the lower dosage regimen (FPV 18 mg/kg and RTV 3 mg/kg BID) in accordance with the regimen approved for this age group. This dose change can be implemented gradually as the subject 'grows into' the new dose or at the time of their 6th birthday at the investigator's discretion.

Change 14:

Additional text added:

8.3 Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov.

Change 15:

Amend:

8.7 Investigator Access to Data and Provision of Study Results

Original Text:

GSK will provide the investigator with a copy of the CRF data collected from the site. When a clinical study report is completed, GSK will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subject.

Revised Text:

8.8 Investigator Access to Data and Provision of Study Results

GSK will provide the investigator with a copy of the CRF data collected from the site. When a clinical study report is completed, GSK will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subject.

The results summary will be posted to the Clinical Study Register no later than 12 months after the last subject's last visit (LSLV) or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

11.16. Appendix 16: Protocol Amendment 9

Title: APV20002 - A 48 week phase II, open-label, 2-cohort, multicentre study to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of GW433908 and GW433908/RTV when administered to HIV-1 infected protease inhibitor (PI) naïve and PI-experienced pediatric subjects aged 4 weeks to <2 years.

This protocol amendment will apply to all study sites.

This amendment is being implemented to specify a change of study sponsor, to provide information on an external review committee, to update recruitment status and to clarify guidance on dosing for subjects reaching 2 years and 6 years of age during the study.

The amendment consists of the following changes:

1. Change of study sponsor

   Reason for change: ViiV Healthcare was established as a new specialist HIV company by GSK and Pfizer. Sponsorship of this study transfers from GSK to ViiV Healthcare.

2. Establishment of an External Review Committee

   Reason for change: An External Review Committee (ERC) will be established and utilized in this study to provide external oversight of study conduct and medical review of safety and/or efficacy issues.

3. Update on recruitment status

   Reason for change: Further subjects have been recruited since Protocol Amendment 8 became effective.

4. Clarification of guidance on dosing for subjects reaching 2 years and 6 years of age during the study

   Reason for change: Dosing recommendations for patients reaching 2 and 6 years of age during the study to allow staged dose reductions to the recommended doses of these ages apply to all subjects regardless of the cohort they were originally enrolled into.

Individual Changes:

Change 1:

Amend:

TITLE PAGE

Original Text:

Author: PPD

Revised Text:

Author: PPD

Change 2:

Amend:

SPONSOR SIGNATORY PAGE:

Original Text:

Sponsor Signatory:

Judith Ng-Cashin, MD
Vice President, Infectious Diseases Medicine Development Centre

Revised Text:

Sponsor Signatory:

James M. Goodrich, Ph.D., M.D.
Vice President Global Medical Strategy, ViiV Healthcare

Change 3:

Amend:

SPONSOR INFORMATION PAGE

Original Text:

Title:	A 48 Week Phase II, Open-label, 2-cohort, Multicentre Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of GW433908 and GW433908/RTV When Administered to HIV-1 Infected Protease Inhibitor (PI) Naïve and PI-Experienced Pediatric Subjects aged 4 weeks to <2 years.
Study Number:	APV20002

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Sponsor Medical Representatives:

PPD, MD
GlaxoSmithKline
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD

Mobile: PPD

Revised Text:

Title:	A 48 Week Phase II, Open-label, 2-cohort, Multicentre Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of GW433908 and GW433908/RTV When Administered to HIV-1 Infected Protease Inhibitor (PI) Naïve and PI-Experienced Pediatric Subjects aged 4 weeks to <2 years.
Study Number:	APV20002

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is responsible for implementing and managing all aspects of this study.

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of GSK and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Medical Monitor Contact Information:

PPD , MD
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Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD

Mobile: PPD

Regulatory Agency Identifying Number(s): US IND 58,627.

Change 4:

Amend:

TRADEMARK INFORMATION

Original Text:

Trademarks of the GlaxoSmithKline group of companies
AGENERASE
EPIVIR
LEXIVA
TELZIR
TRIZIVIR
ZIAGEN

Trademarks not owned by the GlaxoSmithKline group of companies
Norvir
Kaletra
Winnonlin

Revised Text:

Trademarks of ViiV Healthcare
EPIVIR
LEXIVA
TELZIR
TRIZIVIR
ZIAGEN

Trademarks not owned by ViiV Healthcare
Agenerase
Norvir
Kaletra
Winnonlin

Change 5:

Amend:

PROTOCOL SUMMARY PAGE, 3rd paragraph

Original Text:

Amprenavir, delivered as AGENERASE oral solution, requires large dosing volumes and is approved for restricted use by children of at least 4 years of age who are unable to swallow AGN capsules. This restriction in use is due mainly to concerns about the large volume of excipients, including PEG400 and propylene glycol, required for dosing [Agenerase Package Insert, 2005]. Further, due to the high propylene glycol content in AGN oral solution and the high ethanol content of ritonavir (RTV) oral solution, co-administration of AGN oral solution and RTV oral solution is contraindicated.

Revised Text:

Amprenavir, delivered as Agenerase oral solution, requires large dosing volumes and is approved for restricted use by children of at least 4 years of age who are unable to swallow AGN capsules. This restriction in use is due mainly to concerns about the large volume of excipients, including PEG400 and propylene glycol, required for dosing [Agenerase Package Insert, 2005]. Further, due to the high propylene glycol content in AGN oral solution and the high ethanol content of ritonavir (RTV) oral solution, co-administration of AGN oral solution and RTV oral solution is contraindicated. **At the holder's request, the Marketing Authorisation for AGN was withdrawn in the EU on April 29, 2010 and in the USA on August 18, 2009.**

Change 6:

Amend:

PROTOCOL SUMMARY, Dose Rationale, 7th paragraph

Original Text:

Per protocol amendment 8, since APV parameters following FPV/RTV 45/7 mg/kg BID were closer to adult targets in the newly enrolled subjects and in the original 6 month to 24 month olds upon exclusion of the one low outlier and since APV parameters following

FPV/RTV 60/7 mg/kg BID were significantly higher than adult targets, subjects enrolled in the future will receive FPV/RTV 45/7 mg/kg BID continuously without an increase to FPV/RTV 60/7 mg/kg BID at Week 2. Some subjects with consistently high Cτ values following FPV/RTV 60/7 mg/kg BID have had their dose reduced to FPV/RTV 45/7 mg/kg BID. Other subjects previously enrolled and currently receiving FPV/RTV 60/7 mg/kg may have their dose modified at the discretion of the investigator and sponsor.

Revised Text:

Per protocol amendment 8, since APV parameters following FPV/RTV 45/7 mg/kg BID were closer to adult targets in the newly enrolled subjects and in the original 6 month to 24 month olds upon exclusion of the one low outlier and since APV parameters following FPV/RTV 60/7 mg/kg BID were significantly higher than adult targets, subjects enrolled in the future will receive FPV/RTV 45/7 mg/kg BID continuously without an increase to FPV/RTV 60/7 mg/kg BID at Week 2. Some subjects with consistently high Cτ values following FPV/RTV 60/7 mg/kg BID have had their dose reduced to FPV/RTV 45/7 mg/kg BID. Other subjects previously enrolled and currently receiving FPV/RTV 60/7 mg/kg may have their dose modified at the discretion of the investigator and **GSK**.

Change 7:

Amend:

PROTOCOL SUMMARY, STUDY DESIGN

Original Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

As per Amendments 7 and 8, the approximate number of additional subjects required in APV20002 is illustrated in the following table.

Single dose PK data for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in this and previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Enrolment into Arm B (unboosted FPV cohorts 1 and 2) as per amendment 5 has been deferred.

Recruitment Status for APV20002 – from (FSFV) Oct 03 to 21 Sep. 09

Age (yrs) Cohorts	No. of Subjects originally planned	Cumulative enrolment and current status	No. still to be recruited to receive latest dose as per current protocol
1A 6 months - <2yr PI-naïve/exp FPV/RTV (boosted)	**12**	21[1] enrolled 12 ongoing	Approx 4 more subjects
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	**12**	**25[1] enrolled** 22 Ongoing	Approx 4 more subjects

1. Current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments.

Refer to Section 3.1 (Figure 1 and Figure 2) for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 8, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit and will undergo plasma PK serial sampling at Week 2 (over 4 hours) and Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Per Amendment 8, approximately 4 new subjects will be enrolled at this dose regimen (45/7 mg/kg BID) .

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence multiple dosing with FPV 45 mg/kg BID + RTV 10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is based on the Week 2 plasma PK data from the initial 12 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo plasma PK serial sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit. Approximately 8-12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 2 Arm A to receive this dosing regimen.

Enrolment of Arm B (FPV BID)

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 5, the decision to open the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) will be deferred until the Week 2 PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Revised Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

Single dose PK data for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Enrolment into Arm B (unboosted FPV cohorts 1 and 2) as per amendment 5 has been deferred.

Recruitment Status for APV20002 – from (FSFV) Oct 03 to Oct. 10

Age (yrs) **Cohorts**	**No. of Subjects originally planned**	**Cumulative enrolment and current status**
1A 6 months - <2yr PI-naïve/exp FPV/RTV (boosted)	12	**29[1] enrolled** **12 ongoing**
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	12	**29[1] enrolled** **15 ongoing**

1. Current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments.

Refer to Section 3.1 (Figure 1 and Figure 2) for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 8, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit and will undergo plasma PK serial sampling at Week 2 (over 4 hours) and Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence multiple dosing with FPV 45 mg/kg BID + RTV 10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is based on the Week 2 plasma PK data from the initial 12 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo plasma PK serial sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit. Approximately 8-12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 2 Arm A to receive this dosing regimen.

Enrolment of Arm B (FPV BID)

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 5, the decision to open the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) will be deferred until the Week 2 PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Change 8:

Amend:

1.2 Rationale, 2nd and 3rd paragraph

Original Text:

In the NNRTI class, no liquid formulation of efavirenz is currently available [Sustiva Package Insert, 2007], and the other NNRTI approved for use in children, nevirapine (NVP), is available as an oral solution but is associated with rare but potentially life threatening adverse reactions [Viramune Package Insert, 2007].

In the PI class, only five agents- APV, indinavir (IDV), nelfinavir (NFV), RTV, and lopinavir/ritonavir (LPV/RTV) - are currently approved for use in HIV-1 infected children. The lower age limits for which these PIs are approved for use differ between countries but range from >1 month (RTV) or ≥6 months (LPV/RTV) in some countries, to 2 years of age or older for the other currently approved PIs.

Revised Text:

In the NNRTI class, **efavirenz (EFZ) and nevirapine (NVP) are available as liquid formulations. NVP is associated with rare but potentially life threatening adverse reactions whilst EFZ is associated with neuropsychiatric adverse reactions** [Viramune Package Insert, 2010] [Sustiva Package Insert, 2010].

In the PI class, **six** agents - APV, indinavir (IDV), nelfinavir (NFV), RTV lopinavir/ritonavir (LPV/RTV), and **darunavir** - are currently approved for use in HIV-1 infected children. The lower age limits for which these PIs are approved for use differ between countries but range from >1 month (RTV) or ≥6 months (LPV/RTV) in some countries, to 2 years of age or older for the other currently approved PIs **(6 years or older for darunavir)**.

Change 9:

Amend:

3.1 Study Design

Original Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

As per Amendments 7 and 8, the approximate number of additional subjects required in APV20002 is illustrated in Table 1.

SDV for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in this and previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Arm B (unboosted FPV cohorts 1 and 2) as per amendment 5 has been deferred.

Table 1 Recruitment Status for APV20002 – from (FSFV) Oct 03 to 21 Sep. 09

Age (yrs) Cohorts	No. of Subjects originally planned	Cumulative enrolment and current status	No. still to be recruited to receive latest dose as per current protocol
1A 6 months - <2yr PI-naïve/exp FPV/RTV (boosted)	**12**	21[1] enrolled 12 ongoing	Approx 4 more subjects
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	**12**	**25[1] enrolled** 22 Ongoing	Approx 4 more subjects

1. Notes
2. 1. Current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments
3. 2. Approximately 8 more subjects required to complete the study

Table 2 Number of Additional Subjects Required in APV20002 (as of Protocol Amendments 5 and 7)

		Approximate Number of Subjects Required		
Cohort	**Age**	**Arm A FPV/ RTV BID PI Naïve or Experienced**		**Arm B FPV BID PI Naive**
		SDV[1]	**Initiate multiple-dosing at baseline**	
1	6 months – <2 years	6-10	**12[2]**	NA[4]
2	4 weeks – <6 months	6-10	**8-12[3]**	NA[4]

1. Recruitment complete for Cohort 1 Arm A SDV and Cohort 2 Arm A SDV
2. Subjects initiate multiple dosing with FPV/RTV 45/7 mg/kg BID from baseline, after Week 2 PK, subjects will receive FPV/RTV 60/7 mg/kg BID (Amendment 5)
3. Subjects initiate multiple dosing with FPV/RTV 45/10 mg/kg BID from baseline (Amendment 7)
4. Not Applicable as Arm B enrolment is deferred

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments.

Refer to Figure 1 and Figure 2 for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 8, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit and will undergo plasma PK serial sampling at Week 2 (over 4 hours) and Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Approximately 4 additional PI-naïve or PI-experienced subjects are to be enrolled in Cohort 1 Arm A to receive this dosing regimen following amendment 8**.** Existing subjects in Cohort 1 Arm A whose dose of FPV was increased to 60 mg/kg BID at Week 2 as per amendment 5 may have their dose adjusted based on ongoing viral load, pharmacokinetic and safety assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence appropriate multiple dosing with FPV 45 mg/kg BID + RTV 10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is be based on the Week 2 plasma PK data from the initial 12 subjects in Arm A SDV of Cohort 2 who underwent single dose

assessments. Subjects in Cohort 2 Arm A will undergo serial plasma PK sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit. Approximately 8-12 PI-naïve or PI-experienced subjects are to be enrolled in Cohort 2 Arm A to receive this dosing regimen.

Enrolment of Arm B (FPV BID)

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 5, the decision to open the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) will be deferred until the Week 2 PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Figure 1 Study Design for Cohort 1 Arm A: PI-naïve or PI-experienced subjects 6 months to <2 years of age

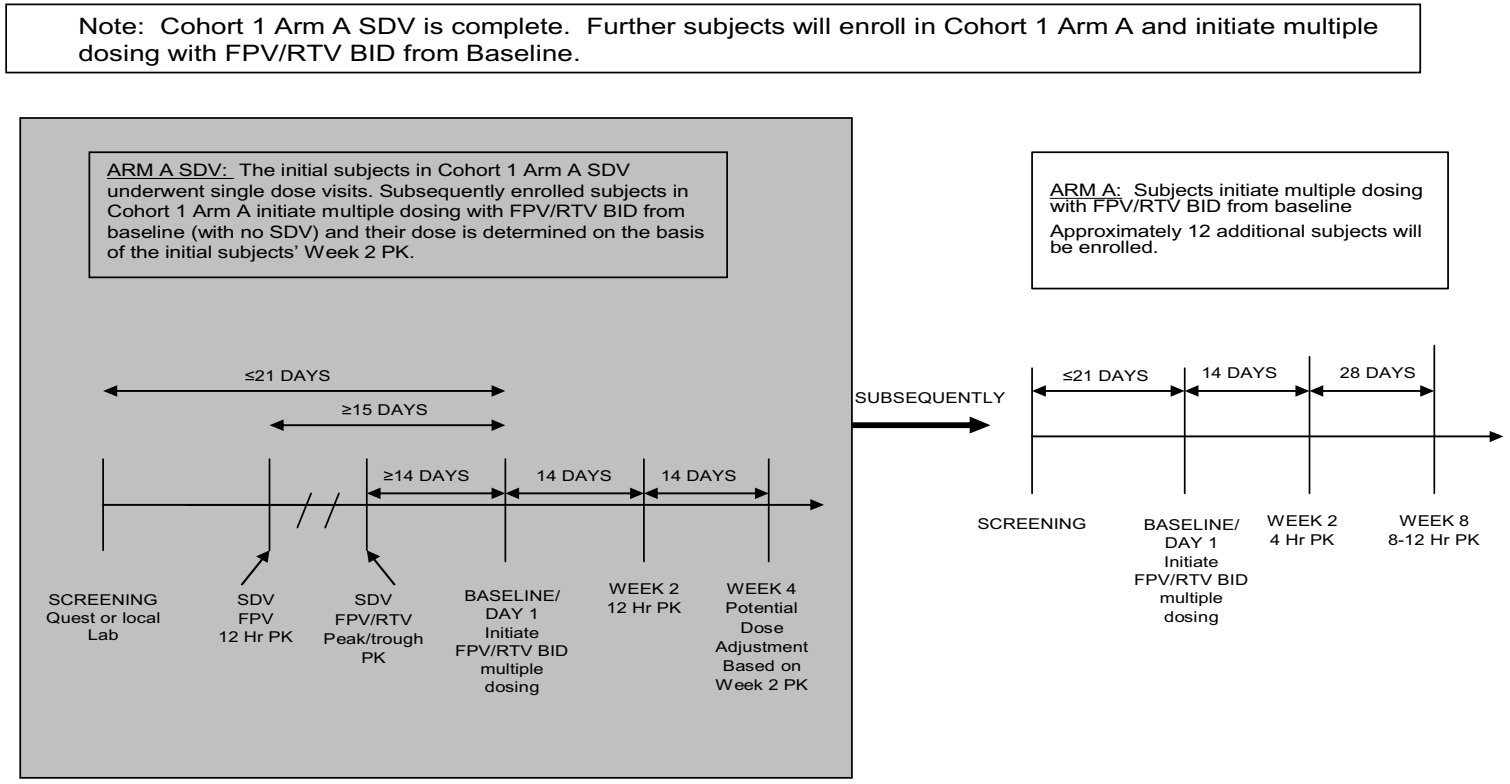
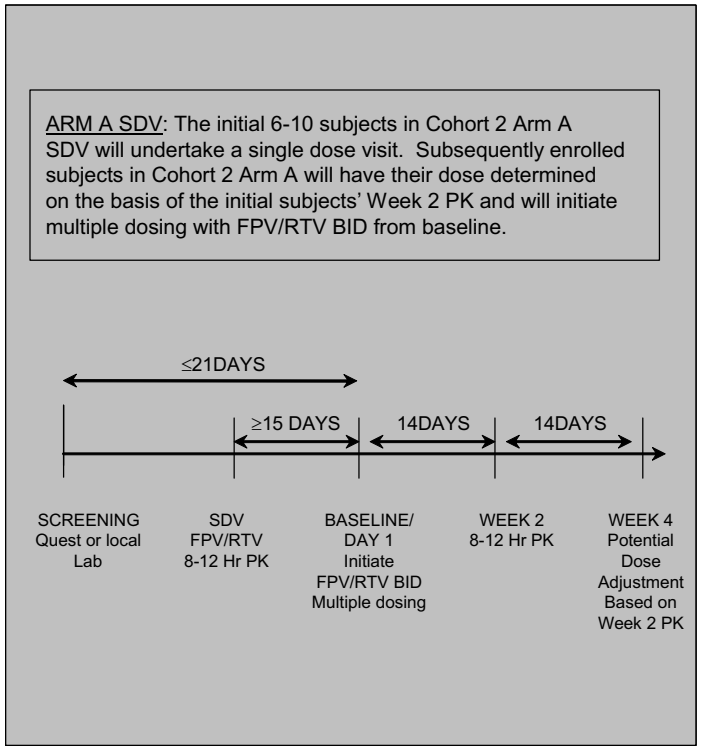
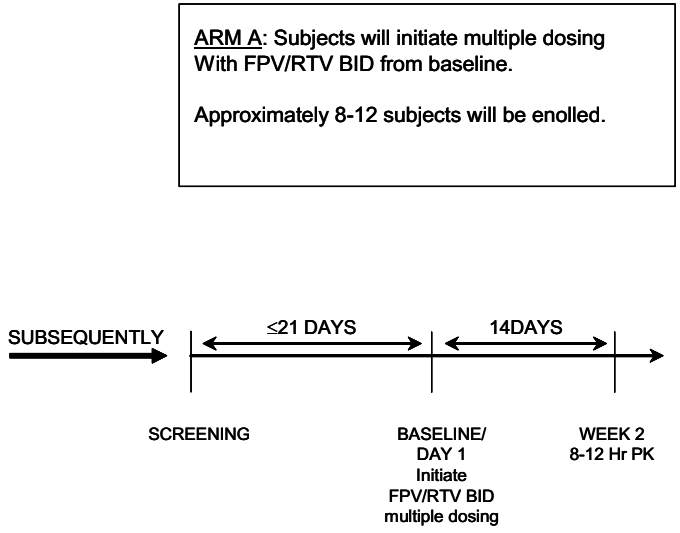


Figure 2 Study Design for Cohort 2 Arm A: PI-naïve or PI-experienced subjects 4 weeks to <6 months of age

Note: Cohort 2 Arm A SDV is complete.
Further subjects will enroll in Cohort 2 Arm A and initiate multiple dosing with FPV/RTV BID from Baseline





Revised Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

SDV for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Arm B (unboosted FPV cohorts 1 and 2) as per amendment 5 has been deferred.

Table 1 Recruitment Status for APV20002 – from (FSFV) Oct 03 to Oct 10

Age (yrs) Cohorts	No. of Subjects originally planned	Cumulative enrolment and current status
1A 6 months - <2yr PI-naïve/exp FPV/RTV (boosted)	12	**29[1] enrolled** **12 ongoing**
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	12	**29[1] enrolled** **15 ongoing**

1. Current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments

Overview

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

The initial group of subjects who were enrolled into the study underwent a single dose visit (SDV) before commencing multiple dosing with for example FPV/RTV at Baseline and were referred to as Arm A SDV. As per Amendments 5 and 7, no additional subjects are required to undergo SDV assessments.

Refer to Figure 1 and Figure 2 for schematics outlining the study design for Cohort 1 Arm A and Cohort 2 Arm A, respectively.

Enrolment of Arm A (FPV/RTV BID)

Arm A SDV: Subjects Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 5, no additional subjects in this age group are required to undertake SDV assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, no additional subjects in this age group are required to undertake SDV assessments.

Arm A: Subjects Not Undertaking Single Dose Visit Assessments

Cohort 1 (6 months to <2 years)

Per Amendment 8, all new subjects who enrol in Cohort 1 Arm A should commence multiple dosing with FPV 45 mg/kg BID + RTV 7 mg/kg BID at the Baseline visit and will undergo plasma PK serial sampling at Week 2 (over 4 hours) and Week 8 (over 8-12 hours; 12 hour sample optional). Refer to Section 3.3.4 for further information. Existing subjects in Cohort 1 Arm A whose dose of FPV was increased to 60 mg/kg BID at Week 2 as per amendment 5 may have their dose adjusted based on ongoing viral load, pharmacokinetic and safety assessments.

Cohort 2 (4 weeks to <6 months)

Per Amendment 7, all new subjects who enrol in Cohort 2 Arm A will commence appropriate multiple dosing with FPV 45 mg/kg BID + RTV 10 mg/kg BID on study Day 1 without undertaking a SDV. The dose is be based on the Week 2 plasma PK data from the initial 12 subjects in Arm A SDV of Cohort 2 who underwent single dose assessments. Subjects in Cohort 2 Arm A will undergo serial plasma PK sampling over 8-12 hours (12 hour sample optional) at the Week 2 visit.

Enrolment of Arm B (FPV BID)

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 5, the decision to open the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) will be deferred until the Week 2 PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Figure 1 Study Design for Cohort 1 Arm A: PI-naïve or PI-experienced subjects 6 months to <2 years of age

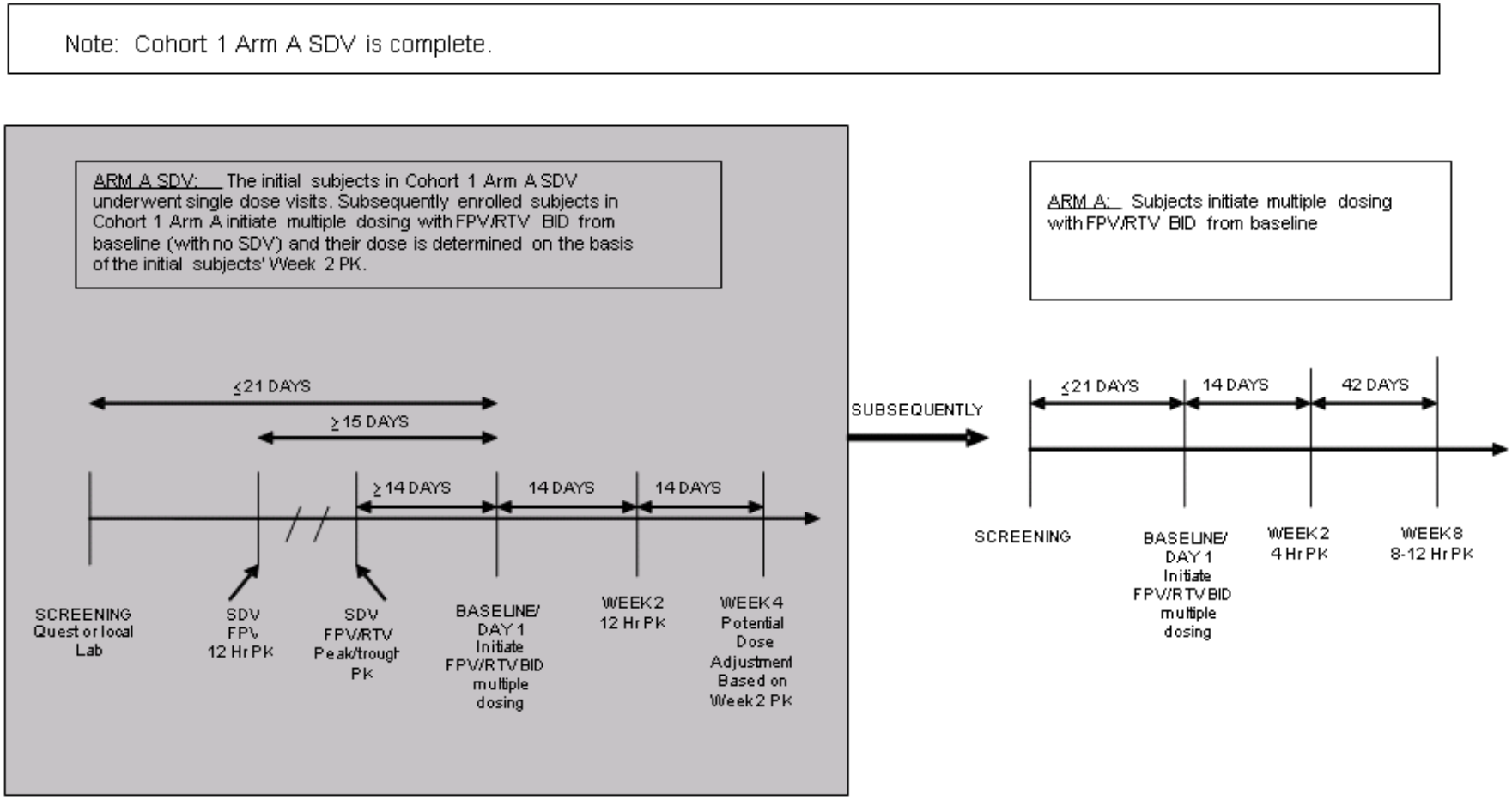
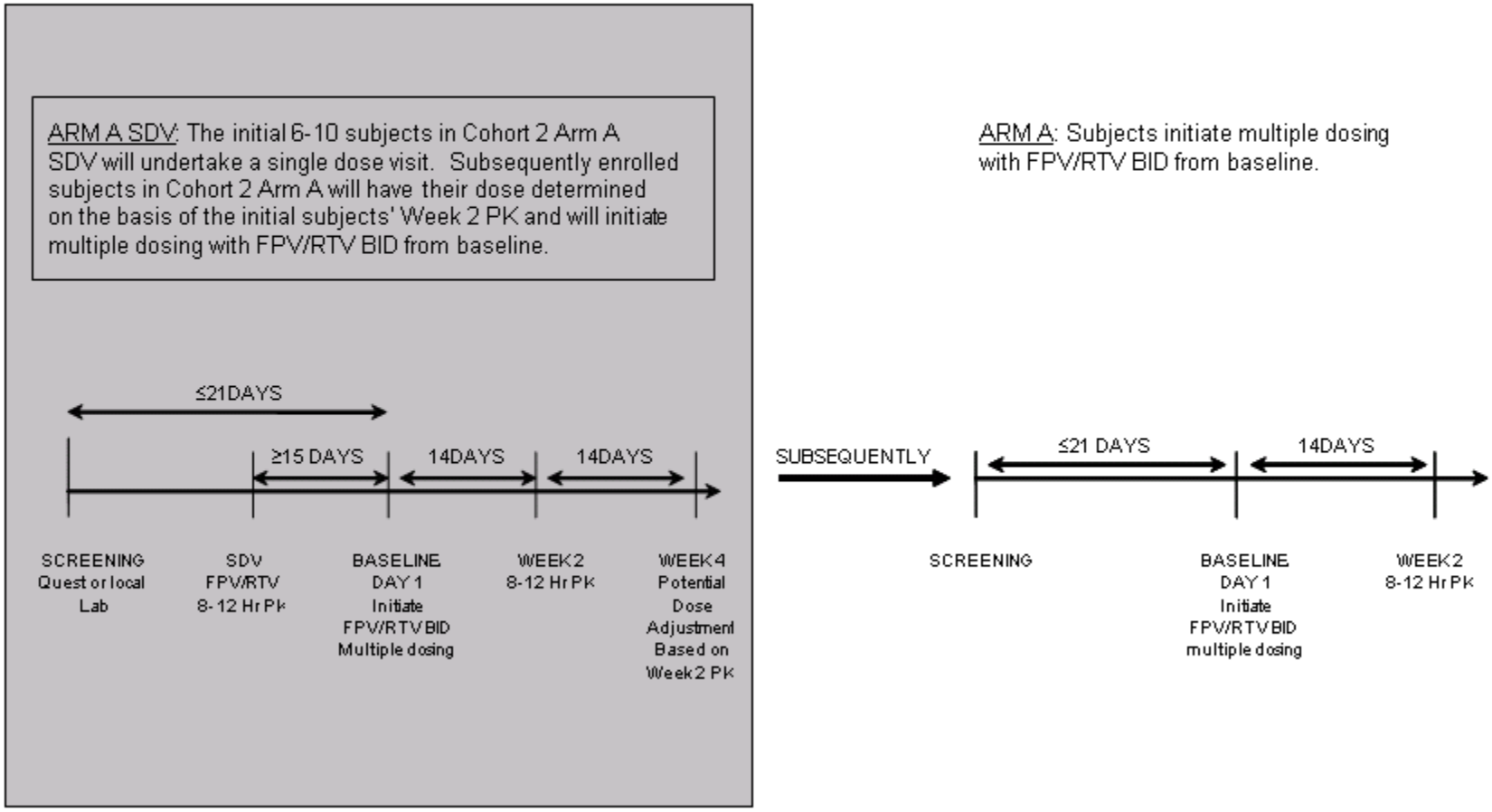


Figure 2 Study Design for Cohort 2 Arm A: PI-naïve or PI-experienced subjects 4 weeks to <6 months of age

Note: Cohort 2 Arm A SDV is complete.



Change 10:

Amend:

3.2. Study Population, 1st Paragraph

Original Text:

HIV-1 infected pediatric subjects 4 weeks to <2 years of age with screening plasma HIV-RNA ≥400copies/mL and who meet the eligibility criteria will be recruited into the study. As of Amendment 8, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 4 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 20-25 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Revised Text:

HIV-1 infected pediatric subjects 4 weeks to <2 years of age with screening plasma HIV-RNA ≥400copies/mL and who meet the eligibility criteria will be recruited into the study. As of Amendment 8, Cohort 1 Arm A (6 months to <2 years) **was to** enrol approximately 4 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 20-25 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Change 11:

Amend:

3.2.2. Exclusion Criteria

Original Text:

13. Treatment with other investigational drugs/therapies within 28 days prior to receiving study medication (note: treatments available through a Treatment IND or other expanded-access mechanism will be evaluated on a case-by-case basis in consultation with the sponsor).

Revised Text:

13. Treatment with other investigational drugs/therapies within 28 days prior to receiving study medication (note: treatments available through a Treatment IND or other expanded-access mechanism will be evaluated on a case-by-case basis in consultation with **GSK**).

Change 12:

Amend:

3.3.4.1 Rationale for Drug Dose Selection for Cohort 1 (6 months to 2 years), last paragraph

Original Text:

Per protocol amendment 8, since APV parameters following FPV/RTV 45/7 mg/kg BID were closer to adult targets in the newly enrolled subjects and in the original 6 month to 24month olds upon exclusion of the one low outlier and since APV parameters following FPV/RTV 60/7 mg/kg BID were significantly higher than adult targets, subjects enrolled in the future will receive FPV/RTV 45/7 mg/kg BID continuously without an increase to FPV/RTV 60/7 mg/kg BID at Week 2. Some subjects with consistently high C□ values following FPV/RTV 60/7 mg/kg BID have had their dose reduced to FPV/RTV 45/7 mg/kg BID. Other subjects previously enrolled and currently receiving FPV/RTV 60/7 mg/kg may have their dose modified at the discretion of the investigator and Sponsor.

Revised

Per protocol amendment 8, since APV parameters following FPV/RTV 45/7 mg/kg BID were closer to adult targets in the newly enrolled subjects and in the original 6 month to 24month olds upon exclusion of the one low outlier and since APV parameters following FPV/RTV 60/7 mg/kg BID were significantly higher than adult targets, subjects enrolled in the future will receive FPV/RTV 45/7 mg/kg BID continuously without an increase to FPV/RTV 60/7 mg/kg BID at Week 2. Some subjects with consistently high Cτ values following FPV/RTV 60/7 mg/kg BID have had their dose reduced to FPV/RTV 45/7 mg/kg BID. Other subjects previously enrolled and currently receiving FPV/RTV 60/7 mg/kg may have their dose modified at the discretion of the investigator and **GSK**.

Change 13:

Amend:

3.3.5.1. Dosage Regimen Adjustment Criteria,

Original Text:

Dose Adjustment Due to Subject Age exceeding 2 and 6 years

Subjects reaching and exceeding 2 years of age during the study in Cohort 1 should transition to the lower dose of FPV and RTV to 23 mg/kg and 3 mg/kg BID respectively, in accordance with the dosage regimen recommended for this age group in protocol APV29005. The change in dosage can be staged gradually over multiple visits and will be based on ongoing viral load, pharmacokinetic and safety assessments, at the investigator's discretion.

Subjects reaching and exceeding 6 years of age in Cohort 2 may transition to the lower dosage regimen (FPV 18 mg/kg and RTV 3 mg/kg BID) in accordance with the regimen approved for this age group. This dose change can be implemented gradually as the subject 'grows into' the new dose or at the time of their 6th birthday at the investigator's discretion.

Revised Text:

Dose Adjustment Due to Subject Age exceeding 2 and 6 years

Subjects reaching and exceeding 2 years of age during the study should transition to the lower dose of FPV and RTV to 23 mg/kg and 3 mg/kg BID respectively, in accordance with the dosage regimen recommended for this age group in protocol APV29005. The change in dosage can be staged gradually over multiple visits and will be based on ongoing viral load, pharmacokinetic and safety assessments, at the investigator's discretion.

Subjects reaching and exceeding 6 years of age may transition to the lower dosage regimen (FPV 18 mg/kg and RTV 3 mg/kg BID) in accordance with the regimen approved for this age group. This dose change can be implemented gradually as the subject 'grows into' the new dose or at the time of their 6th birthday at the investigator's discretion.

Change 14:

Amend:

3.3.7.2. Toxicity Management

Original Text:

Grade 4 Toxicity/Adverse Event

Study drug will be permanently discontinued in subjects who develop a Grade 4 AE or toxicity. However, if the investigator has compelling evidence that the AE is not causally related to the study drug(s), dosing may continue after discussion with and assent from the sponsor. Subjects experiencing Grade 4 AEs requiring permanent discontinuation of study drug therapy should be followed weekly until resolution of the AE and encouraged to complete the withdrawal study evaluation. A follow-up visit should be performed 4 weeks after the last dose of study drug.

Subjects with Grade 4 clinically asymptomatic laboratory abnormalities should be investigated for all potentially non-drug related causes and study drug(s) may be continued if the investigator has compelling evidence that the toxicity is NOT related to the study drug, following discussion with the sponsor.

Revised Text:

Grade 4 Toxicity/Adverse Event

Study drug will be permanently discontinued in subjects who develop a Grade 4 AE or toxicity. However, if the investigator has compelling evidence that the AE is not causally related to the study drug(s), dosing may continue after discussion with and assent from **GSK**. Subjects experiencing Grade 4 AEs requiring permanent discontinuation of study drug therapy should be followed weekly until resolution of the AE and encouraged to complete the withdrawal study evaluation. A follow-up visit should be performed 4 weeks after the last dose of study drug.

Subjects with Grade 4 clinically asymptomatic laboratory abnormalities should be investigated for all potentially non-drug related causes and study drug(s) may be continued if the investigator has compelling evidence that the toxicity is NOT related to the study drug, following discussion with **GSK**.

Change 15:

Amend:

3.3.8. Subject Management Options, last Paragraph

Original Text:

If a subject develops an AIDS diagnosis (CDC stage C) or other evidence of disease progression such that the treating clinician believes that changing therapy is required even though the above criteria have not been met, the investigator should contact the sponsor for further discussion on a case by case basis.

Revised Text:

If a subject develops an AIDS diagnosis (CDC stage C) or other evidence of disease progression such that the treating clinician believes that changing therapy is required even though the above criteria have not been met, the investigator should contact **GSK** for further discussion on a case by case basis.

Change 16:

Amend:

3.3.10.1. GSK Supplied Background NRTI Options, 10th Paragraph

Original Text:

All GSK supplied background NRTIs will be handled and stored in accordance with the product label or information provided by the sponsor.

Revised Text:

All GSK supplied background NRTIs will be handled and stored in accordance with the product label or information provided by **GSK**.

Change 17:

Amend:

4.3. Study Drug Accountability Procedures, 2nd Paragraph

Original Text:

All study drugs will be handled and stored in accordance with the product label or information provided by the sponsor.

Revised Text:

All study drugs will be handled and stored in accordance with the product label or information provided by **GSK**.

Change 18:

Amend:

5.8. Safety, 2nd Paragraph

Original Text:

Scheduled laboratory evaluations within the study will be undertaken by a central laboratory nominated by the sponsor. However, evaluation of hematology and clinical chemistry may be undertaken at a local accredited laboratory with the approval of GSK.

Revised Text:

Scheduled laboratory evaluations within the study will be undertaken by a central laboratory nominated by **GSK**. However, evaluation of hematology and clinical chemistry may be undertaken at a local accredited laboratory with the approval of GSK.

Change 19:

Amend:

5.9.1. Premature Discontinuation from the Study, 2nd Paragraph

Original Text:

Subjects may be prematurely discontinued from the study for any of the following reasons:

- Subject, subject's parent/guardian or investigator non-compliance.

- At the request of the subject's parent/guardian, investigator or sponsor.
- Progression of any medical condition which, in the opinion of the principal investigator, should preclude further participation.
- If the subject requires treatment with any of the medications listed in the Exclusion Criteria (Section 3.2.2).
- If the subject requires cytotoxic chemotherapy or radiation therapy (with the exception of local treatment for Kaposi's sarcoma).
- If the subject requires another investigational drug which when combined with the study drug would, in the opinion of the investigator or sponsor, jeopardize the validity of the subject's continued participation.

Revised Text:

Subjects may be prematurely discontinued from the study for any of the following reasons:

- Subject, subject's parent/guardian or investigator non-compliance.
- At the request of the subject's parent/guardian, investigator or **GSK**.
- Progression of any medical condition which, in the opinion of the principal investigator, should preclude further participation.
- If the subject requires treatment with any of the medications listed in the Exclusion Criteria (Section 3.2.2).
- If the subject requires cytotoxic chemotherapy or radiation therapy (with the exception of local treatment for Kaposi's sarcoma).
- If the subject requires another investigational drug which when combined with the study drug would, in the opinion of the investigator or **GSK**, jeopardize the validity of the subject's continued participation.

Change 20:

Amend:

7.1. Definition of an AE, 5th Paragraph

Original Text:

For GSK clinical trials, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

Revised Text:

For **ViiV Healthcare** clinical trials, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

Change 21:

Amend:

7.12. SAEs Involving a Non-GSK Product

Original Text:

7.12. SAEs Involving a Non-GSK Product

In those instances where an SAE has occurred in a subject receiving a non-GSK product as a comparator or concurrent medication, the report must be sent to the appropriate project contact for SAE receipt in the same time frames as if it were a GSK product (see Section 7.8, "Prompt Reporting of SAEs to GSK").

Revised Text:

7.12. SAEs Involving a Non-ViiV Healthcare Product

In those instances where an SAE has occurred in a subject receiving a **non-ViiV Healthcare product** as a comparator or concurrent medication, the report must be sent to the appropriate project contact for SAE receipt in the same time frames as if it were a **ViiV Healthcare product** (see Section 7.8, "Prompt Reporting of SAEs to GSK").

Change 22:

Amend:

8.8. Investigator Access to Data and Provision of Study Results, 3rd Paragraph

Original Text:

The results summary will be posted to the Clinical Study Register no later than 12 months after the last subject's last visit (LSLV) or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

Revised Text:

A results summary will be posted to a publicly available study register no later than 12 months after the last subject's last visit (LSLV) or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV.

Change 23:

Amend:

8.9. Information Disclosure and Inventions

Original Text:

Ownership:

All data and records provided by GSK or generated during the study (other than a subject's medical records) and all inventions discovered in the course of conducting the study are the property of GSK. If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed, that contract's ownership provisions shall apply rather than this statement.

Revised Text:

Ownership:

All data and records provided by GSK or generated during the study (other than a subject's medical records) and all inventions discovered in the course of conducting the study are the property of **ViiV Healthcare**. If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed, that contract's ownership provisions shall apply rather than this statement.

Change 24:

Additional text added:

8.10. External Review Committee

As per Amendment 9, an External Review Committee (ERC) will be established and utilized in this study. The ERC will provide external oversight of study conduct and medical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for ERC review is described in the charter, which is available upon request.

11.17. Appendix 17: Protocol Amendment 10

Title: APV20002 - A 48 week phase II, open-label, 2-cohort, multicentre study to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of GW433908 and GW433908/RTV when administered to HIV-1 infected protease inhibitor (PI) naïve and PI-experienced pediatric subjects aged 4 weeks to <2 years.

This protocol amendment will apply to all study sites.

This amendment is being implemented to amend information on the content of propylene glycol in FPV oral suspension, to close unboosted FPV Cohorts 1B and 2B and remove objectives and endpoints pertaining to unboosted FPV and to correct study sponsor information.

This amendment is considered substantial since a Dear Investigator Letter was sent to active study sites informing them of new information on the overall propylene glycol content of FPV oral suspension.

The amendment consists of the following changes:

1. Amend information on overall propylene glycol content in FPV oral suspension

   Reason for change: FPV oral suspension contains 10 mg/ml of propylene glycol as a solubilising agent for the preservatives. The contribution of propylene glycol arising from the two flavouring agents has recently been identified. Propylene glycol is present in these flavouring agents at 10 mg/ml, resulting in a total propylene glycol concentration of 20 mg/ml in the oral suspension.

2. Close unboosted FPV Cohorts 1B and 2B and remove objectives and endpoints pertaining to unboosted FPV.

   Reason for change: Based on the PK data from the age-specific FPV/RTV cohorts, the dose volumes of unboosted FPV oral suspension necessary to administer the calculated therapeutic dose in children aged <2 years would be approximately twice the boosted dose volumes. Enrolment into the unboosted FPV cohorts is therefore not advised due to these large volumes of FPV oral suspension that would need to be administered as they could result in poor adherence, likely leading to an inadequate virologic response and subsequent resistance.

3. Change of study sponsor information

   Reason for change: Study APV20002 is sponsored by ViiV Healthcare UK Limited and ViiV Healthcare Company.

Individual Changes:

Change 1:

Amend:

TITLE PAGE

Original Text:

Author: PPD

Revised Text:

Author: PPD

Change 2:

Amend:

SPONSOR INFORMATION PAGE

Original Text:

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is responsible for implementing and managing all aspects of this study.

ViiV Healthcare
980 Great West Road
Brentford
Middlesex
TW8 9GS
UK
Telephone: +44 (0)20 8380 6200

ViiV Healthcare
Five Moore Drive
Research Triangle Park
North Carolina USA
27709-3398
Telephone: +1 877 844 8872

Revised Text:

This study is sponsored by ViiV Healthcare **UK Limited and ViiV Healthcare Company.** GlaxoSmithKline is responsible for implementing and managing all aspects of this study.

ViiV Healthcare **UK Limited**
980 Great West Road
Brentford
Middlesex
TW8 9GS
UK
Telephone: +44 (0)20 8380 6200

ViiV Healthcare **Company**
Five Moore Drive
Research Triangle Park
North Carolina USA
27709-3398
Telephone: +1 877 844 8872

Change 3:

Amend:

PROTOCOL SUMMARY, 4th Paragraph

Original Text:

The FPV oral suspension incorporates minimal propylene glycol thereby facilitating its administration to children of all ages and allows co-administration with RTV oral solution.

Revised Text:

The FPV oral suspension incorporates **less** propylene glycol **than AGN oral solution** thereby facilitating its administration to children of all ages and allows co-administration with RTV oral solution.

Change 4:

Amend:

PROTOCOL SUMMARY, **Dose Rationale**, 9th Paragraph

Original Text:

Per Protocol Amendment 5, enrolment in the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is deferred until serial PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Revised Text:

Per Protocol Amendment 10, enrolment in the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is closed. Based on the PK data from the age-specific FPV/RTV cohorts, the dose volumes of unboosted FPV oral suspension necessary to administer the calculated therapeutic dose in children aged <2 years would be approximately twice the boosted dose volumes. Enrolment into the unboosted FPV cohorts is therefore not advised due to these large volumes of FPV oral suspension that would need to be administered as they could result in poor adherence, likely leading to an inadequate virologic response and subsequent resistance.

Change 5:

Amend:

STUDY OBJECTIVES

Original Text:

Primary

- To define the FPV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected PI-naïve pediatric subjects aged 4 weeks to <2 years (deferred per amendment 5)
- To define the FPV/RTV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the safety and tolerability of FPV (deferred per amendment 5) and FPV/RTV when administered as a component of combination therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years

Secondary

- To evaluate the antiviral activity of FPV (deferred per amendment 5) and FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the immunologic activity of FPV (deferred per amendment 5) and FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess systemic exposure to FPV when administered to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess plasma RTV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- To investigate the relationship of steady-state plasma APV PK parameters to changes in plasma HIV-1 RNA concentrations, CD4+ percentages and/or the occurrence of adverse events

- To assess subject adherence and parent/guardian perceptions of study medications
- To assess viral resistance patterns and to compare these patterns with treatment outcome (where permissible by blood volumes)

Revised Text:

Primary

- To define the FPV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected PI-naïve pediatric subjects aged 4 weeks to <2 years (deferred per amendment 5). **This objective has been removed with enrolment into the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) closed as per Protocol Amendment 10.**
- To define the FPV/RTV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the safety and tolerability of FPV/RTV when administered as a component of combination therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years. **The objective to evaluate the safety and tolerability of FPV BID dosage regimens has been removed as per Protocol Amendment 10.**

Secondary

- To evaluate the antiviral activity of FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the immunologic activity of FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess systemic exposure to FPV when administered to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess plasma RTV $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{\tau,ss}$ following multiple dose administration of FPV/RTV BID
- To investigate the relationship of steady-state plasma APV PK parameters to changes in plasma HIV-1 RNA concentrations, CD4+ percentages and/or the occurrence of adverse events
- To assess subject adherence and parent/guardian perceptions of study medications
- To assess viral resistance patterns and to compare these patterns with treatment outcome (where permissible by blood volumes)

The secondary objectives to evaluate the antiviral and immunologic activity of FPV have been removed as per Protocol Amendment 10.

Change 6:

Amend:

STUDY ENDPOINTS, Primary

Original Text:

- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV BID (deferred per amendment 5).
- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- Plasma unbound APV Cτ,ss and percent protein binding
- The incidence and nature of adverse events, laboratory abnormalities, and treatment –limiting toxicities
- Proportion of subjects who permanently discontinue FPV (deferred per amendment 5) or FPV/RTV due to adverse events.

Revised Text:

- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV BID (deferred per amendment 5). **This endpoint has been removed with enrolment into the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) closed as per Protocol Amendment 10.**
- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- Plasma unbound APV Cτ,ss and percent protein binding
- The incidence and nature of adverse events, laboratory abnormalities, and treatment –limiting toxicities
- Proportion of subjects who permanently discontinue FPV/RTV due to adverse events. **The endpoint 'Proportion of subjects who permanently discontinue FPV due to adverse events' has been removed as per Protocol Amendment 10.**

Change 7:

Amend:

STUDY DESIGN, 4th Paragraph

Original Text:

Enrolment into Arm B (unboosted FPV cohorts 1 and 2) as per amendment 5 has been deferred.

Revised Text:

Enrolment into Arm B (unboosted FPV cohorts 1 and 2) as per amendment **10** has been **closed**.

Change 8:

Amend:

STUDY DESIGN, **Overview**, 1st Paragraph

Original Text:

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

Revised Text:

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment **10**, enrolment in the Arm B cohorts (unboosted FPV) is **closed**.

Change 9:

Amend:

STUDY DESIGN, **Overview**, **Enrolment of Arm B (FPV BID)**

Original Text:

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 5, the decision to open the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) will be deferred until the Week 2 PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Revised Text:

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 10, enrolment in the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is closed. Based on the PK data from the age-specific FPV/RTV cohorts, the dose volumes of unboosted FPV oral suspension necessary to administer the calculated therapeutic dose in children aged <2 years would be approximately twice the boosted dose volumes. Enrolment into the unboosted FPV

cohorts is therefore not advised due to these large volumes of FPV oral suspension that would need to be administered as they could result in poor adherence, likely leading to an inadequate virologic response and subsequent resistance.

Change 10:

Amend:

PLANNED SAMPLE SIZE, 1st Paragraph

Original Text:

The sample size of 48 subjects was selected as an appropriate number to allow an accurate description of plasma APV PK, safety and tolerability of FPV BID, (N=24 for PK and safety; enrolment deferred per Amendment 5) and FPV/RTV BID, Arm A (N=24 for PK and safety). Safety and tolerability assessment of the FPV/RTV BID regimen (Arm A) will be for the duration of the study or until a subject permanently discontinues study drug. If less than 8 subjects in a cohort and dosage regimen complete the steady-state PK analysis on Week 2, additional subjects may be enrolled as replacement subjects. Additionally, if dose modification to the cohort dose is warranted, a further 8 subjects in each arm may be recruited to provide steady-state PK data on the revised dose.

Revised Text:

The sample size of 48 subjects was selected as an appropriate number to allow an accurate description of plasma APV PK, safety and tolerability of FPV BID, (N=24 for PK and safety; enrolment **closed per Amendment 10**) and FPV/RTV BID, Arm A (N=24 for PK and safety). Safety and tolerability assessment of the FPV/RTV BID regimen (Arm A) will be for the duration of the study or until a subject permanently discontinues study drug. If less than 8 subjects in a cohort and dosage regimen complete the steady-state PK analysis on Week 2, additional subjects may be enrolled as replacement subjects. Additionally, if dose modification to the cohort dose is warranted, a further 8 subjects in each arm may be recruited to provide steady-state PK data on the revised dose.

Change 11:

Amend:

STUDY POPULATION, 2nd Paragraph

Original Text:

Following Amendments 5 and 8, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 25 subjects in total to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 29 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Revised Text:

Following Amendments 5 and 8, Cohort 1 Arm A (6 months to <2 years) will enrol approximately 25 subjects in total to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 29 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is **closed**.

Change 12:

Amend:

1.2 Rationale, 7th Paragraph

Original Text:

The FPV oral suspension incorporates minimal propylene glycol which allows administration to children of all ages and co-administration with RTV oral solution.

Revised Text:

The FPV oral suspension incorporates **less** propylene glycol **than AGN oral solution** which allows administration to children of all ages and co-administration with RTV oral solution.

Change 13:

Amend:

2. STUDY OBJECTIVES AND ENDPOINTS

Original Text:

2.1 Study Objectives

Primary

- To define the FPV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected PI-naïve pediatric subjects aged 4 weeks to <2 years (deferred per amendment 5)
- To define the FPV/RTV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the safety and tolerability of FPV (deferred per amendment 5) and FPV/RTV when administered as a component of combination therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years

Secondary

- To evaluate the antiviral activity of FPV (deferred per amendment 5) and FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the immunologic activity of FPV (deferred per amendment 5) and FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess systemic exposure to FPV when administered to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess plasma RTV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- To investigate the relationship of steady-state plasma APV PK parameters to changes in plasma HIV-1 RNA concentrations, CD4+ percentages and/or the occurrence of adverse events
- To assess subject adherence and parent/guardian perceptions of study medications
- To assess viral resistance patterns and to compare these patterns with treatment outcome (where permissible by blood volumes)

2.2 Study Endpoints

Primary

- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV BID (deferred per amendment 5).
- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- Plasma unbound APV Cτ,ss and percent protein binding
- The incidence and nature of adverse events, laboratory abnormalities, and treatment-limiting toxicities
- Proportion of subjects who permanently discontinue FPV (deferred per amendment 5) or FPV/RTV due to adverse events.

Revised Text:

2.1 Study Objectives

Primary

- To define the FPV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected PI-naïve pediatric subjects aged 4 weeks to <2 years (deferred per amendment 5). **This objective has been removed with enrolment into the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) closed as per Protocol Amendment 10.**

- To define the FPV/RTV BID dosage regimens which will provide target steady-state plasma APV exposure to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the safety and tolerability of FPV/RTV when administered as a component of combination therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years. **The objective to evaluate the safety and tolerability of FPV BID dosage regimens has been removed as per Protocol Amendment 10.**

Secondary

- To evaluate the antiviral activity of FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To evaluate the immunologic activity of FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess systemic exposure to FPV when administered to HIV-1 infected pediatric subjects aged 4 weeks to <2 years
- To assess plasma RTV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- To investigate the relationship of steady-state plasma APV PK parameters to changes in plasma HIV-1 RNA concentrations, CD4+ percentages and/or the occurrence of adverse events
- To assess subject adherence and parent/guardian perceptions of study medications
- To assess viral resistance patterns and to compare these patterns with treatment outcome (where permissible by blood volumes)

The secondary objectives to evaluate the antiviral and immunologic activity of FPV have been removed as per Protocol Amendment 10.

2.2 Study Endpoints

Primary

- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV BID (deferred per amendment 5). **This endpoint has been removed with enrolment into the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) closed as per Protocol Amendment 10.**
- Plasma APV AUCτ,ss, Cmax,ss and Cτ,ss following multiple dose administration of FPV/RTV BID
- Plasma unbound APV Cτ,ss and percent protein binding
- The incidence and nature of adverse events, laboratory abnormalities, and treatment-limiting toxicities
- Proportion of subjects who permanently discontinue FPV/RTV due to adverse events. **The endpoint 'Proportion of subjects who permanently discontinue FPV due to adverse events' has been removed as per Protocol Amendment 10.**

Change 14:

Amend:

3.1. Study Design, 4th Paragraph

Original Text:

Arm B (unboosted FPV cohorts 1 and 2) as per amendment 5 has been deferred.

Revised Text:

Arm B (unboosted FPV cohorts 1 and 2) as per amendment **10** has been **closed**.

Change 15:

Amend:

3.1. Study Design, Overview, 1st Paragraph

Original Text:

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment 5, enrolment in the Arm B cohorts (unboosted FPV) is deferred.

Revised Text:

Cohort 1 Arm A (FPV/RTV, 6 months to <2years) and Cohort 2 Arm A (FPV/RTV, 4 weeks to <6 months) are open in parallel. Cohort 1 Arm A and Cohort 2 Arm A will recruit either PI-naïve or experienced subjects. As per Amendment **10**, enrolment in the Arm B cohorts (unboosted FPV) is **closed**.

Change 16:

Amend:

3.1. Study Design, **Overview, Enrolment of Arm B (FPV BID)**

Original Text:

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 5, the decision to open the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) will be deferred until the Week 2 PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Revised Text:

Cohort 1 (6 months to <2 years) and Cohort 2 (4 weeks to <6 months)

Per Protocol Amendment 10, enrolment in the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is closed. Based on the PK data from the age-specific FPV/RTV cohorts, the dose volumes of unboosted FPV oral suspension necessary to administer the calculated therapeutic dose in children aged <2 years would be approximately twice the boosted dose volumes. Enrolment into the unboosted FPV cohorts is therefore not advised due to these large volumes of FPV oral suspension that would need to be administered as they could result in poor adherence, likely leading to an inadequate virologic response and subsequent resistance.

Change 17:

Amend:

3.2 Study Population, 1st Paragraph

Original Text:

HIV-1 infected pediatric subjects 4 weeks to <2 years of age with screening plasma HIV-RNA ≥400copies/mL and who meet the eligibility criteria will be recruited into the study. As of Amendment 8, Cohort 1 Arm A (6 months to <2 years) was to enrol approximately 4 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 20-25 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is deferred.

Revised Text:

HIV-1 infected pediatric subjects 4 weeks to <2 years of age with screening plasma HIV-RNA ≥400copies/mL and who meet the eligibility criteria will be recruited into the study. As of Amendment 8, Cohort 1 Arm A (6 months to <2 years) was to enrol approximately 4 additional subjects to receive FPV/RTV BID. Cohort 2 Arm A (4 weeks to <6 months) will enrol approximately 20-25 subjects in total to receive FPV/RTV BID. Enrolment in the unboosted FPV BID cohorts (Arm B) is **closed**.

Change 18:

Amend:

3.3.1 Study Drugs, 3rd Paragraph

Original Text:

The FPV 50 mg/mL (43.2mg/mL APV molar equivalents) suspension is a white to off-white bubblegum and peppermint flavoured suspension for oral administration using a dosing syringe. Each mL of suspension contains 50 mg of FPV, equivalent to 43.2mg/mL of APV. The suspension contains the following inactive ingredients:

hydroxypropylmethyl cellulose, polysorbate 80, methylparaben, propylparaben, propylene glycol (overall 10 mg/mL), sucralose, calcium chloride, flavours and purified water. The FPV oral suspension is manufactured by GSK in Mississauga, Ontario, Canada.

Revised Text:

The FPV 50 mg/mL (43.2mg/mL APV molar equivalents) suspension is a white to off-white bubblegum and peppermint flavoured suspension for oral administration using a dosing syringe. Each mL of suspension contains 50 mg of FPV, equivalent to 43.2mg/mL of APV. The suspension contains the following inactive ingredients: hydroxypropylmethyl cellulose, polysorbate 80, methylparaben, propylparaben, propylene glycol (overall **20 mg**/mL), sucralose, calcium chloride, flavours and purified water. The FPV oral suspension is manufactured by GSK in Mississauga, Ontario, Canada.

Change 19:

Amend:

3.3.4.2. Rationale for Drug Dose Selection for Cohort 2 (4 weeks to 6 months), 2nd Paragraph

Original Text:

Per Protocol Amendment 5, enrolment of the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is deferred until serial PK data from the age-specific FPV/RTV cohorts are available to assist in the dose selection for the corresponding unboosted FPV cohort and any concerns regarding the high FPV dosing volumes have been addressed.

Revised Text:

Per Protocol Amendment **10**, enrolment of the unboosted cohorts (Cohort 1 Arm B and Cohort 2 Arm B) is **closed.**

Change 20:

Amend:

6.1. Sample Size Determination, 1st Paragraph

Original Text:

The sample size of 48 subjects was selected as an appropriate number to allow an accurate description of plasma APV PK, safety and tolerability of FPV BID, Arm B (N=24 for PK and safety; enrolment deferred per Amendment 5) and FPV/RTV BID, Arm A (N=24 for PK and safety). Safety and tolerability assessment of the FPV/RTV BID regimen (Arm A) will be for the duration of the study or until a subject permanently discontinues study drug. If less than 8 subjects in a cohort and dosage regimen complete the steady-state PK analysis on Week 2, additional subjects may be enrolled as

replacement subjects. Additionally, if dose modification to the cohort dose is warranted, a further 8 subjects in each arm may be recruited to provide steady-state PK data on the revised dose.

Revised Text:

The sample size of 48 subjects was selected as an appropriate number to allow an accurate description of plasma APV PK, safety and tolerability of FPV BID, Arm B (N=24 for PK and safety; enrolment **closed** per Amendment **10**) and FPV/RTV BID, Arm A (N=24 for PK and safety). Safety and tolerability assessment of the FPV/RTV BID regimen (Arm A) will be for the duration of the study or until a subject permanently discontinues study drug. If less than 8 subjects in a cohort and dosage regimen complete the steady-state PK analysis on Week 2, additional subjects may be enrolled as replacement subjects. Additionally, if dose modification to the cohort dose is warranted, a further 8 subjects in each arm may be recruited to provide steady-state PK data on the revised dose.

11.18. Appendix 18: Protocol Amendment 11

Title: APV20002 - A 48 week phase II, open-label, 2-cohort, multicentre study to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of GW433908 and GW433908/RTV when administered to HIV-1 infected protease inhibitor (PI) naïve and PI-experienced pediatric subjects aged 4 weeks to <2 years.

This protocol amendment will apply to all study sites.

This amendment is being implemented to include information on 3TC and ABC tablets to be provided by GSK as background NRTI options, to update the list of drugs not to be co-administered with FPV and RTV, to provide the option to discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis, and to update information on posting study results on publicly available clinical trials registers and publication.

The amendment consists of the following changes:

1. 3TC and ABC tablets provided by GSK as background NRTI options

   Reason for change: Some subjects have reached an age and weight that would allow them to switch from 3TC and ABC solutions to scored tablets.

2. Updated list of drugs not to be co-administered with FPV and RTV

   Reason for change: based on recent drug interaction data studies, the list of drugs not to be co-administered with FPV and RTV has been amended. Information on drug interactions relevant to abacavir and lamivudine has also been added.

3. Discontinuation of PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis

   Reason for change:

   FPV/RTV regimens for pediatric subjects 4 weeks to <2 years of age have been determined based on 24-week PK, safety and efficacy results from this study. Further collection of plasma APV, FPV and RTV trough concentrations should also not inform any further individualised dose adjustments as ongoing subjects are receiving recommended FPV/RTV regimens and any further dosing changes would follow the approved dosing recommendations without PK sampling, including a transition to FPV/RTV 18/3 mg/kg BID at 6 years.

4. Information on posting study results on publicly available clinical trials registers and publication updated.

   Reason for change: GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit, to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the

scientific literature, and to post further study information to the GSK Clinical Study Register to supplement the results summary when manuscript publication in a peer-reviewed journal is not feasible.

Individual Changes:

Change 1:

Amend: 3.2.2 Exclusion Criteria, Exclusion criterion 12

Original Text:

12. Treatment with any of the following medications within 28 days prior to receiving study medication or the anticipated need during the study:

    - Amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, simvastatin, terfenadine, and triazolam (these drugs have been excluded for safety reasons).
    - Carbamazepine, dexamethasone, phenobarbital, primidone, rifampin, St Johns Wort, (these drugs have been excluded because they have the potential to decrease plasma protease inhibitor concentrations).

Revised Text:

12. Treatment with any of the following medications within 28 days prior to receiving study medication or the anticipated need during the study:

    - Amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, simvastatin, terfenadine, and triazolam (these drugs have been excluded for safety reasons).
    - Carbamazepine, dexamethasone, phenobarbital, primidone, rifampin, St Johns Wort, (these drugs have been excluded because they have the potential to decrease plasma protease inhibitor concentrations).

    Note: per Protocol Amendment 11, the list of drugs not to be co-administered with FPV and RTV has been updated (see Section 3.3.10, "Concurrent Medications and Non-Drug Therapies"). As recruitment is closed, the exclusion criteria have not been amended.

Change 2:

Amend: 3.3.2 Background NRTI Options Provided by GlaxoSmithKline

Original Text:

Abacavir and 3TC will be provided by GSK as optional background NRTIs for subjects of at least 3 months of age who are determined to be susceptible to ABC and/or 3TC.

Susceptibility will be determined by investigator discretion and/or investigator interpretation of screening resistance viral genotype data, if available. ABC and 3TC are licensed for the treatment of pediatric subjects of at least 3 months of age in the USA, the European Union, and South Africa.

The ABC oral solution contains 20 mg/mL of ABC in aqueous solution and the inactive ingredients strawberry and banana flavours, citric acid (anhydrous), methylparaben, propylparaben, propylene glycol, saccharin sodium, sodium citrate, and sorbitol solution. The ABC oral solution is manufactured by GSK in Mississauga, Ontario, Canada.

The 3TC oral solution contains 10 mg/mL of 3TC in aqueous solution and the inactive ingredients strawberry and banana flavours, citric acid (anhydrous), methylparaben, propyparaben, propylene glycol, sodium citrate (dihydrous) and sucrose (20% w/v). The 3TC oral solution is manufactured by GSK in Mississauga, Ontario, Canada.

In the event that a subject permanently discontinues study medication, GSK will no longer provide background 3TC and ABC medications.

Revised Text:

Abacavir and 3TC will be provided by GSK as optional background NRTIs for subjects of at least 3 months of age who are determined to be susceptible to ABC and/or 3TC. Susceptibility will be determined by investigator discretion and/or investigator interpretation of screening resistance viral genotype data, if available.

ABC and 3TC oral solutions are licensed for the treatment of pediatric subjects of at least 3 months of age in the USA, the European Union, and South Africa. **Scored 3TC tablets are licensed in the USA, the European Union, and South Africa for the treatment of pediatric subjects weighing greater than or equal to 14kg for whom a solid dosage form is appropriate. Scored ABC tablets are licensed in the USA and the European Union for the treatment of pediatric subjects weighing greater than or equal to 14kg for whom a solid dosage form is appropriate. Scored ABC tablets will only be provided by GSK for subjects in South Africa when a licence has been granted there.**

The ABC oral solution contains 20 mg/mL of ABC in aqueous solution and the inactive ingredients strawberry and banana flavours, citric acid (anhydrous), methylparaben, propylparaben, propylene glycol, saccharin sodium, sodium citrate, and sorbitol solution. The ABC oral solution is manufactured by GSK in Mississauga, Ontario, Canada.

The ABC tablet contains ABC sulfate equivalent to 300 mg ABC and the inactive ingredients colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate, Type A. The tablet is coated with a film that is made of methylhydroxypropylcellulose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin. ABC tablets are manufactured by GSK in Ware, Hertfordshire, United Kingdom.

The 3TC oral solution contains 10 mg/mL of 3TC in aqueous solution and the inactive ingredients strawberry and banana flavours, citric acid (anhydrous), methylparaben,

propyparaben, propylene glycol, sodium citrate (dihydrous) and sucrose (20% w/v). The 3TC oral solution is manufactured by GSK in Mississauga, Ontario, Canada.

The 3TC tablet contains 150 mg of 3TC and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablet is coated with a film that is made of hypromellose, titanium dioxide, macrogol, and polysorbate 80. 3TC tablets are manufactured by GSK in Ware, Hertfordshire, United Kingdom.

In the event that a subject permanently discontinues study medication, GSK will no longer provide background 3TC and ABC medications.

Change 3:

Amend: 3.3.5 Dosages and dosing

Original Text:

FPV and RTV will be administered according to the doses described in Section 3.3.4.

Both the FPV and RTV oral formulations should be administered with food. If vomiting or spitting up occurs within 30 minutes of administration, parents/guardians should be instructed to re-administer the study medications.

The recommended dose of ABC is 8 mg/kg BID (up to a maximum of 600 mg/day).

The recommended dose of 3TC is 4 mg/kg BID (up to a maximum of 300 mg/day).

Revised Text:

FPV and RTV will be administered according to the doses described in Section 3.3.4.

Both the FPV and RTV oral formulations should be administered with food. If vomiting or spitting up occurs within 30 minutes of administration, parents/guardians should be instructed to re-administer the study medications.

The recommended dose of ABC **solution** is 8 mg/kg BID (up to a maximum of 600 mg/day).

For ABC tablets, the recommended dose is one-half of a scored tablet taken twice daily in children weighing between 14kg and 21kg and one-half of a scored tablet taken in the morning and one whole tablet taken in the evening in children weighing between 21kg and 30kg.

The recommended dose of 3TC **solution** is 4 mg/kg BID (up to a maximum of 300 mg/day).

For 3TC tablets, the recommended dose is one-half of a scored tablet taken twice daily in children weighing between 14kg and 21kg and one-half of a scored tablet

taken in the morning and one whole tablet taken in the evening in children weighing between 21 kg and 30 kg.

Change 4:

Amend: 3.3.5.1 Dosage Regimen Adjustment Criteria, Dose Adjustment Due to Subject Age exceeding 2 and 6 years

Original Text:

Subjects reaching and exceeding 2 years of age during the study should transition to the lower dose of FPV and RTV to 23 mg/kg and 3 mg/kg BID respectively, in accordance with the dosage regimen recommended for this age group in protocol APV29005. The change in dosage can be staged gradually over multiple visits and will be based on ongoing viral load, pharmacokinetic and safety assessments, at the investigator's discretion.

Subjects reaching and exceeding 6 years of age may transition to the lower dosage regimen (FPV 18 mg/kg and RTV 3 mg/kg BID) in accordance with the regimen approved for this age group. This dose change can be implemented gradually as the subject 'grows into' the new dose or at the time of their 6th birthday at the investigator's discretion.

Revised Text:

Subjects reaching and exceeding 2 years of age during the study should transition to the lower dose of FPV and RTV to 23 mg/kg and 3 mg/kg BID respectively, in accordance with the dosage regimen recommended for this age group in protocol APV29005. The change in dosage can be staged gradually over multiple visits and will be based on ongoing viral load, pharmacokinetic and safety assessments, at the investigator's discretion.

Subjects reaching and exceeding 6 years of age may transition to the lower dosage regimen (FPV 18 mg/kg and RTV 3 mg/kg BID) in accordance with the regimen approved for this age group. This dose change can be implemented gradually as the subject 'grows into' the new dose or at the time of their 6th birthday at the investigator's discretion.

In consultation with the investigator, GSK may discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis once a subject has reached and exceeded 2 years and has initiated the 23/3 mg/kg BID dosing regimen after Week 48. Any further dosing changes would follow the approved dosing recommendations without PK sampling, including a transition to FPV/RTV 18/3 mg/kg BID at 6 years.

Change 5:

Amend: 3.3.10. Concurrent Medications and Non-Drug Therapies, 7th and 8th paragraph

Original Text:

FPV and RTV should not be co-administered with amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, simvastatin, terfenadine and triazolam. Co-administration may result in competitive inhibition of metabolism of these medications and may cause serious or life-threatening adverse events. Co-administration of FPV or FPV/RTV with rifabutin results in significant increases in plasma rifabutin levels, therefore the dose of rifabutin should be reduced by at least 50% when co-administered with FPV and by at least 75% when co-administered with FPV/RTV. Caution should be used and subjects should be monitored closely for signs of toxicity.

FPV and RTV should not be co-administered with carbamazepine, dexamethasone, phenobarbital, primidone, rifampin and St. John's Wort because the PI concentrations may be significantly decreased, reducing efficacy.

Revised Text:

FPV and RTV should not be co-administered with **alfuzosin,** amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, **halofantrine,** lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, **PDE5 inhibitors including sildenafil,** simvastatin, terfenadine and triazolam. Co-administration may result in competitive inhibition of metabolism of these medications and may cause serious or life-threatening adverse events. Co-administration of FPV or FPV/RTV with rifabutin results in significant increases in plasma rifabutin levels, therefore the dose of rifabutin should be reduced by at least 50% when co-administered with FPV and by at least 75% when co-administered with FPV/RTV. Caution should be used and subjects should be monitored closely for signs of toxicity.

Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression, have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this interaction is also expected with other corticosteroids metabolized via the P450 3A pathway.

Concomitant use of fluticasone propionate and ritonavir should be avoided unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

FPV and RTV should not be co-administered with carbamazepine, dexamethasone, phenobarbital, primidone, rifampin and St. John's Wort because the PI concentrations

may be significantly decreased, reducing efficacy. **FPV and RTV should also not be co-administered with hepatitis C virus (HCV) protease inhibitors telaprevir and boceprevir because both APV and HCV PI concentrations may be significantly decreased, with the possibility of sub-therapeutic concentrations.**

Change 6:

Amend: 3.3.10.1 GSK Supplied Background NRTI Options, Sections on interactions relevant to abacavir and lamivudine added

Interactions Relevant to Abacavir

Based on the results of *in vitro* experiments and the known major metabolic pathways of ABC, the potential for drug interactions involving ABC is low.

ABC shows no potential to inhibit metabolism mediated by the cytochrome P450 3A4 enzyme. It has also been shown *in vitro* not to interact with drugs that are metabolised by CYP 3A4, CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for drug interactions with antiretroviral protease inhibitors and other drugs metabolised by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between ABC, zidovudine and 3TC.

Ethanol - The metabolism of ABC is altered by concomitant ethanol resulting in an increase in AUC of ABC of about 41%. Given the safety profile of ABC, these findings are not considered clinically significant. ABC has no effect on the metabolism of ethanol.

Methadone - In a PK study, co-administration of 600 mg ABC twice daily with methadone showed a 35% reduction in ABC Cmax and a one hour delay in tmax, but AUC was unchanged. The changes in ABC PK are not considered clinically relevant. In this study, ABC increased the mean methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.

Retinoids - Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with ABC is possible but has not been studied.

Refer to the local prescribing information for additional information on concurrent therapies.

Interactions Relevant to Lamivudine

The likelihood of interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active

renal secretion via the organic cationic transport system, e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

Active substances shown to be predominately excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.

Zidovudine - A modest increase in Cmax (28%) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of lamivudine.

Trimethoprim/sulphamethoxazole - Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see Dosage and Administration). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole for the treatment of Pneumocystis carinii pneumonia and toxoplasmosis has not been studied.

Zalcitabine - Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

Refer to the local prescribing information for additional information on concurrent therapies.

Change 7:

Amend: 3.3.10.1 GSK Supplied Background NRTI Options, Packaging and Labeling of GSK Supplied Background NRTI Options, Handling of GSK Supplied Background NRTI Options, Table

Original Table:

All GSK supplied background NRTIs should be stored until the time of dispensing as follows:

Abacavir oral solution	**US/Canada/Latin America** – Store between 20°C - 25°C (68°F - 77°F) **DO NOT FREEZE.** May be refrigerated. **Europe/ South Africa** – Store below 30°C **DO NOT FREEZE**
Lamivudine oral solution	**US/Canada/Latin America** – Store in tightly closed bottles at 25°C (77°F) **Europe/ South Africa** – Store at or below 25°C

Revised Table:

All GSK supplied background NRTIs should be stored until the time of dispensing as follows:

Abacavir oral solution	**US/Canada/Latin America** – Store between 20°C - 25°C (68°F - 77°F) **DO NOT FREEZE.** May be refrigerated. **Europe/ South Africa** – Store below 30°C **DO NOT FREEZE**
Abacavir tablet*	**South Africa – Store at or below 30°C.**
Lamivudine oral solution	**US/Canada/Latin America** – Store in tightly closed bottles at 25°C (77°F) **Europe/ South Africa** – Store at or below 25°C
Lamivudine tablet	**South Africa – Store at or below 30°C.**

***Only supplied when licensed in South Africa.**

Change 8:

Amend: 5.7 Bioanalysis and Pharmacokinetic Samples, Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter

Original Text:

All subjects will undergo additional plasma trough PK sampling of 1.0mL of whole blood (just prior to receiving a scheduled dose of FPV/RTV BID) at Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter.

In addition, at Week 16 (both Cohorts) and Week 36 (Cohort 1 only), subjects will have a plasma trough PK sample of 2.0mL whole blood collected (prior to receiving the scheduled dose of FPV/RTV BID) to determine the unbound concentration of APV.

Revised Text:

All subjects will undergo additional plasma trough PK sampling of 1.0mL of whole blood (just prior to receiving a scheduled dose of FPV/RTV BID) at Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter.

In addition, at Week 16 (both Cohorts) and Week 36 (Cohort 1 only), subjects will have a plasma trough PK sample of 2.0mL whole blood collected (prior to receiving the scheduled dose of FPV/RTV BID) to determine the unbound concentration of APV.

In consultation with the investigator, GSK may discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis once a subject has reached and exceeded 2 years and has initiated the 23/3 mg/kg BID dosing regimen after Week 48. Any further dosing changes would follow the approved dosing recommendations without PK sampling, including a transition to FPV/RTV 18/3 mg/kg BID at 6 years.

Change 9:

Amend: Section 8.8.

Original Text:

8.8. Investigator Access to Data and Provision of Study Results

GSK will provide the investigator with a copy of the CRF data collected from the site. When a clinical study report is completed, GSK will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subject.

A results summary will be posted to a publicly available study register no later than 12 months after the last subject's last visit (LSLV) or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV.

Revised Text:

8.8. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

GSK will provide the investigator with a copy of the CRF data collected from the site. When a clinical study report is completed, GSK will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subject.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

Change 10:

Amend: 10. TABLES, Revised Flow Chart of Laboratory Scheduled Assessments (Per Amendments 5 and 7), Footnote 10

Original Text:

Samples for APV/RTV trough concentration determination collected 12 hours after the last dose at Week 8 (Cohort 2 Arm A only) and Weeks 12, 16, 24, 36, 48, and every 12 weeks thereafter (both cohorts).

Revised Text:

Samples for APV/RTV trough concentration determination collected 12 hours after the last dose at Week 8 (Cohort 2 Arm A only) and Weeks 12, 16, 24, 36, 48, and every 12 weeks thereafter (both cohorts). **In consultation with the investigator, GSK may discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis once a subject has reached and exceeded 2 years and has initiated the 23/3 mg/kg BID dosing regimen after Week 48. Any further dosing changes would follow the approved dosing recommendations without PK sampling, including a transition to FPV/RTV 18/3 mg/kg BID at 6 years.**

11.19. Appendix 19: Protocol Amendment 12

Title: APV20002 - A 48 week phase II, open-label, 2-cohort, multicentre study to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of GW433908 and GW433908/RTV when administered to HIV-1 infected protease inhibitor (PI) naïve and PI-experienced pediatric subjects aged 4 weeks to <2 years.

This protocol amendment is considered minor as it is being implemented to provide additional clarity regarding the optional extended study participation for currently enrolled subjects in South Africa who have successfully completed the primary endpoint in 2011. The primary change in the protocol is provide additional RTV formulation treatment options for the South African subjects because the RTV manufacturer is discontinuing sale of the protocol-mandated RTV oral solution. This amendment will apply to the subjects enrolled in APV20002 as of November 1, 2019 at study sites in South Africa.

As the protocol was last amended in 2012, in the amended version, in addition to the information regarding additional RTV formulations that can be used, and clarification for the still-enrolled South African subjects that they may continue participate in the study until they are of a sufficient weight (≥39 Kg) and are able to take FPV tablets, at which time they will be withdrawn. Additional updates have been made to the safety and dosing sections including updating the FPV and RTV dosing tables for children more than 6 years of age have been updated, updates to the list of drugs not to be co-administered with FPV and RTV have been added, and additional information regarding abacavir hypersensitivity. Minor updates have also been made to ensure that relevant treatment guidelines and publications are cited, to indicate that AGN has been discontinued, to update the name of the study medical monitor, and to correct grammar and punctuation.

The amendment consists of the following changes shown in order of occurrence in the protocol:

1. Update name and contact information for the ViiV Healthcare Medical Monitor

Reason for the change: For clarification purposes, the Sponsor of the APV20002 Study is ViiV Healthcare. ViiV Healthcare engages its affiliate, GlaxoSmithKline, to perform certain clinical services on its behalf; the appropriate ViiV Healthcare medical monitor contact information has subsequently been updated.

2. Include additional RTV formulation treatment options, descriptions and dosing instructions for the additional RTV formulations and update the RTV and FPV dosing tables for heavier weight subjects.

Reason for the change: Sale of the oral RTV solution is being discontinued by the manufacturer in South Africa. Subjects enrolled in South Africa sites who successfully completed 48 weeks of treatment are permitted to remain in the study until they reach a weight of 39 kg at which time they must be withdrawn (subjects at 39 kg or more would have commercial access to FPV tablets outside of the APV20002 study). As the study was not originally anticipated to extend for this

length of time, the dosing tables were updated for both FPV and RTV to provide dosing instructions for these older and larger weight subjects. The dosing tables have been updated for weights through 38 kg for FPV and up to 100 mg BID for RTV (maximum recommended dose)

3. In Section 1.3.2 FPV Pediatric Clinical Data references to subsequently published pediatric study results have been added here (and in the Reference section) as well as referring to local labels for summaries of the available data.

Reason for change: The most current information on the primary endpoint results from these pediatric studies are available in the individual publications and in the local product information:

4. Updated list of drugs not to be co-administered with FPV and RTV

Reason for change: based on recent drug interaction data studies, the list of drugs not to be co-administered with FPV and RTV has been amended. Information on drug interactions relevant to abacavir and lamivudine has also been updated.

5. Updated the information on Abacavir HSR

Reason for change: Since the last update, new information became available that the risk for abacavir HSR to occur is significantly increased for patients who test positive for the HLA-B*5701 allele. Additional information regarding HLA-B*5701 testing and information regarding suspected abacavir hypersensitivity reactions and rash management have been updated.

6. The section regarding prompt reporting of SAES to GSK was moved to Section 7.9 and the previous Section 7.9 (Regulatory Reporting Requirements For SAEs) was moved to Section 7.8.

Reason for change: to improve flow and understanding.

7. Efficacy: Viral load measurements, after 2013, are being performed using the Abbott Realtime HIV-1 assay instead of the Roche Amplicor assay.

Reason for change: the Roche assay was discontinued by the manufacturer. The Abbott assay has a LLOD of 40 copies/mL. This change only impacts subjects enrolled in the South African sites.

8. Assent forms will also be obtained from subjects still enrolled in the study as of Nov 1, 2019.

Reason for change: Informed consent was originally obtained from the carers as the subjects were 2 years or younger at enrolment. The enrolled subjects who chose to participate after successfully completing 48 weeks of treatment at the South African sites are now of an age where they can also give assent for study participation.

Individual Changes

Note: minor punctuation or grammar corrections have not been included in the list of changes. Updated references are indicated in the individual changes for the sections in which they are cited. Specific revisions to the text are shown in bold.

Change 1: **Medical Monitor Contact Information**

Original Text:

PPD , MD
GlaxoSmithKline
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD
Mobile: PPD

Revised Text

PPD , MD PhD
ViiV Healthcare
5 Moore Drive
P.O. 13398
Research Triangle Park USA 27709
Mobile: PPD

Change 2

Changes within the Protocol Summary Section

2nd Paragraph

Original Text:

Agenerase (AGN, amprenavir, APV) is a protease inhibitor (PI) developed for the treatment of HIV disease. Although AGN has demonstrated antiviral activity and is generally safe when given in combination with other antiretroviral agents to subjects at all stages of HIV infection, the pill count with the capsule formulation and substantial volume of oral solution required (1.5mL/kg BID) are less than optimal and may impact long term adherence to therapy. To reduce the pill burden of APV delivered as AGN, a t and oral suspension formulation of fosamprenavir (FPV, GW433908, LEXIVA™/ TELZIR™), the phosphate ester prodrug of APV, have been developed to facilitate dosing of adult and pediatric HIV-1 infected patients. The safety and efficacy of FPV-containing regimens was demonstrated in three Phase III clinical trials in adults.

The use of combination therapy with at least 3 drugs, including either a PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI), plus a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone is the current standard of care and recommended for initial treatment of HIV-infected adults and children [US Department of Health and Human Services, 2006; Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2006; South Africa Guidelines, 2005]. There

remains a need for additional therapies for HIV infected children, in particular there are limited choices for a third agent to be given in combination with two NRTIs, and the choices are even more limited in children <2 years of age.

Revised Text

Agenerase (AGN, amprenavir, APV) **was** a protease inhibitor (PI) developed for the treatment of HIV disease. Although AGN demonstrated antiviral activity and **was** generally safe when given in combination with other antiretroviral agents to subjects at all stages of HIV infection, the pill count with the capsule formulation and substantial volume of oral solution required (1.5mL/kg BID) **was** less than optimal and **could** impact long term adherence to therapy. To reduce the pill burden of APV delivered as AGN, a tablet and oral suspension formulation of fosamprenavir (FPV, GW433908, LEXIVA™/ TELZIR™), the phosphate ester prodrug of APV, **was** developed to facilitate dosing of adult and pediatric HIV-1 infected patients. The safety and efficacy of FPV-containing regimens was demonstrated in three Phase III clinical trials in adults.

The use of combination therapy with 3 drugs, including either a PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI) **or an integrase inhibitor**, plus a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone is the current standard of care for and is recommended for initial treatment of **most** HIV-infected adults and children **[DHHS, 2019; EACS, 2018; Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children; 2019].** There remains a need for additional therapies for HIV infected children, in particular there are limited choices for a third agent to be given in combination with two NRTIs, and the choices are even more limited in children <2 years of age.

Protocol Summary, Dose Rationale, 10th Paragraph

Original Text:

None

Revised Text (paragraph added)

Per Protocol Amendment 12, as sale of RTV oral solution is being discontinued by the manufacturer in South Africa, additional RTV formulation options have been added for the South African sites. The RTV dosing is based upon the weight of the child and include RTV supplied as 100 mg tablets, capsules or powders/sachets.

Protocol Summary, Study Design, 1st Paragraph

Original Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks

until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

Single dose PK data for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Enrolment into Arm B (unboosted FPV cohorts 1 and 2) as per amendment 10 has been closed.

Recruitment Status for APV20002 – from (FSFV) Oct 03 to Oct 10

Age (yrs) Cohorts	No. of Subjects originally planned	Cumulative enrolment and current status
1A 6months - <2yr PI-naïve/exp FPV/RTV (boosted)	12	29[1] enrolled 12 ongoing
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	12	29[1] enrolled 15 ongoing

1. Current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments

Revised Text

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART. **Per protocol amendment 12; only subjects at sites in South Africa remain enrolled as supplies of oral FPV suspension are not commercially available in South Africa. Subjects successfully completing 48 weeks of therapy and receiving clinical benefit who weigh less than 39 kg may continue to receive FPV oral suspension provided by GSK. Once subjects reach a weight of 39 kg, South African treatment guidelines**

permit the use of the FPV tablets in children weighing ≥39 kg and these subjects will be withdrawn as FPV tablets are commercially available in South Africa.

Single dose PK data for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Enrolment into Arm B (unboosted FPV cohorts 1 and 2) as per amendment 10 has been closed.

Recruitment Status for APV20002 – **from Oct 2003 (FSFV) to Jul 2011 (cutoff for 48 week CSR**

Age (yrs) Cohorts	No. of Subjects originally planned	Cumulative enrolment and current status
1A 6 months - <2yr PI-naïve/exp FPV/RTV (boosted)	12	**26[1] enrolled** **11 ongoing[2]**
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	12	**28[1] enrolled** **14 ongoing[2]**

1. **A total of 59 patients were enrolled but 5 were discontinued after receiving single dose of FPV;** current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments
2. **Ongoing as of cutoff for 48 week CSR (July 2011)**

Protocol Summary Study Drugs and Dosages

Original text:

Study drugs are defined as FPV and RTV. FPV will be administered as a 50mg/mL (43.2mg/mL APV molar equivalents) oral suspension. RTV will be given as an 80mg/mL oral solution. Both the FPV and RTV oral formulations should be administered with food. If vomiting or spitting up occurs within 30 minutes of administration, parents/guardians should be instructed to re-administer the study medications.

Revised Text

Study drugs are defined as FPV and RTV. FPV will be administered as a 50 mg/mL (43.2 mg/mL APV molar equivalents) oral suspension. RTV will be **administered** as an 80 mg/mL oral solution, **as a 100 mg capsule or tablet, or as a 100 mg powder packet/sachet**. Choice of appropriate formulation will depend on participant's weight, availability of formulation and participant/caregiver preference. Both the FPV and RTV oral formulations should be administered with food. If vomiting or spitting up occurs

within 30 minutes of administration, parents/guardians should be instructed to re-administer the study medications.

Protocol Summary Measurements and Evaluations

Original text:

Schedules showing the timing of study procedures and laboratory evaluations for all subjects are shown in Section 10. Subjects will attend the clinic at Screening (within approximately 21 days prior to Baseline/Day 1), Day 1 (Baseline), and Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART. A follow-up visit will be performed 4 weeks after the permanent discontinuation of study drug.

Cohort 1 (6 months to <2 years) Arm A: Plasma samples for evaluation of PK parameters will be collected over 4 hours at Week 2 and over 8-12 hours (12 hour sample optional) at Week 8. Plasma trough PK samples will be collected at Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter.

Cohort 2 (4 weeks to <6 months) Arm A: Plasma PK samples will be collected over 8-12 hours (12 hour sample optional) at Week 2. Plasma trough PK samples will be collected at Weeks 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.

Revised Text

Schedules showing the timing of study procedures and laboratory evaluations for all subjects are shown in Section 10. Subjects will attend the clinic at Screening (within approximately 21 days prior to Baseline/Day 1), Day 1 (Baseline), and Weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects **who successfully complete 48 weeks on therapy** may continue to receive FPV oral suspension **provided by GSK** until they no longer derive clinical benefit, **weigh 39 kg or more,** or according to prior agreements between GSK and participating study sites for provision of ART. A follow-up visit will be performed 4 weeks after the permanent discontinuation of study drug.

Cohort 1 (6 months to <2 years) Arm A: Plasma samples for evaluation of PK parameters will be collected over 4 hours at Week 2 and over 8-12 hours (12 hour sample optional) at Week 8. Plasma trough PK samples will be collected at Weeks 12, 16, 24, 36, 48 and every 12 weeks thereafter. **Protocol amendment 11 (effective date October 26, 2012) provided the option to discontinue PK sampling once a subject had reached and exceeded 2 years and had initiated the 23/3 mg/kg FPV/RTV BID dosing regimen. PK sampling was discontinued after approval of the amended protocol in South Africa.**

Cohort 2 (4 weeks to <6 months) Arm A: Plasma PK samples will be collected over 8-12 hours (12 hour sample optional) at Week 2. Plasma trough PK samples will be collected at Weeks 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter. **PK sampling was subsequently discontinued after approval of APV20002 protocol amendment 11, by which time the last enrolled subject had been enrolled in the study for more than 48 weeks.**

Change 3

Amend: Section 1 Introduction

Section 1.1 Background

Original text:

Agenerase (AGN, amprenavir, APV) is a protease inhibitor (PI) for the treatment of HIV disease. Although AGN has demonstrated antiviral activity and is generally safe when given in combination with other antiretroviral agents to subjects at all stages of HIV infection, the pill count with the capsule formulation and substantial volume of oral solution required (1.5mL/kg BID) are less than optimal and may impact long term adherence to therapy. To reduce the pill burden of APV delivered as AGN, a tablet and oral suspension formulation of fosamprenavir (FPV, GW433908, LEXIVA/ TELZIR), the phosphate ester prodrug of APV, have been developed to facilitate dosing of adult and pediatric HIV-1 infected patients.

The safety and efficacy of three FPV-containing regimens has been demonstrated in three Phase III clinical trials, APV30001 (antiretroviral [ART]-naïve subjects), APV30002 (ART-naïve subjects), and APV30003 (PI-experienced subjects). [GlaxoSmithKline Document Number GM2002/00054/00, Study APV30002; GlaxoSmithKline Document Number RM2002/00088/00, Study APV30001; GlaxoSmithKline Document Number RM2002/00140/00, Study APV30003]. Based on these studies, three dosing regimens in adults are approved in the United States (US); for ART-naïve subjects, FPV 1400mg BID, FPV 700mg BID + ritonavir (RTV) 100mg BID or FPV 1400mg QD + RTV 200mg QD and for PI-experienced subjects, FPV 700mg BID + RTV 100mg BID. In Europe, the FPV 700mg BID + RTV 100mg BID regimen was approved for PI-naïve or experienced HIV-1 infected adults. A further study in ART-naïve adults (ESS100732, KLEAN) demonstrated non-inferiority of FPV 700mg BID + RTV 100mg BID compared to lopinavir (LPV)/ RTV (Kaletra) BID [GlaxoSmithKline Document Number RM2006/00010/00, Study ESS100732].

Revised Text

Agenerase (AGN, amprenavir, APV) **was** a protease inhibitor (PI) for the treatment of HIV disease. Although AGN demonstrated antiviral activity and **was** generally safe when given in combination with other antiretroviral agents to subjects at all stages of HIV infection, the pill count with the capsule formulation and substantial volume of oral solution required (1.5mL/kg BID) **were** less than optimal and may **have impacted** long term adherence to therapy. To reduce the pill burden of APV delivered as AGN, a tablet and oral suspension formulation of fosamprenavir (FPV, GW433908, LEXIVA/

TELZIR), the phosphate ester prodrug of APV, **were** developed to facilitate dosing of adult and pediatric HIV-1 infected patients.

The safety and efficacy of three FPV-containing regimens has been demonstrated in three Phase III clinical trials, APV30001 (antiretroviral [ART]-naïve subjects), APV30002 (ART-naïve subjects), and APV30003 (PI-experienced subjects). [GlaxoSmithKline Document Number GM2002/00054/00, Study APV30002; GlaxoSmithKline Document Number RM2002/00088/00, Study APV30001; GlaxoSmithKline Document Number RM2002/00140/00, Study APV30003]. Based on these studies, **four** dosing regimens in adults are approved in the United States (US) for ART-naïve subjects: FPV 1400 mg BID, FPV 700 mg BID + ritonavir (RTV) 100 mg BID or FPV 1400 mg QD + RTV 200 mg QD or **FPV 1400 mg QD + RTV 100 mg QD** and for PI-experienced subjects: FPV 700 mg BID + RTV 100 mg BID. In Europe, the FPV 700 mg BID + RTV 100 mg BID regimen was approved for PI-naïve or experienced HIV-1 infected adults. A further study in ART-naïve adults (ESS100732, KLEAN) demonstrated non-inferiority of FPV 700 mg BID + RTV 100 mg BID compared to lopinavir (LPV)/ RTV (Kaletra) BID [GlaxoSmithKline Document Number RM2006/00010/00, Study ESS100732].

Change 4

Amend Section 1.2 Rationale

Original text:

The use of combination therapy with at least 3 drugs, including either a PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI), plus a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone is the current standard of care and recommended for initial treatment of HIV-infected adults and children [US Department of Health and Human Services, 2006; Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2006; South Africa Guidelines, 2005]. There remains a need for additional therapies for HIV infected children, in particular there are limited choices for a third agent to be given in combination with two NRTIs, and the choices are even more limited in children <2 years of age.

Revised Text

The use of combination therapy with 3 drugs, including either a PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI) **or an integrase inhibitor**, plus a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone is the current standard of care for and is recommended for initial treatment of **most** HIV-infected adults and children **[DHHS, 2019; EACS, 2018; Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children; 2019].** There remains a need for additional therapies for HIV infected children, in particular there are limited choices for a third agent to be given in combination with two NRTIs, and the choices are even more limited in children <2 years of age.

At the time the APV20002 study was collecting the primary outcome data (through Week 48), in the NNRTI class, efavirenz (EFZ) and nevirapine (NVP) **were** available as liquid formulations. NVP is associated with rare but potentially life threatening adverse reactions whilst EFZ is associated with neuropsychiatric adverse reactions [Viramune Package Insert, 2010] [Sustiva Package Insert, 2010].

Similarly, at the time the APV20002 study was collecting the primary outcome data (through Week 48), in the PI class, six agents - APV, indinavir (IDV), nelfinavir (NFV), RTV lopinavir/ritonavir (LPV/RTV), and darunavir **were** approved for use in HIV-1 infected children. **APV has subsequently been discontinued.** The lower age limits for which these PIs **were** approved for use **varies** between countries. **Deleted text: but range from >1 month (RTV) or 6 months (LPV/RTV) in some countries, to 2 years of age or older for the other currently approved PIs (6 years or older for darunavir).**

LPV/RTV is a PI **combination frequently** used in children. Several studies support the use of LPV/RTV in children. An early study in children 6 months to 12 years of age demonstrated the antiviral activity of LPV/RTV over a 24 week period, with plasma HIV-1 RNA levels of <400 copies/mL being achieved in 82% of ART-naïve children and 66% of children with a mixture of NRTI-experience and NRTI + PI-experience, and accompanying improvements in CD4+ lymphocyte counts, after 24 weeks of therapy [Violari, 2000]. In a later study, 100 children ages 6 months to 12 years who were either ART naïve or ART-experienced but NNRTI naïve, received LPV/RTV as part of an ART regimen. At Week 48, 79% of subjects had plasma HIV-1 RNA levels of <400 copies/mL with corresponding mean increases in CD4+ cell counts from baseline [Post, 2010; Ross, 2015; Saez-Llorens, 2003]. Recently, data on the use of LPV/RTV in infants <6 weeks of age has been presented. In this study, 8 infants ages ≥14 days to ≤6 weeks received standard dose LPV/RTV over 24 weeks. LPV/RTV AUCs were significantly lower than seen in an older cohort ages 6 weeks to 6 months, yet the regimen resulted in virological suppression (plasma HIV-1 RNA <400 copies/mL) in 7/8 subjects [Pinto, 2007].

Although **these** PI therapies available for the treatment of HIV-1 infected children effectively inhibit HIV replication, most display limitations, such as lack of suitable formulations, inflexible dosing schedules and clinical side effects. For instance, no liquid formulation is available for indinavir and it is more difficult to assure adequate fluid intake to avoid renal complications in children than in adults. The powder formulation of nelfinavir is difficult to administer to children, and consequently the adult tablets are used which results in a restrictive dosing schedule [Gibb, 2000b]. The major limitations to the pediatric formulation of RTV are the taste, vomiting as an adverse event and high alcohol content [Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Use of Antiretroviral Agents in Pediatric HIV Infection. Updated April 16, 2019. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed August 20, 2019.

Pelton, 1998]. Although Kaletra is now widely used in treating HIV infected children, the pediatric liquid formulation of LPV/RTV does have a similar alcohol content (42%) to

that in the RTV liquid (43%) [Kaletra Package Insert, **2019;** Norvir, Package Insert, 2017]. Deleted text: ,

Change 5

Amend: 1.3.2.FPV Pediatric Clinical Data

Original Text:

Pharmacokinetic, safety, and antiviral response data in pediatric subjects 2 to 18 years of age receiving FPV with or without RTV are available from Study APV29005 (24 week data; BID regimens) and Study APV20003 (48 week data; QD regimens). Additionally, 48 week data from a small number of pediatric subjects <2 years of age receiving FPV/RTV in Study APV20002 have also been reported. Refer to the Fosamprenavir Investigator's Brochure Supplement for summaries of the available data from these studies.

Revised Text

Pharmacokinetic, safety, and antiviral response data in pediatric subjects 2 to 18 years of age receiving FPV with or without RTV are available from Study APV29005 **[Fortuny, 2014],** and Study APV20003 **[Chadwick, 2007].** Additionally, 48 week data from the pediatric subjects <2 years of age receiving FPV/RTV in Study APV20002 have also been reported **[Cotton, 2014; 2014; Ross, 2015].** Overall the safety profile of fosamprenavir with and without ritonavir in paediatric patients was comparable to that observed in adult clinical studies**. Refer to the local product information for summaries of the available data from these studies.**

Change 6

Amend: Section 3.1 Study Design

Original Text:

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART.

Single dose visits (SDVs) for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in previous protocol amendments (3, 5, 7 and 8). The evaluable PK data for approximately 50 to 60 subjects will be analysed at the end of the study and will include subjects who have been on different dosing regimens.

Arm B (unboosted FPV cohorts 1 and 2) as per amendment 10 has been closed.

Table 6 Recruitment Status for APV20002 – from (FSFV) Oct 03 to Oct. 10

Age (yrs) Cohorts	No. of Subjects originally planned	Cumulative enrolment and current status
1A 6months - <2yr PI-naïve/exp FPV/RTV (boosted)	12	29[1] enrolled 12 ongoing
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	12	29[1] enrolled 15 ongoing

1. Current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments

Revised Text

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study to be conducted in approximately 48 HIV-1 infected pediatric subjects 4 weeks to <2 years old. This study may be performed at study centers in North and South America, Europe, and Africa or in other regions as appropriate. Subjects successfully completing 48 weeks of therapy in APV20002 may continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. In countries where local availability is delayed or the drug is not yet available through national treatment programs, subjects may continue to receive FPV until they no longer derive clinical benefit or according to prior agreements between GSK and participating study sites for provision of ART**. Per protocol amendment 12; only subjects at sites in South Africa remain enrolled as supplies of oral FPV suspension are not commercially available in South Africa. Subjects successfully completing 48 weeks of therapy and receiving clinical benefit who weigh less than 39 kg may continue to receive FPV oral suspension provided by GSK. Once subjects reach a weight of 39 kg, South African treatment guidelines permit the use of the FPV tablets in children weighing ≥39 kg and these subjects will be withdrawn as FPV tablets are commercially available in South Africa.**

Single dose visits (SDVs) for both Cohort 1 Arm A and 2 Arm A are complete.

Dose recommendations have been modified in previous protocol amendments (3, 5, 7 and 8). **Protocol amendment 10 allows for the discontinuation of collection of samples for PK analysis after the age of the subjects exceeds 2 years and the subjects have successfully completed 48 weeks of treatment. Therefore,** the evaluable PK data for

approximately 50 to 60 subjects will be analysed **when it is available for all subjects successfully completing 48 weeks of therapy** and will include subjects who have been on different dosing regimens.

Arm B (unboosted FPV cohorts 1 and 2) as per amendment 10 has been closed.

Table 7 Recruitment Status for APV20002 – from Oct 2003 (FSFV) to Jul 2011 (cutoff for 48 week CSR

Age (yrs) Cohorts	No. of Subjects originally planned	Cumulative enrolment and current status
1A **6 months** - <2yr PI-naïve/exp FPV/RTV (boosted)	12	**26[1] enrolled** **11 ongoing[2]**
2A 4wks - <6mo PI-naïve/exp FPV/RTV (boosted)	12	**28[1] enrolled** **14 ongoing[2]**

1. **A total of 59 patients were enrolled but 5 discontinued after receiving single dose of FPV;** current total enrolled patients exceeds the original cohort target because of dose changes in previous amendments
2. **Ongoing as of cutoff for 48 week CSR (July 2011)**

Change 7

Amend: Section 3.2.3 Other Study Eligibility Criteria Considerations

Original Text:

In order to assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drugs: Such documents may include, but are not limited to, the Fosamprenavir Investigator's Brochure Supplement and local product information or the International Product Information.

Revised text:

In order to assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drugs: Such documents may include, but are not limited to, the **Text deleted <Fosamprenavir Investigator's Brochure Supplement>,** local product information or the International Product Information.

Change 8

Amend: Section 3.3.1 Study Drugs; 2-6th paragraphs

Original Text:

In this study FPV will be provided by GSK. In all countries, RTV oral solution will be obtained locally and reimbursed, if acceptable to regulatory authorities. GSK will provide RTV by other means if reimbursement is not acceptable. Both FPV and RTV will be considered study drugs. Therefore, in the event that a subject permanently discontinues FPV, the subject will discontinue from this protocol and GSK will no longer supply FPV or RTV for that subject.

The FPV 50mg/mL (43.2mg/mL APV molar equivalents) suspension is a white to off-white bubblegum and peppermint flavoured suspension for oral administration using a dosing syringe. Each mL of suspension contains 50mg of FPV**,** equivalent to 43.2mg/mL of APV. The suspension contains the following inactive ingredients: hydroxypropylmethyl cellulose, polysorbate 80, methylparaben, propylparaben, propylene glycol (overall 20mg/mL), sucralose, calcium chloride, flavours and purified water. The FPV oral suspension is manufactured by GSK in Mississauga, Ontario, Canada.

The RTV oral solution manufactured by Abbott Laboratories contains 80mg/mL of RTV in a peppermint and caramel flavoured vehicle and will be administered via a dosing syringe. The RTV solution contains the following inactive ingredients: ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid, saccharin sodium, peppermint oil, creamy caramel flavouring and FD&C Yellow No. 6.

Revised text:

In this study, FPV **oral suspension** will be provided by GSK. In all countries, RTV oral solution, **powder, tablets or capsules** will be obtained locally and reimbursed if acceptable to regulatory authorities. GSK will provide RTV by other means where reimbursement is not acceptable, **or GSK may provide RTV if local supplies are not available and RTV is able to be obtained from other c**ountries. Both FPV and RTV will be considered study drugs. Therefore, in the event that a subject permanently discontinues FPV **oral suspension**, the subject will discontinue from this protocol and GSK will no longer supply FPV or RTV for that subject.

The FPV 50 mg/mL (43.2mg/mL APV molar equivalents) suspension is a white to off-white bubblegum and peppermint flavoured suspension for oral administration using a dosing syringe. Each mL of suspension contains 50 mg of FPV**,** equivalent to 43.2 mg/mL of APV. The suspension contains the following inactive ingredients: hydroxypropylmethyl cellulose, polysorbate 80, methylparaben, propylparaben, propylene glycol (overall 20 mg/mL), sucralose, calcium chloride, flavours and purified water. The FPV oral suspension is manufactured by GSK in Mississauga, Ontario, Canada.

The RTV oral solution manufactured by **Abbvie** contains 80 mg/mL of RTV in a peppermint and caramel flavoured vehicle and will be administered via a dosing syringe. The RTV solution contains the following inactive ingredients: ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid, saccharin sodium, peppermint oil, creamy caramel flavouring and FD&C Yellow No. 6.

The RTV 100 mg oral powder/sachets manufactured by Abbvie also contains the inactive ingredients: copovidone, sorbitan monolaurate, and colloidal silicon dioxide, and are sugar-free.

The 100 mg RTV tablets manufactured by Abbvie contains the inactive ingredients copovidone, anhydrous dibasic calcium phosphate, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The film coating contains: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, polyethylene glycol 3350, colloidal silicon dioxide, and polysorbate 80. The 100 mg RTV tablets are white, film-coated, ovaloid tablets and are sugar-free.

The 100 mg soft gelatin RTV capsules manufactured by Abbvie contains ritonavir 100 mg (SSSS enantiomer); other ingredients include ethanol (12 % v/v), butylated hydroxytoluene (antioxidant), oleic acid, polyoxyl 35 castor oil, water, gelatin, sugar, sorbitol, glycerin, titianium dioxide, medium chain triglycerides, lecithin and black ink.

Change 9

Amend: Section 3.3.2 Background NRTI Options Provided by GlaxoSmithKline; 7th paragraph

Original Text:

The 3TC tablet contains 150mg of 3TC and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablet is coated with a film that is made of hypromellose, titanium dioxide, macrogol, and polysorbate 80. 3TC tablets are manufactured by GSK in Ware, Hertfordshire, United Kingdom.

Revised text:

The 3TC tablet contains 150 mg of 3TC and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablet is coated with a film that is made of hypromellose, **magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate**, titanium dioxide, and polysorbate 80. 3TC tablets are **white, diamond-shaped and scored and** manufactured by GSK in Ware, Hertfordshire, United Kingdom.

Change 10

Amend: Section 3.3.3 Background ART Not Provided by GlaxoSmithKline

Revised Section Heading: 3.3.3.Background ART Not Provided by GlaxoSmithKline/ViiV Healthcare

Original Text:

GSK will not provide or reimburse background ART other than ABC or 3TC.

Revised text:

GSK/**ViiV Healthcare** will not provide or reimburse background ART other than ABC or 3TC.

Change 11

Amend: Section 3.3.5 Dosages and dosing; 1st and 5th paragraphs

Original Text paragraph 1:

FPV and RTV will be administered according to the doses described in Section 3.3.4.

Revised text paragraph 1:

FPV and RTV will be administered according to the doses described in Section 3.3.4 **and in Section 3.3.5**.1.

Original text paragraph 5

The recommended dose of 3TC solution is 4mg/kg BID (up to a maximum of 300mg/day).

Revised text paragraph 5

The recommended dose of 3TC solution is **currently** 4 mg/kg BID (up to a maximum of 300 mg/day). **The dosing recommendation in the local label should be followed.**

Change 12

Amend: Section 3.3.5.1 Dosage Regimen Adjustment Criteria in Dose Adjustment Due to Subject Age exceeding 2 and 6 years; 1st and 3rd paragraphs

Original Text paragraph 1:

Subjects reaching and exceeding 2 years of age during the study should transition to the lower dose of FPV and RTV to 23mg/kg and 3mg/kg BID respectively, in accordance with the dosage regimen recommended for this age group in protocol APV29005. The change in dosage can be staged gradually over multiple visits and will be based on ongoing viral load, pharmacokinetic and safety assessments, at the investigator's discretion.

Revised text paragraph 1:

Subjects reaching and exceeding 2 years of age during the study should transition to the lower dose of FPV and RTV to 23 mg/kg and 3 mg/kg BID respectively **<Text deletion: in accordance with the dosage regimen recommended for this age group in protocol APV29005**>. The change in dosage can be staged gradually over multiple visits and will be based on ongoing viral load, pharmacokinetic and safety assessments, at the investigator's discretion.

Original Text paragraph 3:

In consultation with the investigator, GSK may discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis once a subject has reached and exceeded 2 years and has initiated the 23/3mg/kg BID dosing regimen after Week 48. Any further dosing changes would follow the approved dosing recommendations without PK sampling, including a transition to FPV/RTV 18/3mg/kg BID at 6 years.

Revised text paragraph 3:

In consultation with the investigator, GSK may discontinue PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis once a subject has reached and exceeded 2 years and has initiated the 23/3 mg/kg BID dosing regimen after Week 48. Any further dosing changes would follow the approved dosing recommendations without PK sampling, including a transition to FPV/RTV 18/3mg/kg BID at 6 years. **Note: after Protocol Amendment 11 became effective, PK sampling and monitoring of plasma APV, FPV and RTV concentration on an individual basis was discontinued.**

Change 13

Amend: Section 3.3.7.3 Specific Events; 4th-paragraphs

Original Text

The appearance of rash in the absence of other symptoms or signs is not indicative of hypersensitivity to ABC. Subjects receiving ABC who develop rash of any grade should be evaluated for the possibility of hypersensitivity as outlined below.

Study treatment should be managed as outlined in the following table:

Rash Management

Event	Action to be Taken		
	FPV BID or FPV/RTV BID	**ABC**	**3TC**
Grade 1 rash alone	Therapy can continue	Evaluate for the possibility of hypersensitivity. If there is no evidence of any other organ system involvement and the subject has no constitutional symptoms (fever, malaise, fatigue, headache), ABC may be continued with the warning to discontinue immediately and permanently if other signs and/or symptoms consistent with HSR appear.	Therapy can continue
Grade 1 rash with symptoms indicating multi-organ involvement[1]	Discontinue FPV BID or FPV/RTV BID. Therapy should not be reinitiated unless the investigator has compelling evidence that the rash is not caused by FPV.	Discontinue ABC immediately and permanently[2]	Therapy can continue
Grade 2 rash alone	Therapy can continue	Follow Grade 1 rash alone instructions	Therapy can continue
Grade 2 rash with symptoms indicating multi-organ involvement[1]	Discontinue FPV BID or FPV/RTV BID. Therapy should not be reinitiated unless the investigator has compelling evidence that the rash is not caused by FPV.	Discontinue ABC immediately and permanently[2]	Discontinue 3TC. Therapy should not be reinitiated unless the investigator has compelling evidence that the rash is not caused by 3TC.
Grade 3/4 rash alone or with symptoms indicating multi-organ involvement[1]	Discontinue FPV BID or FPV/RTV BID and do not reinitiate therapy[3]	Discontinue ABC immediately and permanently[3]	Discontinue 3TC[3]

1. Symptoms include: systemic symptoms (fever, GI symptoms including nausea, vomiting, diarrhea or abdominal pain) or allergic symptoms, or mucosal involvement, or severe tiredness, achiness or generally ill feeling.
2. ABC therapy should be permanently stopped and another NRTI therapy should be initiated.
3. Medications should be permanently stopped and the subject withdrawn from the trial.

Revised text

The appearance of rash in the absence of other symptoms or signs is not indicative of hypersensitivity to ABC. Subjects receiving ABC **as part** of **their NRTI background regimen** should be evaluated for the possibility of a **clinically suspected ABC HSR and managed appropriately** as outlined **in the local prescribing**. Subjects should be instructed to contact the Investigator as soon as possible if they develop a rash while on study.

Subjects who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Erythema Multiforme. SJS, TEN and Erythema Multiforme have been reported very rarely in patients taking ABC-containing products. These patients generally do not have the cluster of additional

symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC HSR, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, ABC (and / or all other concurrent medication(s) suspected in the Investigators causality assessment) should be discontinued, and the subject should not be re-challenged with any ABC-containing medicinal product (i.e., TRIUMEQ, ZIAGEN, TRIZIVIR, EPZICOM or KIVEXA).

As many products other than abacavir also cause rash and/or serious skin reactions, all other medicinal products that the subject is receiving should also be reviewed and discontinued as appropriate.

Study treatment should be managed as outlined in the following table:

Rash Management

Event	Action to be Taken		
	FPV BID or FPV/RTV BID	**ABC**	**3TC**
Grade 1 rash alone	Therapy can continue	Evaluate for the possibility of hypersensitivity. If there is no evidence of any other organ system involvement and the subject has no constitutional symptoms (fever, malaise, fatigue, headache), ABC may be continued **at the investigators discretion** with the warning to discontinue immediately and permanently if other signs and/or symptoms consistent with HSR appear. **The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops**.	Therapy can continue
Grade 1 rash with symptoms indicating multi-organ involvement[1]	Discontinue FPV BID or FPV/RTV BID. Therapy should not be reinitiated unless the investigator has compelling evidence that the rash is not caused by FPV.	Discontinue ABC immediately and permanently[2] **Subjects should be treated as clinically appropriate and followed until resolution of the AE.**	Therapy can continue
Grade 2 rash alone	Therapy can continue	Follow Grade 1 rash alone instructions	Therapy can continue
Grade 2 rash with symptoms indicating multi-organ involvement[1]	Discontinue FPV BID or FPV/RTV BID. Therapy should not be reinitiated unless the investigator has compelling evidence that the rash is not caused by FPV.	Discontinue ABC immediately and permanently[2] **The subject should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.**	Discontinue 3TC. Therapy should not be reinitiated unless the investigator has compelling evidence that the rash is not caused by 3TC.
Grade 3/4 rash alone or with symptoms indicating multi-organ involvement[1]	Discontinue FPV BID or FPV/RTV BID and do not reinitiate therapy[3] **Subjects should be treated as clinically appropriate and followed until resolution of the AE.**	Discontinue ABC immediately and permanently[3] **Subjects should be treated as clinically appropriate and followed until resolution of the AE**.	Discontinue 3TC[3] **Subjects should be treated as clinically appropriate and followed until resolution of the AE.**

1. Symptoms include: systemic symptoms (fever, GI symptoms including nausea, vomiting, diarrhea or abdominal pain) or allergic symptoms, or mucosal involvement, or severe tiredness, achiness or generally ill feeling.
2. ABC therapy should be permanently stopped and another NRTI therapy should be initiated.
3. Medications should be permanently stopped and the subject withdrawn from the trial. .

Change 14

Amend: Section 3.3.7.4 Abacavir Hypersensitivity Reaction, 1st paragraph

Original text

In clinical studies, approximately 5% of subjects receiving ABC develop a hypersensitivity reaction (HSR) that in rare cases has proved fatal. However, in the PENTA 5 study [Gibb, 2000a] only 1 of the 92 ART-naïve, symptomatic children, aged 3 months to 16 years who were treated with a regimen containing ABC developed a classical hypersensitivity reaction. In CNAA3006, which utilized an ABC containing backbone, ABC HSR was observed in 2% of pediatric subjects.

Revised text

In clinical studies, **conducted before the introduction of screening for the HLA-B*5701 allele,** approximately 5% of subjects receiving ABC develop a hypersensitivity reaction (HSR) that in rare cases has proved fatal. However, in the PENTA 5 study [Gibb, 2000a] only 1 of the 92 ART-naïve, symptomatic children, aged 3 months to 16 years who were treated with a regimen containing ABC developed a classical hypersensitivity reaction. In CNAA3006, which utilized an ABC containing backbone, ABC HSR was observed in 2% of pediatric subjects. **The risk for abacavir HSR to occur is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of *HLA-B*5701* and subsequently avoiding ABC in *HLA-B*5701* positive patients, significantly reduced the incidence of clinically suspected ABC HSR from 7.8% (66 of 847) to 3.4% (27 of 803) (p<0.0001) [Mallal, 2008]. In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of subjects who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively [Post, 2010; Squires, 2010].**

It is recommended that any HIV-infected patient without prior exposure to abacavir be screened for HLA-B*5701 allele. Screening is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended. In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision making. Even in the absence of the HLAB* 5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Amend: Section 3.3.7.4 Abacavir Hypersensitivity Reaction, paragraph 9

Original text

Some subjects with hypersensitivity were initially thought to have onset respiratory diseases (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis, or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in

ABC being continued or re-introduced, leading to more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. If hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC (ZIAGEN, TRIZIVIR™ or the ABC/3TC fixed dose combination) should be restarted.

Revised text

Some subjects with hypersensitivity were initially thought to have onset respiratory diseases (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis, or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in ABC being continued or re-introduced, leading to more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. If hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC (ZIAGEN, TRIZIVIR, KIVEXA, **TRIUMEQ or any other ABC-containing product**) should be restarted.

Amend: Section 3.3.7.4 Abacavir Hypersensitivity Reaction, paragraphs 11-13

Original text

Subjects who develop a hypersensitivity reaction must discontinue ABC and must NEVER be rechallenged with any medicinal product that contains ABC (ZIAGEN, TRIZIVIR or the ABC/3TC fixed dose combination). Restarting any ABC-containing product following a hypersensitivity reaction results in a prompt return of symptoms within hours. **This recurrence of the hypersensitivity reaction may be more severe than on initial presentation and may include life-threatening hypotension and death.**

There have been infrequent reports of hypersensitivity reactions following reintroduction of ABC, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal or a respiratory symptom).

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms of a hypersensitivity reaction.

Revised text

Subjects who develop a hypersensitivity reaction must discontinue ABC and must NEVER be rechallenged with any medicinal product that contains ABC (ZIAGEN, TRIZIVIR, KIVEXA, TRIUMEQ or any ABC-containing product). Restarting any ABC-containing product following a hypersensitivity reaction results in a prompt return of symptoms within hours. **This recurrence of the hypersensitivity reaction may be more severe than on initial presentation and may include life-threatening hypotension and death.**

There have been infrequent reports of hypersensitivity reactions following reintroduction of ABC, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal or a respiratory symptom).

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms of a hypersensitivity reaction **(i.e., patients previously considered to be abacavir tolerant).**

Amend: Section 3.3.7.4 Abacavir Hypersensitivity Reaction, Management of Hypersensitivity Reactions, 3rd paragraph

Original text

Subjects who develop a hypersensitivity reaction must discontinue ABC and must NEVER be rechallenged with any medicinal product that contains ABC (ZIAGEN, TRIZIVIR or the ABC/3TC fixed dose combination). Restarting any ABC-containing product following a hypersensitivity reaction results in a prompt return of symptoms within hours. **This recurrence of the hypersensitivity reaction may be more severe than on initial presentation and may include life-threatening hypotension and death.**

Revised text

Subjects who develop a hypersensitivity reaction must discontinue ABC and must NEVER be rechallenged with any medicinal product that contains ABC (ZIAGEN, TRIZIVIR, KIVEXA, TRIUMEQ or any ABC-containing product). Restarting any ABC-containing product following a hypersensitivity reaction results in a prompt return of symptoms within hours. **This recurrence of the hypersensitivity reaction may be more severe than on initial presentation and may include life-threatening hypotension and death.**

Amend: Section 3.3.7.4 Abacavir Hypersensitivity Reaction, Special considerations following an interruption of abacavir therapy, 1st-5th paragraph

Original text

If therapy with ABC has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC (ZIAGEN, TRIZIVIR or the ABC/3TC fixed dose combination) should be restarted.**

There have been infrequent reports of hypersensitivity reaction following reintroduction of an ABC-containing product where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart any ABC-containing product in these patients, this should be done only under direct medical supervision.

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to re-start an ABC-containing product, this must be done only if medical care can be accessed readily by the patient or others.

Revised text

If therapy with ABC has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC (ZIAGEN, TRIZIVIR, KIVEXA, TRIUMEQ or any ABC-containing fixed dose combination) should be restarted.**

There have been infrequent reports of hypersensitivity reaction following reintroduction of an ABC-containing product where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart any ABC-containing product in these patients, this should be done only under direct medical supervision.

Rarely, patients who have stopped ABC for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re- initiating abacavir therapy. Subjects must be made aware that HSR can occur with reintroduction of ABC or any other medicinal product containing abacavir and that reintroduction of ABC or any other medicinal product containing abacavir should be undertaken only if medical care can be readily accessed.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of
ABC in patients of unknown HLA-B*5701 status who have previously tolerated ABC. Re-initiation of ABC in such patients who test positive for the HLA B*5701 allele is not recommended.

Amend: Section 3.3.7.4 Abacavir Hypersensitivity Reaction, Essential Patient Information, 3rd paragraph

Original text

- Parents/legal guardians must be reminded that subjects who are hypersensitive to ABC must never take any ABC-containing medicinal product (ZIAGEN, TRIZIVIR or the ABC/3TC fixed dose combination) again.

Revised text

- Parents/legal guardians must be reminded that subjects who are hypersensitive to ABC must never take any ABC-containing medicinal products (ZIAGEN, TRIZIVIR, KIVEXA, **TRIUMEQ or any ABC-containing** fixed-dose combination) again.

Amend: Section 3.3.7.4 Abacavir Hypersensitivity Reaction, Reporting of Hypersensitivity Reactions

Original text

All cases of potential ABC hypersensitivity should be reported as Serious Adverse Events (SAE) (see Section 7.8). In addition to reporting the case as an SAE, the HSR CRF should be completed and faxed to GSK within one week of the onset of the hypersensitivity reaction.

Revised text

All cases of potential ABC hypersensitivity should be reported as Serious Adverse Events (SAE) (see Section 7.8). In addition to reporting the case as an SAE, the HSR CRF should be completed and **sent** to GSK within one week of the onset of the hypersensitivity reaction.

Amend: Section 3.3.7.4 Abacavir Hypersensitivity Reaction, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis or Erythema Multiforme, 2nd paragraph

Original text

If a serious skin reaction develops, the ABC-containing product should be discontinued, and the patient should not be rechallenged with any ABC-containing medicinal product (ZIAGEN, TRIZIVIR or the ABC/3TC fixed dose combination).

Revised text

If a serious skin reaction develops, the ABC-containing product should be discontinued, and the patient should not be rechallenged with any ABC-containing medicinal product (ZIAGEN, TRIZIVIR, **KIVEXA, TRIUMEQ or any ABC-containing fixed dose combination).**

Change 15

Amend: Section 3.3.8 Subject Management Options, 4th paragraph

Original text

If a subject develops an AIDS diagnosis (CDC stage C) or other evidence of disease progression such that the treating clinician believes that changing therapy is required even though the above criteria have not been met, the investigator should contact GSK for further discussion on a case by case basis.

Revised text

If a subject develops an AIDS diagnosis (CDC stage C) or other evidence of disease progression such that the treating clinician believes that changing therapy is required even though the above criteria have not been met, the investigator should contact **ViiV Healthcare** for further discussion on a case by case basis.

Change 16

Amend: Section 3.3.10, Concurrent Medications and Non-Drug Therapies. Fosamprenavir and Ritonavir, 1st paragraph

Original text

FPV and RTV are metabolized in the liver by cytochrome P450 3A4 (CYP3A4). APV and RTV are predominantly CYP3A4 inhibitors. Caution should be used when co-

administering medications that are substrates, inhibitors, or inducers of CYP3A4. In addition, RTV has an affinity for other cytochrome P450 isozymes including CYP2D6, CYP2C9, CYP2C19, CYP2A6, CYP1A2 and CYP2E1, and appears to increase the activity of glucuronosyl transferases.

Revised text

FPV and RTV are metabolized in the liver by cytochrome P450 3A4 (CYP3A4). APV and RTV are predominantly CYP3A4 inhibitors. **When FPV and RTV are co-administered, the ritonavir metabolic drug interaction profile may predominate because ritonavir is a more potent CYP3A4 inhibitor. The full prescribing information for ritonavir must therefore be consulted prior to initiation of therapy with FPV and RTV.**

Amend: Section 3.3.10, Concurrent Medications and Non-Drug Therapies. Fosamprenavir and Ritonavir, 3rd paragraph

Original text

FPV and RTV should not be co-administered with alfuzosin, amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, halofantrine, lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, PDE5 inhibitors including sildenafil, simvastatin, terfenadine and triazolam. Co-administration may result in competitive inhibition of metabolism of these medications and may cause serious or life-threatening adverse events. Co-administration of FPV or FPV/RTV with rifabutin results in significant increases in plasma rifabutin levels, therefore the dose of rifabutin should be reduced by at least 50% when co-administered with FPV and by at least 75% when co-administered with FPV/RTV. Caution should be used and subjects should be monitored closely for signs of toxicity

Revised text

FPV and RTV should not be co-administered with alfuzosin, amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, halofantrine, lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, **ketaconazole, rifampicin**, PDE5 inhibitors including sildenafil, simvastatin, terfenadine and triazolam. Co-administration may result in competitive inhibition of metabolism of these medications and may cause serious or life-threatening adverse events. Co-administration of FPV or FPV/RTV with rifabutin results in significant increases in plasma rifabutin levels, therefore the dose of rifabutin should be reduced by at least 50% when co-administered with FPV and by at least 75% when co-administered with FPV/RTV. Caution should be used and subjects should be monitored closely for signs of toxicity.

Amend: Section 3.3.10, Concurrent Medications and Non-Drug Therapies. Fosamprenavir and Ritonavir, 6th paragraph

Original text

APV and RTV interact with CYP3A4 and are predominantly CYP3A4 inhibitors. Medications which interact with CYP3A4, either as substrates, inhibitors, or inducers of the isozyme and which should be used with caution include, but are not limited to: alprazolam, amlodipine, atorvastatin, cerivastatin, cimetidine, clarithromycin, clindamycin, clonazepam, codeine, dapsone, diltiazem, disopyramide, erythromycin, estrogens and progestogens, felodipine, fluvastatin, glucocorticoids, imipramine, isradipine, itraconazole, ketoconazole, loratadine, miconazole, nicardipine, nifedipine, nimodipine, nisoldipine, pravastatin, verapamil and zolpidem.

Revised text

APV and RTV interact with CYP3A4 and are predominantly CYP3A4 inhibitors. Medications which interact with CYP3A4, either as substrates, inhibitors, or inducers of the isozyme, or **medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP 3A4)** should be used with caution include, but are not limited to: alprazolam, amlodipine, atorvastatin, cerivastatin, cimetidine, clarithromycin, clindamycin, clonazepam, codeine, dapsone, diltiazem, disopyramide, erythromycin, estrogens and progestogens, felodipine, fluvastatin, glucocorticoids, imipramine, isradipine, itraconazole, loratadine, miconazole, nicardipine, nifedipine, nimodipine, nisoldipine, pravastatin, verapamil and zolpidem.

Amend: Section 3.3.10, Concurrent Medications and Non-Drug Therapies. Fosamprenavir and Ritonavir, 8-10th paragraphs

Original text

RTV is an inhibitor of CYP2D6 and an inducer of CYP1A2, CYP2C9 and glucuronosyl transferase. Medications which interact with CYP2D6, CYP1A2, CYP2C9, and/or glucuronosyl transferase should be used with caution and include but are not limited to: bisoprolol, codeine, chlorpromazine, cyclobenzaprine, desipramine, doxepin, fluphenazine, fluoxetine, haloperidol, hydrocodone, methamphetamine, metoprolol, mexilitine, morphine, propranolol, oxycodone, paroxetine, perphenazine, risperidone, thioridazine, timolol, tramadol, trazodone, and venlafaxine.

Because RTV oral solution contains alcohol, drugs such as metronidazole that may inhibit alcohol metabolism should be avoided.

IMPORTANT: For further information refer to Fosamprenavir Investigator's Brochure Supplement and local product information or the International Product Information for more complete information.

Revised text

RTV is not recommended for use with digoxin, voriconazole, blonanserin, salmeterol and other drugs not recommended for use with FPV above. RTV is an inhibitor of CYP2D6 and an inducer of CYP1A2, CYP2C9 and glucuronosyl transferase. Medications which interact with CYP2D6, CYP1A2, CYP2C9, and/or glucuronosyl transferase should be used with caution and include but are not limited to: bisoprolol,

codeine, chlorpromazine, cyclobenzaprine, desipramine, doxepin, fluphenazine, fluoxetine, haloperidol, hydrocodone, methamphetamine, metoprolol, mexilitine, morphine, propranolol, oxycodone, paroxetine, perphenazine, risperidone, thioridazine, timolol, tramadol, trazodone, and venlafaxine.

Because RTV oral solution contains alcohol, drugs such as metronidazole that may inhibit alcohol metabolism should be avoided.

IMPORTANT: For further information refer **<deleted text Fosamprenavir Investigator's Brochure Supplement and>** to local product information or the International Product Information for more complete information.

Change 17

Amend: Section 3.3.10.1, GSK Supplied Background NRTI Options, Interactions Relevant to Lamivudine, 7th paragraph

Original text

None

Added text

Emtricitabine: Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicines are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these medicines in combination therapy may be limited. 3TC is not recommended for use in combination with emtricitabine.

Change 18

Amend: Section 4.1, Study Drug Packaging and Labeling, 3rd paragraph

Original text

RTV oral solution will be provided locally by the investigator as required and should be stored according to the local product information.

Revised text

RTV oral solution will be provided locally by the investigator as required and should be stored according to the local product information. **GSK will provide RTV by other means where reimbursement is not acceptable, or GSK may provide RTV if local supplies are not available and RTV is able to be obtained from other countries**.

Change 19

Amend: Section 4.2, Study Drug Handling, 2nd paragraph

Original text

FPV will be shipped to the investigational sites by GSK. In all countries, RTV oral solution will be obtained locally and reimbursed if acceptable to regulatory authorities. GSK will provide RTV by other means where reimbursement is not acceptable. At each visit, the investigator or designated site staff should dispense sufficient amount of study drug to provide adequate supply for each subject until the next scheduled visit. All study drug that is not utilized during the study will be destroyed at the completion of the trial. Drug disposition records will be regularly reviewed by the study monitor.

Revised text

FPV will be shipped to the investigational sites by GSK. In all countries, RTV oral solution, powder, tablets or capsules will be obtained locally and reimbursed if acceptable to regulatory authorities. GSK will provide RTV by other means where reimbursement is not acceptable, or GSK may provide RTV if local supplies are not available and RTV is able to be obtained from other countries. At each visit, the investigator or designated site staff should dispense sufficient amount of study drug to provide adequate supply for each subject until the next scheduled visit. All study drug that is not utilized during the study will be destroyed at the completion of the trial. Drug disposition records will be regularly reviewed by the study monitor.

Amend: Section 4.2, Study Drug Handling, 6th paragraph

Original text

None

Revised text

Note per Amendment 12; for subjects weighing less than 33 kg, if RTV oral solution is not available, the RTV powder can be substituted. For doses less than 100 mg or partial doses between 100 mg increments the following instructions should be followed. Mix 1 packet/sachet of oral powder (100 mg) with 9.4 mL of liquid (such as water, chocolate milk, or infant formula) in a mixing cup. Once mixed, use an oral dosing syringe to measure and administer the prescribed volume. Once the powder is mixed, the dosage must be consumed within 2 hours. Discard any mixture remaining in the mixing cup. Additional guidance is provided in Section 11.6.

Amend: Section 4.2, Study Drug Handling, 8th paragraphs

Original text

Study medications should be stored until the time of dispensing as follows:

FPV 50 mg/mL oral suspension	Store below 30°C (86°F) **DO NOT FREEZE**
RTV 80 mg/mL oral solution	Store according to local product information

Revised text

Study medications should be stored until the time of dispensing as follows:

FPV 50 mg/mL oral suspension	Store below 30°C (86°F) **DO NOT FREEZE**
RTV 80 mg/mL oral solution	Store according to local product information
RTV oral powder	**Store according to local product information**
RTV 100 mg tablet	**Store according to local product information**
RTV 100 mg soft gelatin capsules	**Store according to local product information**

Change 20

Amend: Section 5.5, Efficacy, 2nd paragraph

Original text

- Quantitative plasma HIV-1 RNA (Roche Amplicor HIV-1 Monitor Test; version 1.5, ultrasensitive limit of detection (LOD) = 50copies/mL). Samples with >75,000copies/mL will be retested using the Roche Amplicor HIV-1 Monitor Test, version 1.5, standard assay LOD = 400copies/mL. (NOTE: At the Screening and Baseline (Day 1) visits, the Roche Amplicor HIV-1 Monitor Test, version 1.5, standard assay will be used).

Revised text

- Quantitative plasma HIV-1 RNA (Roche Amplicor HIV-1 Monitor Test; version 1.5, ultrasensitive limit of detection (LOD) = 50 copies/mL). Samples with >75,000 copies/mL will be retested using the Roche Amplicor HIV-1 Monitor Test, version 1.5, standard assay LOD = 400 copies/mL. (NOTE: At the Screening and Baseline (Day 1) visits, the Roche Amplicor HIV-1 Monitor Test, version 1.5, standard assay will be used). **Per Protocol Amendment 12: the Roche Amplicor HIV-1 Monitor Test Version 1.5 was subsequently discontinued after the July 2011 cut-off date for the week 48 CSR. By January 2013, only two APV20002 study sites, both in South Africa had actively enrolled subjects; and efficacy for these subjects was evaluated using the Abbott Realtime HIV-1 Test, which has a LOD of 40 copies/mL.**

Change 21

Amend: Section 5.9.1, Withdrawal, 1st paragraph

Original text

Subjects who prematurely discontinue from the study, whether voluntarily or not, should have the Withdrawal visit assessments performed (refer to Section 10). A Follow-up visit will be performed 4 weeks after the Withdrawal visit.

Revised text

Subjects who prematurely discontinue from the study, whether voluntarily or not, should have the Withdrawal visit assessments performed (refer to Section 10). **Once a subject's weight has increased to 39 kg or more, they should be withdrawn from the study**

(refer to Section 3.1). A Follow-up visit will be performed 4 weeks after the Withdrawal visit.

Change 22

Amend: Section 7.8, Prompt Reporting of SAEs to GSK moved to Section 7.9

Original text

7.8. Prompt Reporting of SAEs to GSK

SAEs must be reported promptly to GSK as described in the following table once the investigator determines that the event meets the protocol definition of an SAE.

7.8.1 Timeframes for Submitting SAE Reports to

	Initial SAE Reports		Additional Information on a Previously Reported SAE	
Type of SAE	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hrs	"SAE" CRF pages	24 hrs	Updated "SAE" CRF pages

7.8.2. Transmission of the SAE Reports

Facsimile transmission of the "SAE" CRF is the preferred method to transmit this information to the project contact for SAE receipt. In the absence of facsimile equipment, notification by telephone is acceptable for deaths and life-threatening events, with a copy of the "SAE" CRF sent by overnight mail. For SAEs that are not deaths or life-threatening events, telephone notification, in the absence of facsimile equipment, is not acceptable. Instead, a copy of the "SAE" CRF will be sent by overnight mail. GSK will provide separately a list of project contacts for SAE receipt, fax numbers, and mailing addresses.

Revised text

This section regarding reporting of SAES was moved to Section 7.9 and the previous Section 7.9 (Regulatory Reporting Requirements For SAEs) was moved to Section 7.8.

Change 23

Amend: Section 8.2.4 Subject Informed Consent, Paragraph 3

Original text

None

Revised text

Per protocol amendment 12: Assent forms will also be obtained from subjects still enrolled in the study as of Nov 1, 2019.

Change 24

Amend: Appendix 5: Dosing Table for FPV Oral Suspension

Original text

New tables for higher weight subjects were added

Revised text

Appendix 5: Dosing Table for FPV Oral Suspension

As per Section 3.3.5.1, for subjects exceeding 6 years of age, the following weight-based dosing for FPV should be used:

FPV 18 mg/kg BID (>6 years old)

Weight (kg)	Dose (mg): 18 mg/kg	Amount of 50 mg/mL suspension (mL) per Dose	No. Bottles (225mL) Needed Per Month
25	450	9	3
26	468	9.4	3
27	486	9.7	3
28	504	10.1	3
29	522	10.4	3
30	540	10.8	3
31	558	11.2	3
32	576	11.5	4
33	594	11.9	4
34	612	12.2	4
35	630	12.6	4
36	648	13	4
37	666	13.3	4
38	684	13.7	4

Change 25

Amend: Appendix 6: Dosing Table for RTV Oral Solution, Powder, Capsules and Tablets

Original text

New tables for higher weight subjects were added

Additional table and text:

RTV Oral Solution 7 mg/kg BID (<2 years old)

Weight (kg)	Dose (mg): 7 mg/kg	Amount of 80 mg/mL solution (mL) per Dose
3	21	0.26
3.5	24.5	0.31
4	28	0.35
4.5	31.5	0.39
5	35	0.44
5.5	38.5	0.48
6.0	42	0.53
6.5	45.5	0.57
7.0	49	0.61
7.5	52.5	0.66
8	56	0.70
8.5	59.5	0.74
9	63	0.79
9.5	66.5	0.83
10	70	0.88
10.5	73.5	0.92
11	77	0.96
11.5	80.5	1.01
12	84	1.05
12.5	87.5	1.09
13	91	1.14

As per Section 3.3.5.1, for subjects exceeding 6 years of age, the following weight-based dosing for RTV oral solution should be used:

RTV Oral Solution 3 mg/kg BID (>6 years old)

Weight (kg)	Dose (mg): 3 mg/kg	Amount of 80 mg/mL suspension (mL) per Dose
25	75	0.9
26	78	1.0
27	81	1.0
28	84	1.1
29	87	1.1
30	90	1.1
31	93	1.2
32	96	1.2
≥33[a]	99	1.2

[a] Subjects who are ≥33kg and are receiving RTV oral solution at a dose of 3mg/kg should remain at the recommended optimal dose for ≥33kg (99mg BID for 3mg/kg dosing) even as their weight increases above 33kg. The maximum allowed total daily dose for RTV oral solution is 200mg.

The following weight-based dosing for RTV oral powder can be used if RTV oral solution is not available. For doses less than 100 mg or partial doses between 100 mg increments: Mix 1 packet/sachet of oral powder (100 mg) with 9.4 mL of liquid (such as water, chocolate milk, or infant formula) in a mixing cup. Once mixed, use an oral dosing syringe to measure and administer the prescribed volume. Once the powder is mixed, the dosage must be consumed within 2 hours. Discard any mixture remaining in the mixing cup.

RTV Oral Powder (100 mg sachets) 3 mg/kg BID (>6 year old)

Weight (kg)	Dose (mg): 3 mg/kg	Amount of liquid per dose once the sachet with 100 mg powder is dissolved in 9.4 mL of liquid (10 mg/mL)
25	75	7.5 mL
26	78	7.8 mL
27	81	8.1 mL
28	84	8.4 mL
29	87	8.7 mL
30	90	9.0 mL
31	93	9.3 mL
32	96	9.6 mL
≥33[a]	99	10.0 mL

As per Section 3.3.5.1, for subjects exceeding 6 years of age who weigh ≥33kg and can swallow capsules or tablets whole, the following weight-based dosing for RTV oral 100 mg tablets or 100 mg capsules should be used: 1 capsule or tablet (dose of 100 mg) BID. The maximum allowed total daily dose of RTV capsules or tablets is 200 mg.