DNDi-4in1-01-PHIV Protocol

Synopsis

Phase I/II, open label, randomized crossover pharmacokinetic, safety and acceptability study of the Abacavir/Lamivudine/ Lopinavir/Ritonavir/ - 30/15/ 40/10mg (4-in-1) Fixed-Dose Combination vs. Lopinavir/Ritonavir- 40/10mg pellets plus dual Abacavir/Lamivudine- 60/30mg tablets in HIV infected Children.

Short title	**Lo**pinavir/r/ **L**amivudine/ Abacav**i**r as an easy to use **P**aediatric F**o**rmulation in a **P**hase I/II Study (**LOLIPOP**)
Name of product(s)	**Reference regimen:** LPV/r 40/10 mg pellets (Cipla Ltd), given together with ABC/3TC 60/30 mg dispersible tablet (Cipla Ltd) **Test formulation:** ABC/3TC/LPV/r 30/15/40/10 mg FDC granules in capsule (4-in-1) (Cipla Ltd)
Drug Class	HIV Protease Inhibitor, Nucleoside Reverse Transcriptase Inhibitors
Phase	Phase I/II
Indication	HIV infection
Protocol Number	DNDi-4in1-01-PHIV
Sponsor	DNDi,15 Chemin Louis Dunant, 1202 Geneve Switzerland Phone : +41 22 906 9230
Coordinating Investigator	
Study Statistician	
Protocol Version / Date	Version 1.0 dated July 2018

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ABBREVIATIONS – GLOSSARY OF TERMS

3TC	Lamivudine
ABC	Abacavir
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
API	Active Pharmaceutical Ingredient
ART	Antiretroviral Therapy
ARV	Antiretroviral
AUC	Area under the curve
AZT	Zidovudine
CHAPAS	Children with HIV in Africa - Pharmacokinetics and Adherence of Simple antiretroviral regimens
CI	Confidence Interval
CL/F	Clearance from Plasma
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CROI	Conference on Retroviruses and Opportunistic Infections
CV	Coefficient of variation
DMF	Dimethylformamide
DNA	Deoxyribose nucleic acid
DNDi	Drugs for Neglected Diseases initiative
EFSA	European Food Safety Authority
ECG	Electrocardiogram
EIA	Enzyme Immune Assay
eMTCT	Elimination of Mother to Child transmission
FDA	Food and Drug Administration
FDC	Fixed dose combination
GMR	Geometric mean ratio
GRAS	Generally recognized as safe (US FDA)
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
ICASA	International conference on AIDS and STIs in Africa
JPE	Japanese Pharmaceutical Excipients
LPV/r	Lopinavir/ritonavir
MTCT	Mother to Child transmission
NDA	National drug Authority
NDA	New Drug Application
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NOAEL	No-Observed-Adverse-Effect-Level
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PCR	Polymerase chain reaction
PH Eur	European Pharmacopeia

PHIV	Paediatric HIV
PHPT	Program for HIV Prevention and Treatment
PI	Protease inhibitor or Principal Investigator
PK	Pharmacokinetics
PMTCT	Prevention of Mother to Child Transmission
PP	Per Protocol
RNA	Ribonucleic acid
RTV	Ritonavir
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
Tmax	Time to reach maximum
USP/NF	United States Pharmacopeia (USP) and the National Formulary (NF
VL	Viral Load
WB	Weight Band
WBC	White blood cell
WHO	World Health Organization
WHODD	WHO Drug Dictionary

SYNOPSIS

Clinical Trial Protocol title and short title	Phase I/II, open label, randomized crossover pharmacokinetic, safety and acceptability study of the Abacavir/Lamivudine/ Lopinavir/Ritonavir/ - 30/15/ 40/10mg (4-in-1) vs. Lopinavir/Ritonavir- 40/10mg pellets plus dual Abacavir/Lamivudine- 60/30mg tablets in HIV infected Children.
Protocol Number	DNDi-4in1-01-PHIV
Phase	Phase I/II
Indication	HIV infection
Background and rationale	Recent data indicate the remarkable progress in global efforts towards elimination of mother-to-child transmission of the Human Immunodeficiency Virus (HIV) (eMTCT)[1]. However, despite these laudable achievements, universal coverage of MTCT interventions remains challenging[2, 3], and many children continue to acquire HIV infection in the intra, peri or post-partum periods,[4,5] and consequently, contribute to the existing pool of HIV- infected children. In addition, many HIV infected infants and young children have had varying durations of intra-uterine and peri-natal exposures to Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) for prevention of mother to child transmission (PMTCT) which may impact future antiretroviral (ARV) options[6, 7], underscoring the critical importance of a robust first line regimen that will remain effective in all children, regardless of prior antiretroviral therapy (ART) exposures. The evidence supporting the importance of early initiation of antiretroviral therapy (ART) in children is unequivocal, backed by several studies which have demonstrated that early treatment results in reduced mortality, improved virological and immunological outcomes and reduced incidence of long term central nervous system (CNS) sequelae[8,9,10,11.] Thus, early initiation of paediatric HIV treatment is pivotal towards reduction in childhood mortality in countries which bear the highest burdens of paediatric HIV. Buttressing the significance of early treatment initiation, is the evidence from recent studies that point towards the potential for long term viral remission in children, when treatment is commenced in the perinatal period[12]. Nevirapine, an NNRTI, had been the backbone of ART in children for many years. However, several factors, including its inferior efficacy in children as shown in the IMPAACT 1060 study,[13] and higher risk of treatment failure following perinatal exposure[14], informed a change in guidelines by the World Health Organization (WHO) in 2013, with the recommendation of Lopinavir/r-based ART as first line treatment in HIV infected children under 3 years of age[15]. Despite the high efficacy of ritonavir-boosted Lopinavir in inducing viral suppression in children[16], the acceptability of the liquid formulation by caregivers has been hindered by several factors such as its bitter taste, need for refrigeration, and difficulty with dosing by caregivers[17,18].

	Therefore, there is an urgent need to develop improved formulations based on LPV/r that will overcome these barriers and are well adapted to the needs of children and their caregivers[19]. **Development of New Paediatric Formulations** Cipla Ltd, India, has developed LPV/r adult (200mg/50mg) and paediatric tablets (100mg/25mg) using melt extrusion technology. Cipla Ltd has also developed a novel paediatric LPV/r 'pellets' formulation (mini- 'melt' tablets formulation (in the same 4:1 drug ratio)), which are stored in 40/10 mg capsules. These capsules must be opened, and their content administered orally to small children by mixing the pellets with food. A major advantage of this pellet formulation compared to the liquid is that they are heat stable and therefore don't require refrigeration and that they are alcohol-free DNDi created a paediatric HIV program in 2011 with the aim of formulating a heat-stable, taste masked, solid fixed-dose-combination (FDC) containing dual NRTIs plus LPV/r. A partnership was formed with Cipla Ltd. for the development and supply of this FDC. The LPV/r pellets have been studied in the CHAPAS-2 trial, an open-label comparative bioavailability (randomized crossover) study which compared a twice-daily pellets formulation with the LPV/r syrup in HIV-infected Ugandan infants aged 3months -13 years. The CHAPAS-2 investigators concluded that LPV/r exposure from pellets was comparable to that from the syrup formulation, with no significant differences in sub-therapeutic concentrations. Furthermore, LPV/r pellets were more acceptable than syrups.[20] The effectiveness, safety, population pharmacokinetics and acceptability of the LPV/r pellets are currently being investigated in a phase IIIb trial in HIV infected children weighing >3 ≤ 25Kg (LIVING study) with over 1000 children recruited in Kenya, Uganda and Tanzania across all WHO paediatric ART weight bands. Interim results presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2018 showed that 75% and 80% of children were virologically suppressed after 24 and 48 weeks of treatment respectively[21]. However, the usage of the pellets remains prohibitive in the very young infants, in whom, we have observed difficulties in swallowing, especially below the age of 5 months (information obtained through direct communication with the LIVING study investigators). In partnership with DNDi, Cipla has developed a fully taste masked ABC/3TC/LPV/r/ "4-in-1" granule formulation with good bioavailability in healthy adult volunteers. This formulation is chemically and physically stable and is compatible with dual NRTI powders (ABC/3TC). In addition, this new formulation has a particle size that is 9 times smaller than that of the LPV/r pellets (0.2mm-0.5mm (granules) vs 1.8mm (pellets), and therefore could be facilitate swallowing by the very young children.

The active components of this novel "4-in-1" formulation include abacavir (ABC), lamivudine (3TC) and lopinavir/ritonavir (LPV/r), that have been widely used in adults and children for more than 15 years with their toxicology profile well known (refer to the relevant IBs). The combination of various formulations of lopinavir boosted with ritonavir (solution, heat stable pellets, paediatric tablets) and abacavir plus lamivudine (as individual solutions, single or dual paediatric tablets) constitutes one of the first line regimen recommended by WHO since 2013.

Preclinical Toxicology

The Eudragit E PO: a key excipient for the 4-in-1 paediatric formulation

Eudragit polymers are copolymers derived from esters of acrylic and methacrylic acid whose physicochemical properties are determined by functional groups. The basic copolymer has been employed in preparations for pharmaceutical dosage forms for more than 50 years. It has been used in about 70 paediatric formulations listed in France and Germany and 6 formulations listed in the US. The specifications of this excipient are described in the monographs of several Pharmacopoeias (PH Eur. USP/NF, and the Japanese JPE)

For the LPV/r formulation Eudragit E PO plays a capital role in three ways:

- It allows an efficient taste masking of the LPV granules and a good release at the level of the stomach,
- It allows, when used in the proportion of 3 to 1 "Excipient to Active Pharmaceutical Ingredient (API)" the (chemically as well as physically) formation of a stable solid solution of LPV/r which allows to reach the required blood levels in man. The Active Pharmaceutical Ingredient (API) themselves have a very low solubility and would not allow to reach the required target exposure levels.
- It protects the solid solution and API from moisture, therefore stabilizing it.

But the high amount of the excipient relative to the API had not been used in paediatric formulations in the past. Therefore the elements of the dimethylformamide (DMF) of the excipient manufacturer, Evonik, have been consulted and studied as well as relevant papers such as the Scientific Opinion on the use of Basic Methacrylic Copolymer as a food additive on request of the European Commission[22] and Characterisation and Toxicological behaviour of Basic Methacrylate Copolymer for GRAS evaluation[23]

From the toxicological studies performed with Eudragit EP O (in dogs and rats) and considering the human equivalent doses (HED) of these studies in rats (No Observed Adverse Effect Level (NOAEL) of 2000 mg/kg/bw, a HED of 322 mg/kg) and dogs (NOAEL of 750 mg/kg/bw, a HED of 415 mg/kg) for 4 weeks and comparing with the excipient dose

	administered to children with the LPV/r dose , the HED values above give a good indication of a safety margin compared to the 150 to 72.3 mg/kg dose of excipient to be administered to paediatric patients with the " 4 in 1 Fixed dose combination" for the various weight bands. They support safety of the higher proportions of Eudragit EP O excipient to be administered to paediatric patients. Following FDA recommendation, a Juvenile toxicology study was conducted by DNDi (ref NDA 210168) to determine possible systemic toxicity along with local effects in gastrointestinal tract of high doses of Eudragit®E PO when given orally, twice daily, about 6 hours apart, to 16 juvenile rats/sex/group, for 4 consecutive weeks. The results of this study showed that doses in paediatric patients should range from 90 mg/kg/day to 200 mg/kg/day. Based on the NOAEL of 1000 mg/kg/day (HED is 161.3mg/kg/day) from this study, the safety margins would be 1.8 for 90 mg/kg/day or 0.8 for 200 mg/kg/day. Although the safety margins for this excipient to be used in paediatric formula are rather narrow, safety concerns on this excipient in the 4-in-1 formulation are minimal because: 1. In a juvenile toxicity study, rats were exposed for a duration that is analogous to humans from early infantile up to at least 13 years. No changes in growth and development of juvenile animals were observed; 2. Available literature has shown that the vast majority of Eudragit EPO is not absorbed from GI tract. Therefore, the major concern of this excipient is portal-of-entry effect. The juvenile toxicity study in rats has shown no clinical signs related to alteration of the gastrointestinal function. The FDA agreed '*that daily intake of Eudragit EPO of no more than 200 mg/day (two separate doses, apart at least 6 hours) is associated with minimal safety concern in paediatric patients*' (FDA internal communication). **Clinical Evaluation in Humans:** The pharmacokinetics and safety of the 4 in 1 formulation have been studied in healthy adult volunteers in a phase 1 "Pathfinder" study (Protocol No. 0173-17). This was an open label, balance, randomized, single-dose, two treatments, two sequence, two-period, crossover, bioequivalence study. The primary objective of the study was to compare the rate and extent of absorption of the 4-in-1 fixed dose combination of Abacavir, Lamivudine, Lopinavir and Ritonavir Granules 30 mg / 15 mg / 40mg / 10 mg of Cipla Limited, India. **(Test-T)** versus co-administration of ZIAGEN® (Abacavir) 300 mg tablet of ViiV Healthcare, USA, EPIVIR (Lamivudine) 150 mg tablet of ViiV Healthcare, USA and KALETRA® (Lopinavir and Ritonavir) tablets 200 / 50 mg (2 tablets dose/day) of AbbVie Inc., USA (**reference)**, in 22 healthy, adult, human subjects under fed condition.

The secondary objective was to assess the safety of test product. There were 2 periods in the study, with a screening period of 21 days prior to the dosing in Period-I. In each study period, 31 blood samples, including one pre-dose blood sample, were collected from each subject except for the withdrawn subjects to analyse the pharmacokinetic profile of the test as well as the reference product.

The study results are shown in the table below.

Analyte	PK	RefGeoLSM	TestGeoLSM	Ratio	Lower	Upper	Intra_cv	Power
Lopinavir	LnCmax	10381.350	8395.194	80.9	76.30	85.71	11.2	100.0
	LnAUCt	166756.571	146269.133	87.7	81.64	94.24	13.8	99.9
	LnAUCinf	165830.135	142435.291	85.9	81.33	90.71	9.0	100.0
Ritonavir	LnCmax	1142.738	820.774	71.8	66.01	78.15	16.3	99.5
	LnAUCt	10327.520	8527.386	82.6	78.12	87.27	10.6	100.0
	LnAUCinf	10468.024	8720.009	83.3	78.57	88.31	11.2	100.0
Abacavir	LnCmax	2122.178	1360.702	64.1	58.33	70.47	18.3	98.5
	LnAUCt	6605.065	5847.736	88.5	85.04	92.17	7.7	100.0
	LnAUCinf	6694.720	5937.149	88.7	85.18	92.33	7.7	100.00
Lamivudine	LnCmax	1373.083	1188.570	86.6	80.49	93.09	14.0	99.9
	LnAUCt	8638.109	8318.026	96.3	93.88	98.77	4.9	100.0
	LnAUCinf	8869.200	8563.611	96.6	94.26	98.90	4.6	100.0

healthy, adult, human subjects under fed condition.

Regarding safety results, one (01) AE of vomiting was reported by one (01) subject in Period-II of group-I during the study. The AE occurred after administration of Reference Product-R. The AE was mild in nature and the subject was followed up until resolution of AE. The investigator causality assessment was possibly related for the AE.

Overall, the pharmacokinetic data from this study showed that the 4-in-1 provides comparable systemic exposure to that of concomitantly administered separate products. Concerning the individual components of the 4 in 1 formulation:

- For Lopinavir: T/R Ratio of LnAUCt was 87.7% (90% C.I. 81.64-94.24 and fell within the acceptance range of 80.00-125.00%).
- For Abacavir: T/R Ratio of LnAUCt was 88.5% (90% C.I. 85.04-92.17 and fell within the acceptance range of 80.00-125.00%).
- For Lamivudine: T/R Ratio of LnAUCt was 96.3% (90% C.I. 93.88-98.77 and fell within the acceptance range of 80.00-125.00%).
- For Ritonavir: T/R Ratio of LnAUCt was 82.6% (90% C.I. 78.12-87.27. Lower C.I. and fell slightly outside the acceptance range of 80.00-125.00%). This difference is not clinically significant as Ritonavir used here is merely a PK booster that inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

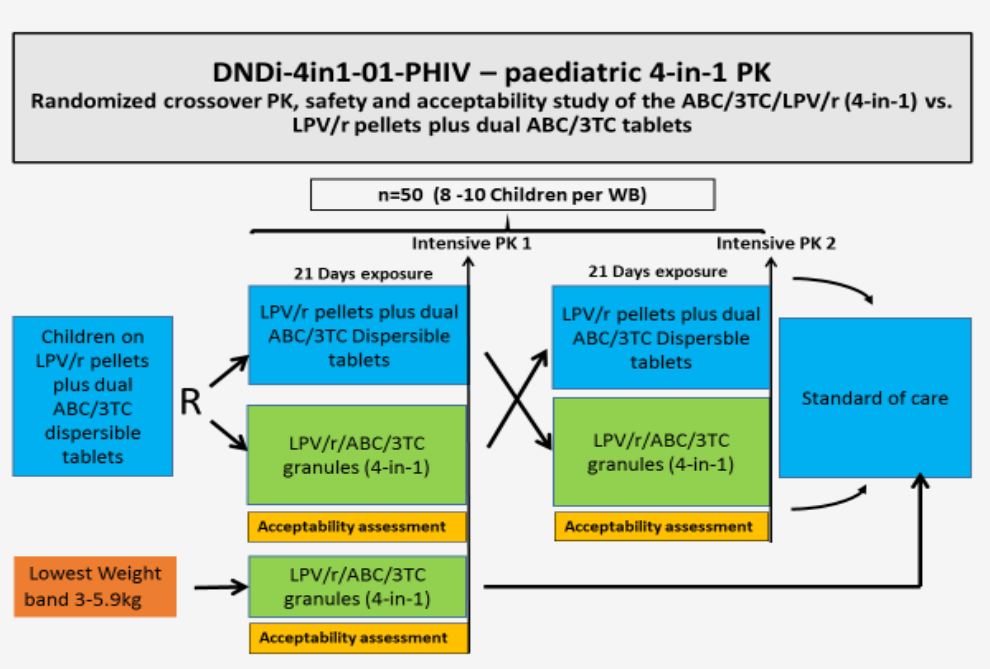
Regarding safety results, one (01) non-serious adverse event (AE) of vomiting was reported by one (01) subject in Period-II of group-I during

	the study. The AE occurred after administration of Reference Product-R. The AE was mild in nature and the subject was followed up until resolution of AE. The investigator causality assessment was possibly related for the AE. There were no deaths, no serious AEs (SAEs) during the conduct of the study. In addition, there were no clinically significant findings in the vital signs assessment, ECG recordings or the laboratory tests in any of the subjects in the study. Taken together, the study results showed that the 4-in-1 formulation was equivalent to the reference product for the most clinically relevant pharmacokinetic parameters of the 4 products, that is, the AUCs of lopinavir, lamivudine and abacavir. Based on this data, it was decided to further document the use of the 4-in-1 in healthy adult volunteers and in HIV-infected children in order to submit it for registration by regulatory authorities. **Rationale for the Present Study** This first study of the 4-in-1 in HIV-infected children is intended to support its adoption by healthcare providers and will provide data that may support its registration in certain countries. The phase I/II study described below will be carried out in HIV-infected children in Uganda weighing 3 to 25 kg (inclusive) and unable to swallow tablets in Uganda and will provide supportive clinical data on the pharmacokinetics, safety, tolerability and acceptability of the 4-in-1. The Lopinavir/Ritonavir pellets plus dual Abacavir/Lamivudine tablets regimen which is current standard of care for children under 3 years of age in Uganda was chosen to provide elements of comparison. The cross-over design is intended to minimize the impact of intra-subject variations, in particular pharmacokinetic ones. A 21-day, twice a day, dosing will enable collection of steady-state pharmacokinetic parameters.
Trial Objectives	**Primary Objective:** • To estimate the population average exposure to LPV, ABC and 3TC provided by the 4-in-1 formulation in HIV-infected children dosed per WHO weight bands. **Secondary objective:** • To determine the proportion of children overall, and within each weight band, with a lopinavir C_{12} <1.0 mg/L while receiving the 4-in-1 formulation • To evaluate and compare the safety and tolerability of the 4-in-1 formulation versus a reference treatment regimen. • To compare the bioavailability of LPV, ABC and 3TC in the 4-in-1 formulation versus a reference treatment regimen. • To assess post exposure CD4 and viral load

	• To assess the factors that contribute to acceptability of the new 4-in-1 formulation.

Trial Endpoints	**Primary EndpointPrimary endpoint**
	• LPV, ABC and 3TC AUC_{0-12} in the 4-in-1 formulation.
	
	Secondary endpoints
	• **Pharmacokinetics:**
	  • LPV C_{12} with the 4-in-1 formulation.
	  • LPV, ABC and 3TC C_{max}, T_{max}, CL/F with the 4-in-1 formulation.
	  • Geometric mean ratio (GMR) of steady state LPV, ABC and 3TC AUC_{0-12} and C_{max} in the 4-in-1 formulation versus the reference treatment regimen.
	
	• **Safety, Tolerability:**
	  • Occurrence of (treatment-emergent) adverse events (TEAEs) as defined by the protocol
	  • Occurrence of severe treatment-emergent adverse events (TEAEs) as defined by the protocol
	  • Occurrence of treatment-emergent AE (TEAEs) /serious TEAE leading to treatment discontinuation
	  • Occurrence of targeted TEAEs for lopinavir/ritonavir as well as NRTIs (examples: gastrointestinal side effects, liver toxicity, ABC-associated hypersensitivity reaction)
	  • Proportion of children with viral load <1000 copies/ml
	  • Changes in CD4 counts and percent compared to baseline
	
	• **Acceptability:**
	  • Factors that affect acceptability of the 4 in1 formulation will be identified by means of a questionnaire and in-depth interviews

Trial Design	Phase I/II, open label, randomized crossover pharmacokinetic, safety and acceptability study of the Abacavir/Lamivudine/ Lopinavir/Ritonavir (30/15/ 40/10mg ;4-in-1) Fixed-Dose Combination vs. Lopinavir/Ritonavir (40/10mg pellets) plus dual Abacavir/Lamivudine (60/30mg tablets) in HIV infected Children. All children, except for children ≥3 and ≤ 5.9kgs (weight band 1), will be randomized in the ratio 1:1 to receive either the 4-in-1 or the pellets in combination to ABC/3TC dispersible tables regimen (crossover design). Randomization will be stratified by weight band: 6 to ≤9.9 kg, 10 to ≤13.9 kg, 14 to ≤19.9 kg, 20 to ≤24.9 kg (weight band 2,3,4 and 5). <u>Weight bands 2, 3, 4 and 5</u> After 21 days of treatment, all these subjects will undergo a seven points intensive PK evaluation; afterwards the subjects will be switched to the alternative formulation (i.e. pellets plus dispersible tablets or 4-in-1

	granules; same weight band determined dose). After a further 21 days of treatment, all subjects will undergo a second 7-points PK evaluation. Children will be administered the same dose of each drug independently of the sequence of administration of the formulations. No dose adjustment will be made between PK visits. Following this second PK assessment all children will be switched back to their pre-enrolment ART regimen (standard of care). <u>Weight band 1</u> For children within the 3 to 5.9kg weight band (inclusive), we anticipate difficulty in recruitment based on the dwindling number of perinatal infections in Uganda. In addition, there is a high likelihood that children in this weight band will be unable to swallow the LPV/r pellets, as we have seen from the LIVING study, and are thus, likely to be receiving either NVP or LPV/r-syrup based ART. Therefore, we will recruit children ≥3 and ≤ 5.9kgs body weight who have been on ART for at least 3 weeks. Following recruitment, these children will not be randomised but will directly receive the 4 in 1 formulation for 21 days, following which, PK samples will be collected to evaluate bioavailability. They will not cross over to the pellets formulation. They will then switch back to their pre-enrolment ART regimen. **Trial Schema:** 
Main Entry Criteria Inclusion Exclusion	**Inclusion criteria for:** • Children > 4 weeks old and weighing ≥3 and <25 kg at the time of enrolment

	• Past or current documentation of a confirmed diagnosis of HIV infection defined as two positive assays from two different samples. The two results may be in any combination of the following: ▪ At any age: HIV-1 DNA PCR positive ▪ Documented past HIV-1 RNA viral load > 1,000 copies/mL plasma ▪ At any age >18 months of age: HIV-1 antibody reactive on two different rapid tests based on national testing algorithm • ARV treatment eligible children with LPV-based treatment indication[1] as defined by country-specific guidelines or the WHO paediatric treatment guidelines and confirmed by the investigator • HIV RNA viral load <1000 copies/mL (suppressed) at the screening visit[1] • Inability to swallow LPV/r tablets • Parent or guardian able and willing to provide written informed consent. • For lowest weight band (≥3 and ≤ 5.9kgs) ONLY: under treatment for at least 3 weeks but not more than 12 weeks. **NB:** Eligible children on AZT/3TC may be enrolled and switched to ABC/3TC if not contraindicated. **Exclusion criteria** The presence of any of the following will exclude a subject from study enrolment: • Planned or concurrent use of NNRTIs, integrase inhibitors, entry inhibitors, or Protease Inhibitors (PIs) other than LPV/r. • Treatment failure with proven resistances to PIs. • Contraindication to use of PIs • Clinical condition requiring the use of a prohibited medication (see section 7.6) in association with LPV/r, ABC/3TC (Refer to section 7.2-7.3 of the IB) • Pulmonary Tuberculosis and any clinically significant disease or finding during screening that, in the investigator's opinion, would compromise participation in this study. • Treatment with experimental drugs (except for LPV/r Pellets) for any indication within 30 days prior to study entry • Anticipated transfer of care to a non-participating health facility during the study period
Study Duration	Enrolment will be stratified by weight band. It is anticipated that enrolment in the lowest weight band (≥3 and ≤ 5.9kgs) may require more time than for the higher weight bands. The study is expected to last about 6 months (lowest weight band may take longer to enrol), including recruitment and intensive PKs. Study participant will be in the study for about 44 days (those >5.9 and <25Kgs)

[1] Does not apply to the youngest children (≥3 and ≤ 5.9kgs)

and 22 days (those ≥3 and ≤ 5.9kgs) from the day of randomization.

Test Drugs

Administration of LPV/r pellets, and ABC/3TC formulations will follow the WHO Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection June 2016 weight band dosing schedule.

We have incorporated dosing for the 4-in1 into the WHO weight band dosing as indicated in Tables below.

Table 2: WHO June 2016 weight band dosing schedule with 4-in-1 incorporated (for this study purpose)

Drug	Strength of tablets (mg)	Number of unit doses by weight-band morning and evening									
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg	
		am	Pm	am	pm	am	Pm	Am	pm	am	pm
ABC/3TC	60/30mg dispersible tablet	1	1	1.5	1.5	2	2	2.5	2.5	3	3
LPV/r	40/10 mg pellets in capsules	2	2	3	3	4	4	5	5	6	6
LPV/r/ABC/3TC	**40/10/30/15 mg granules in capsules**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**5**	**6**	**6**

Statistics
Sample size

Sample size

One of the main objectives of the study is to provide precise estimates of the LPV, ABC and 3TC $AUC_{0\text{-}12}$ in the 4-in-1 formulation.

In the LPV package insert, LPV $AUC_{0\text{-}12}$ was reported as 92.6 ug.h/mL (coefficient of variation (CV): 39.6%) in adults using the tablet and 72.6 ug.h/mL (CV: 42.8%) in children using the oral solution. In HIV-infected children in the ARROW trial[24], ABC $AUC_{0\text{-}12}$ was reported as 7.8 ug.h/mL (CV: 40%) and 3TC $AUC_{0\text{-}12}$ as 6.0 ug.h/mL (CV: 33%).

Tables 1, 2 and 3 below provide the 90% confidence intervals (CI) of estimates of LPV, ABC and 3TC $AUC_{0\text{-}12}$ in the 4-in-1 formulation for combinations of means and CVs surrounding those reported above, for a range of sample sizes.

Table 1: 90% confidence intervals of estimates of LPV $AUC_{0\text{-}12}$ for a range of sample sizes

LPV $AUC_{0\text{-}12}$ (mcg*h/mL)	CV	90% CI of LPV $AUC_{0\text{-}12}$ (mcg*h/mL) when…			
		N=20	N=30	**N=40**	N=50
72.6	40%	(61, 84)	(64, 82)	**(65, 80)**	(66, 79)
	45%	(60, 85)	(62, 83)	**(64, 81)**	(65, 80)
80	40%	(68, 92)	(70, 90)	**(71, 89)**	(72, 88)
	45%	(66, 94)	(69, 91)	**(70, 90)**	(71, 89)
92.6	40%	(78, 107)	(81, 104)	**(83, 102)**	(84, 101)

	45%	(76, 109)	(80, 106)	**(81, 104)**	(83, 102)
100	40%	(85, 115)	(88, 112)	**(89, 111)**	(91, 109)
	45%	(83, 117)	(86, 114)	**(88, 112)**	(89, 111)

Table 2: 90% confidence intervals of estimates of ABC AUC_{0-12} for a range of sample sizes

ABC AUC_{0-12} (mcg*h/mL)	CV	90% CI of ABC AUC_{0-12} (mcg*h/mL) when…			
		N=20	N=30	**N=40**	N=50
6	40%	(5.1, 6.9)	(5.3, 6.7)	**(5.4, 6.6)**	(5.4, 6.6)
	45%	(5.0, 7.0)	(5.2, 6.8)	**(5.3, 6.7)**	(5.4, 6.6)
7	40%	(5.9, 8.1)	(6.1, 7.9)	**(6.3, 7.7)**	(6.3, 7.7)
	45%	(5.8, 8.2)	(6.0, 8.0)	**(6.2, 7.8)**	(6.3, 7.7)
7.8	40%	(6.6, 9.0)	(6.8, 8.8)	**(7.0, 8.6)**	(7.1, 8.5)
	45%	(6.4, 9.2)	(6.7, 8.9)	**(6.9, 8.7)**	(7.0, 8.6)
9	40%	(7.6, 10.4)	(7.9, 10.1)	**(8.0, 10.0)**	(8.1, 9.9)
	45%	(7.4, 10.6)	(7.7, 10.3)	**(7.9, 10.1)**	(8.0, 10.0)

Table 3: 90% confidence intervals of estimates of 3TC AUC_{0-12} for a range of sample sizes

3TC AUC_{0-12} (mcg*h/mL)	CV	90% CI of 3TC AUC_{0-12} (mcg*h/mL) when…			
		N=20	N=30	**N=40**	N=50
5	30%	(4.4, 5.6)	(4.5, 5.5)	**(4.6, 5.4)**	(4.6, 5.4)
	35%	(4.3, 5.7)	(4.5, 5.5)	**(4.5, 5.5)**	(4.6, 5.4)
6	30%	(5.3, 6.7)	(5.4, 6.6)	**(5.5, 6.5)**	(5.6, 6.4)
	35%	(5.2, 6.8)	(5.3, 6.7)	**(5.4, 6.6)**	(5.5, 6.5)
7	30%	(6.2, 7.8)	(6.3, 7.7)	**(6.4, 7.6)**	(6.5, 7.5)
	35%	(6.1, 7.9)	(6.2, 7.8)	**(6.3, 7.7)**	(6.4, 7.6)
8	30%	(7.1, 8.9)	(7.3, 8.7)	**(7.4, 8.6)**	(7.4, 8.6)
	35%	(6.9, 9.1)	(7.1, 8.9)	**(7.3, 8.7)**	(7.3, 8.7)

A sample size of 40 evaluable children provides 90% confidence intervals where all lower and upper limits are within 12% of the true LPV, ABC and 3TC AUC_{0-12}.

Assuming 20% non-evaluable children, a maximum of 50 children will be enrolled

Enrolment will be globally balanced across all weight bands, i.e. at least 8 evaluable children per weight band.

Statistics Summary of analysis	**Summary of the main analyses** Information on screening, enrolment and follow-up of children at each visit time will be provided in a disposition chart. Children characteristics at baseline and over time will be tabulated overall and by formulation. A summary of the subject demographic, medical history, and baseline characteristics will be presented using counts and percentages for categorical variables and descriptive statistics (sample size, mean, standard deviation, median, first quartile, third quartile, minimum and maximum) for continuous variables. To calculate the LPV, ABC and 3TC AUC_{0-12}, a non-compartmental pharmacokinetic analysis will be performed using WinNonLin or a similar program. RTV AUC_{0-12} will be calculated for descriptive purposes only. AUC_{τ} will be determined using the linear trapezoidal method. Other pharmacokinetic parameters of LPV, ABC and 3TC will be calculated. These include: C_{12}, C_{max}, T_{max}, CL/F and C_{min}. C_{max}, C_{min} and T_{max} will be taken directly from the observed concentration-time data. Median (range), means (standard deviations), and geometric means and their two-sided 90% CI for each PK parameter in the 4-in-1 formulation will be calculated, overall, and within each weight band. The overall proportion of children with a LPV C_{12}<1.0 mg/L (the recommended minimum concentration[25] and the two-sided 95% CI will be calculated and compared between formulations using Fisher's exact test. The proportion of children with a LPV C_{12}<1.0 mg/L within each WHO weight band will also be calculated. AUC_{0-12} and C_{max} GMRs of the 4-in-1 formulation versus the reference formulation, as well as their two-sided 90% CI, will be calculated for each drug after log-transformation of within-patient ratios.The analyses of the other study endpoints will be mostly descriptive. Categorical variables will be described using frequencies and proportions, and discrete and continuous variables using means (standard deviations), medians (25th; 75th percentiles) and ranges (minimum-maximum). Time-to-event endpoints will be estimated using the Kaplan-Meier method. Changes in continuous variables from baseline will be assessed using Wilcoxon signed-rank test. Safety and tolerance of the study agents will be evaluated by summarizing the number and percent of subjects with documented Grade 3 or higher adverse events; each summary will be conducted overall and by formulation. Serious Adverse Events will be described by individual narratives based on the SAE reports provided by the site investigators. The proportion of children experiencing an AE or SAE, along with their two-sided 95% CI, will be provided based on the exact binomial distribution and compared between the two formulations using Fisher's exact test. For the qualitative data, all recorded interviews will be verbatim transcribed and translated. All transcripts will be entered in NVIVO 11 for

	subsequent data analysis. Data-driven code-books will be developed adopting an inductive approach, i.e. codes will be assigned grounded in the raw data,and merged into relevant themes or categories to address the research objectives. Data source triangulation will be carried out by combining qualitative data form interviews with study participants and health care providers

SCHEDULE OF EVENTS

Table 1- Schedule of events

SCHEDULE OF EVENTS										
Visit code	**SCR**	**ENR**	**D07**	**D14**	**D21**	**D22**	**D29**	**D36**	**D43**	**D44**
Visits window +/- 2 days	**Day -15 to Day 0**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 44**
Description	**Baseline Screening**	**Enrolment**	**Study visit**	**Study visit**	**Overnight admission (Optional)**	**PK-1**	**Study visit**	**Study visit**	**Overnight admission (Optional)**	**PK-2**
Demographic (child & caregivers)	X									
Address (all caregivers)	X				X				X	
Inclusion criteria	X									
Exclusion criteria	X									
Informed consent process	X									
Randomization		X								
Overnight admission					(X)				(X)	
Acceptability Questionnaire					X[1]				X	
Semi-structured interview					X[2]				X[2]	
LABORATORY										
HIV status	X									
Plasma HIV-1 Viral load	X					X[1]				X
Blood Chemistry[3]	X					X[1]				X
Hematology[4]	X					X[1]				X
Immunology[5]	X					X[1]				X
Intensive PK						X[6]				X[6]
CLINICAL										
Medical history	X									
Physical & medical assessments[7]	X	X	X	X	X		X	X	X	
Study drug dispensation		X	X	X		X[8]	X	X		
Observation of administration		X				X				X
Diary card dispensation to caregivers		X	X	X		X	X	X		
Diary card review or collection by study staff			X	X	X		X	X	X	
Study drug adherence (pill count)			X	X		X	X	X		X
Concomitant treatments recording		X	X	X	X	X	X	X	X	X
Adverse events monitoring		X	X	X	X	X	X	X	X	X
End of Study		PRN	PRN	PRN	PRN	X[1]	PRN	PRN	PRN	X
Total Blood Volume	8mL	-	-	-	-	7.5ml /3.5 mL[9]	-	-	-	7.5mL

1. Only for children not randomized (3-5.9kgs)
2. To be done after 21 days of 4-in-1 formulation administration, either on Day 21 or Day 43.
3. Blood chemistry to include AST, ALT, Creatinine and Total Bilirubin
4. Haematology- 5 parts Differential
5. Immunology - Absolute CD4 count and percentage
6. Visit window period -1 day to + 2 days (PK days should be scheduled not less than 21 days of treatment)
7. Physical and medical assessment includes Vital signs, Weight, Height/Length
8. First intake of new treatment (switch) to happen on **PK-1 Day** after last PK sample taken
9. 7.5 ml for Weigh band 1, and 3.5ml for weight band 2-6.

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