Application for Inclusion of Abacavir, Lamivudine, lopinavir, and ritonavir (ABC/3TC/LPV/r) Formulation in WHO Model List of Essential Medicines for Children

Applicant: Drugs for Neglected Diseases initiative (DNDi)
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1. Summary statement of the proposal for inclusion, change or deletion

In response to a longstanding demand and in line with the WHO(1) recommendations and calls for fixed-dose combinations (FDCs) of paediatric antiretrovirals (ARVs) that allow simplified dosing based on weight-bands, a new formulation; the '4-in-1' fixed-dose combination of abacavir, lamivudine, lopinavir, and ritonavir (ABC/3TC/LPV/r-30/15/40/10mg) has been developed and submitted for United States Food and Drug Administration (USFDA) approval.

This proposal requests for inclusion of the Abacavir, Lamivudine, Lopinavir/ritonavir (ABC/3TC/LPV/r 30/15/40/10mg) fixed dose combination oral granules for the treatment of HIV infection among children living with HIV/AIDS in the WHO Essential Medicines List for Children (EMLc).

2. Name of the WHO technical department and focal point supporting the application

WHO technical department: Global HIV, Hepatitis and STIs Programme and Department of Research for Health

Focal point at WHO: Martina Penazzato, Paediatric HIV lead and GAP-f lead

3. Name of the organization(s) consulted and/or supporting the application

The following organizations have been consulted and /or supporting this application:

- **EGPAF**: Partner organisation with DNDi for introduction of optimised paediatric formulations including 4-in-1
- **Enfants et VIH en Afrique (EVA)**: Partner organisation with DNDi for introduction of optimised paediatric formulations including 4-in-1
- **Médecins sans Frontières:** A founding member of DNDi
- **Cipla Ltd.**: Industrial partner for DNDi 4-in-1 development
- **Unitaid**: Donor for DNDi 4-in-1 development

4. International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine

International Non-proprietary Name (INN): Abacavir, Lamivudine, Lopinavir and Ritonavir

ATC code	Name
J05AR10	lopinavir and ritonavir
J05AR02	lamivudine and abacavir
J05AF06	abacavir
J05AF05	lamivudine

5. Formulation(s) and strength(s) proposed for inclusion, including adult and paediatric (if appropriate)

Dosage form: Granules in capsule to be opened

Strengths: Abacavir 30mg, Lamivudine 15mg, Lopinavir 40mg, Ritonavir 10mg

Each capsule of abacavir, lamivudine, lopinavir and ritonavir granules contains 30 mg of abacavir, 15 mg of lamivudine, 40 mg of lopinavir and 10 mg of ritonavir.

The granules are white to off white coloured blend filled in capsule of size 00 having white opaque body spin printed with 3TC-ABC in black ink and brown opaque cap spin printed with LPV-RTV in black ink.

This formulation is intended for children between 3kg to 24.9kg with dosing according to WHO weight bands.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

Listing is requested on the Model List of Essential Medicines for Children as an individual Fixed Dose Combination of ABC/3TC/LPV/r intended for paediatric use.

TREATMENT DETAILS, PUBLIC HEALTH RELEVANCE AND EVIDENCE APPRAISAL AND SYNTHESIS

7. Treatment details (requirements for diagnosis, treatment, and monitoring).

7.1. WHO guideline recommendations:

Since 2013, the World Health Organization recommended the use of Lopinavir/ritonavir-based regimens in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) as first-line antiretroviral therapy (ART) for all children infected with HIV younger than three years, regardless of non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure(1). The 2018 WHO guidelines for

treating and preventing HIV infection recommended a dolutegravir (DTG)-based regimen in combination with Abacavir(ABC) and Lamivudine(3TC) as the preferred first-line regimen for children for whom approved DTG dosing is available(2) . In the absence of appropriate DTG formulations and dosing for infants and young children, ABC + 3TC in combination with LPV/r are considered as an acceptable alternative given the superiority of LPV/r over non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based regimens(3). Till 2020, implementation of DTG based regimens in children have only been feasible among those weighing 20kgs and above among whom DTG 50 mgs tablets can be utilized , while children weighing less than 20kgs continue to be use LPV/r based regimens(3). ABC + 3TC in combination with LPV/r remains an important alternative regimen for use in first line among infants and young children(2).

7.2. Treatment indications

ABC/3TC/LPV/r oral granules (30/15/40/10mg in capsule) formulation is indicated for the treatment of HIV-1 infection in infants and children weighing 3 kg to 24.9 kg.

7.3. Dosing recommendations

Simplified weight band dosing schedule for ABC/3TC/LPV/r 30/15/40/10mg oral granules

Table 1. Dosage Recommendation of Abacavir, Lamivudine, Lopinavir and Ritonavir Granules Based on Weight Band

The ABC/3TC/LPV/r 30/15/40/10mg oral granules should be administered twice daily with food. The table lists the number of capsules containing abacavir, lamivudine, lopinavir and ritonavir granules to be administered twice-daily, using a simplified weight band-based approach.

Weight Band	**Number of capsules containing abacavir, lamivudine, lopinavir and ritonavir granules* needed to prepare each dose**	
	AM	**PM**
3.0 kg – 5.9 kg	2	2
6.0 kg – 9.9 kg	3	3
10.0 kg – 13.9 kg	4	4
14.0 kg – 19.9 kg	5	5
20.0 kg – 24.9 kg	6	6

* without concomitant efavirenz, nevirapine or nelfinavir

7.4. Administration

Capsules containing abacavir, lamivudine, lopinavir and ritonavir granules should not be swallowed whole, and should be administered with food or liquids.

Instructions for administration with milk/drinking water

I. Obtain the prescribed number of capsules needed for a dose.

II. Dose the required number of capsules one by one.
III. Hold one capsule vertically with the brown cap at the top and white body at the bottom and then gently tap on top of the capsule.
IV. Open the capsule by gently twisting and pulling up the cap
V. Pour the contents of the capsule into a spoon.
VI. Add milk/drinking water to the spoon till the spoon fills and feed to the child immediately.
VII. Repeat this step for the prescribed number of capsules.
VIII. Additional milk/drinking water can be taken after each dose if required.

Instructions for administration with soft food (e.g. porridge or mashed fruit)

I. Prepare porridge / fruit and cool to room temperature.
II. Obtain the prescribed number of capsules needed for a dose.
III. Dose the required number of capsules one by one.
IV. Take a small amount of porridge / fruit on the spoon.
V. Hold one capsule vertically with the brown cap at the top and white body at the bottom and then gently tap on top of the capsule.
VI. Open the capsule by gently twisting and pulling up the cap.
VII. Pour the contents of capsule on the spoon containing porridge / fruit and feed to the child immediately. The porridge / fruit with the drug sprinkled on top should be swallowed immediately and should not be stored for future use.
VIII. Repeat this step for the prescribed number of capsules.
IX. Administration of the required dose should be followed by more food or drinking water/milk, to ensure that no granules remain in the mouth.

7.5. Additional Diagnostic Tests Needed for ABC/3TC/LPV/r

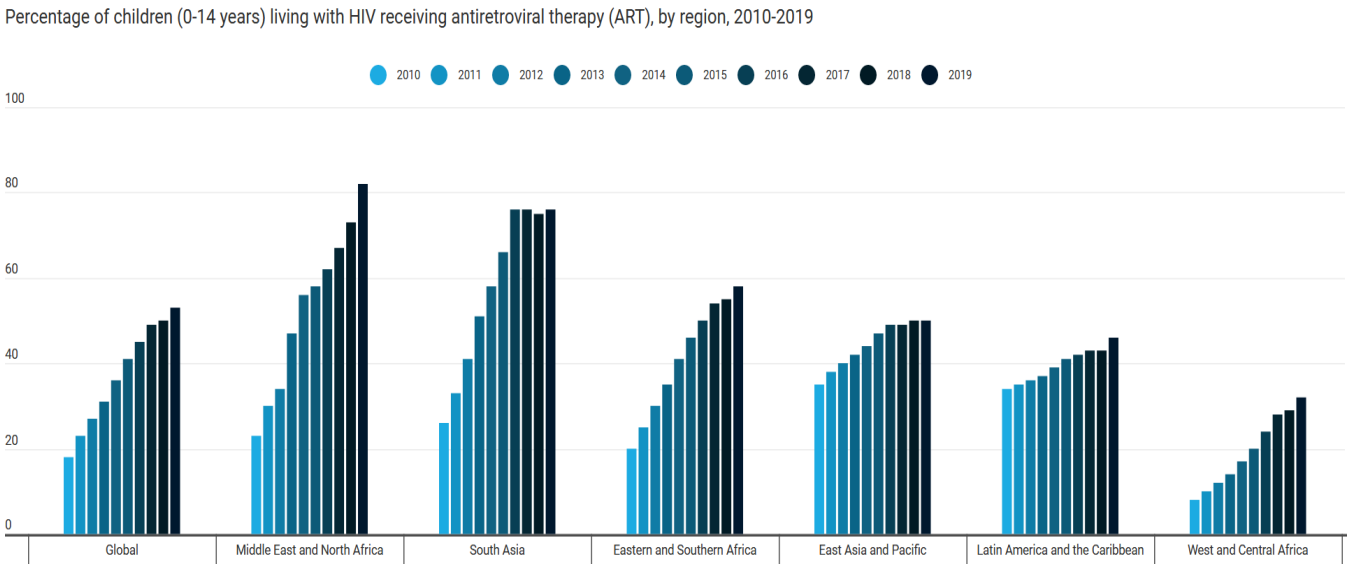
Among people with the HLA-B*5701 allele, the use of Abacavir can cause fatal hypersensitivity and screening for HLA-B*5701 allele prior to initiating therapy with abacavir is recommended in United States, Europe, and Australia(4). However, data on prevalence and usefulness of testing for HLA-B*5701 allele among black African children who comprise majority of children living with HIV globally shows low prevalence(5,6). Furthermore, the prevalence of ABC related adverse events is low, adverse events occurs early in treatment and can be managed. WHO therefore recommends the use of ABC based regimens in first and second line ART regimens without the need for testing(7)

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population(s) and likely impact of treatment on the disease)

8.1. Epidemiologic information on disease burden

HIV infection among children continues to be a significant problem in developing countries despite the global progress made related to HIV prevention and AIDS treatment. Of the estimated 1.8 million

[1.3 million-2.2 million] children under 15 years of age living with HIV, 88 per cent live in sub-Saharan Africa and only 53% of the total were on antiretroviral therapy by end 2019(8).



Source: Global AIDS Monitoring and UNAIDS 2020 estimates(8).

Low treatment coverage for children living with HIV is related to multiple factors, including challenges unique to children's medicines, diagnosis, case-finding and linkage, and retention in care(9). Infant diagnosis rates (both early diagnosis and final diagnosis after 18 months) remain poor in many countries, creating a bottleneck to scaling up treatment for children especially those younger than 18 months of age. Even among children who do get onto treatment, retention among children is hindered by multiple reasons among the lack of appropriate formulations(10) and having sustainable supply of the same, sustaining market share for available paediatric formulations and ensuring access in each country(11)

8.2. Assessment of current use

The ABC/3TC/LPV/r fixed dose combination oral granules formulation is not currently in use

8.3. Target populations

The ABC/3TC/LPV/r FDC is meant for use among infants and young children infected with HIV-1 who cannot yet swallow tablets.

8.4. Likely impact of treatment on the disease

In 2019, an estimated 95,000 children under age 15 died of AIDS-related causes globally(8). Without HIV treatment, 50% of HIV infected children will die by the age of two years and children face a greater risk of progression to AIDS than an adult. Early initiation of antiretroviral therapy in HIV infected children provides undeniable clinical benefits by reducing the risk of death in early childhood(12). The ABC/3TC/LPV/r granules, when they are available, will be recommended for

use in children weighing 3 kilograms and above, allowing their use for early ART initiation among infants infected with HIV-1 and hence contribute to reduction in HIV and AIDS related mortality and morbidity. The formulation is taste masked and has a strawberry flavour and allows easy dosing for caregiver and facilitate swallowing for young children who cannot yet swallow tablets or have challenges with using available LPV/r pellet formulation.

9. Review of benefits: summary of evidence of comparative effectiveness.

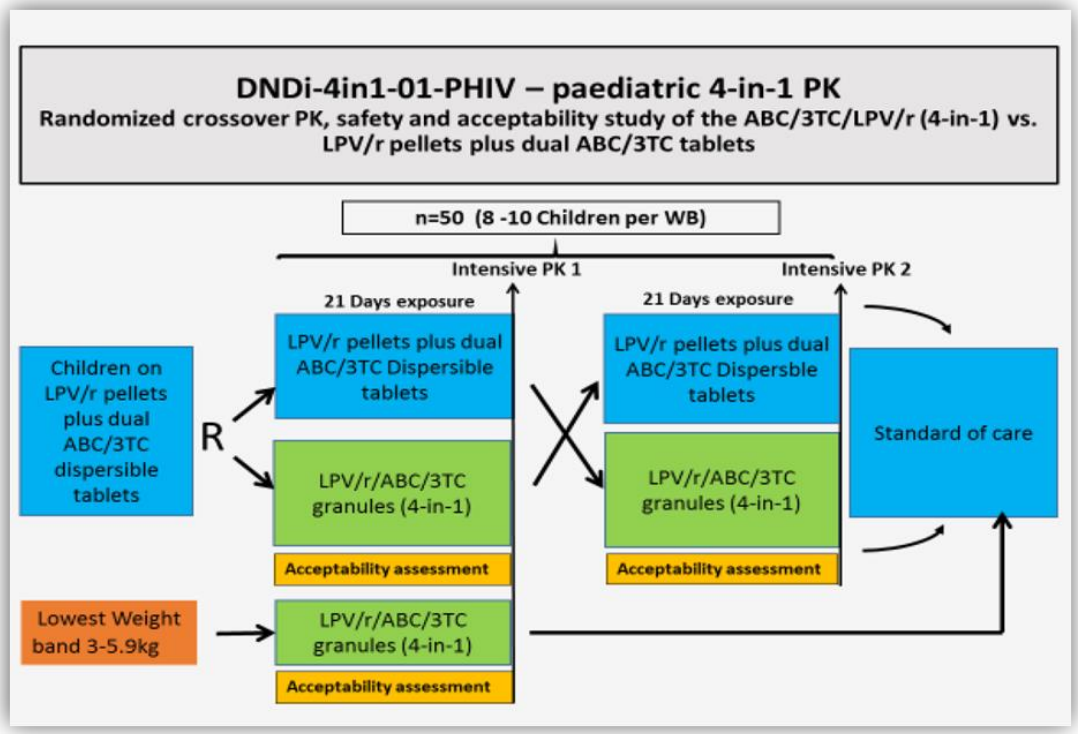
Lopinavir/ritonavir (LPV/r) in combination with abacavir (ABC) and lamivudine (3TC) is a 1st line treatment option for children living with HIV (CLHIV) under 3 years in many countries. To date, this 4-drug combination, currently under FDA review, has not been available for young children in a fixed dose combination (FDC).

A clinical study (LOLIPOP) was set up to assess the pharmacokinetics (PK), safety, and acceptability of the 4-in-1 FDC for the first time in CLHIV.

This is a phase I/II open-label, partially randomized, crossover trial of the 4-in-1 (test formulation [T]) compared to Abacavir/Lamivudine (ABC/3TC) 60/30 mg in dispersible tablets plus Lopinavir/ritonavir (LPV/r) 40/10 mg pellets (reference formulation [R]) in 50 CLHIV in Uganda (NCT03836833)(13).

Study drugs were dosed by WHO weight bands (WB): 3-5.9 kg (WB1), 6-9.9 kg (WB2), 10-13.9 kg (WB3) or14-19.9 kg (WB4). Children in WB2-4 were randomly assigned (1:1) by WB to R followed by T for 21 days each ("RT") or to T followed by R for 21 days each ("TR").

Children in WB1 only received the 4-in-1 for 21 days. Intensive PK sampling was performed after 21 days of treatment with each formulation. Safety was assessed during the whole study period, efficacy at the end of the study and an acceptability questionnaire collected after 21 days on the 4-in-1.

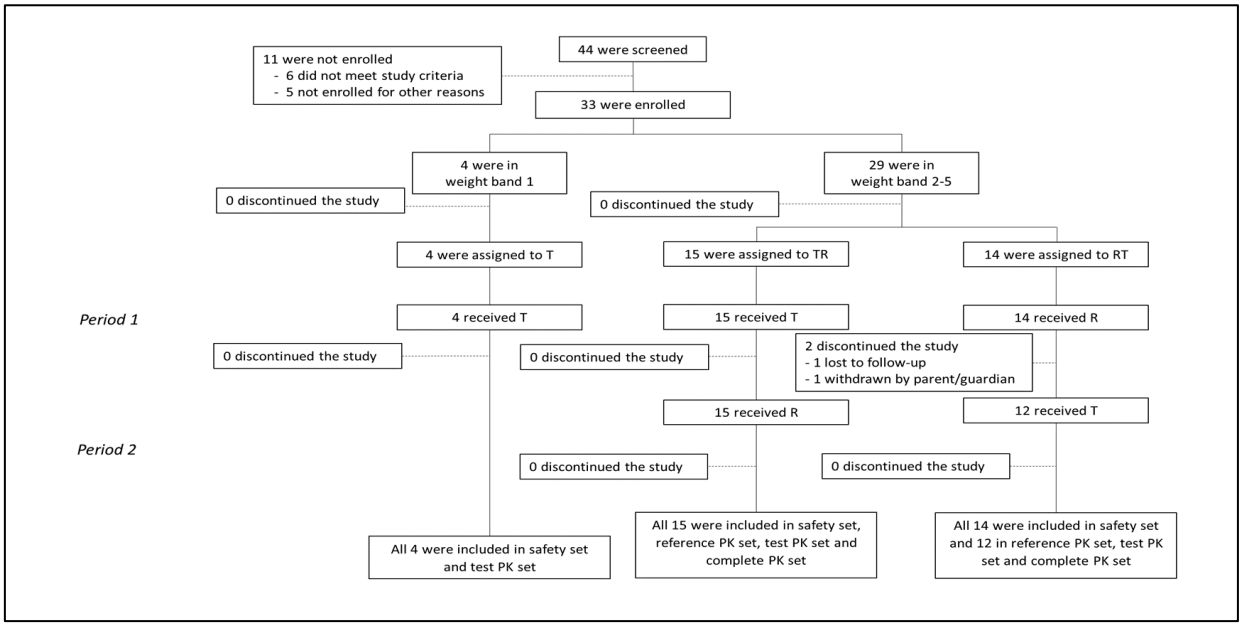


Patient disposition

Enrolment into the study was complicated by the COVID-19 pandemic, we report here interim data on the first 33 enrolled children. As of February 2020, 44 children were screened and 33 were enrolled into the study.

- Of these, 4 patients were in weight band 1 (3-5.9kg).
- Of the 29 in the 6-19.9kg weight bands
    - 15 were assigned to the 4in1 first while 14 were assigned to the reference formulation first.

Datasets are available for all but 2 children. These were not included in the PK set because 1 was lost to follow-up and 1 withdrew consent. Please refer to below disposition figure for more details.



Baseline characteristics (N=33)

Baseline characteristics for gender, age and weight were as expected.

All children were already on LPV/r-based therapy and 76% of them had been on ART for 6 months or more at the time of enrolment.

29 out of the 33 children, (88%) had a viral load below 400 copies/ml at baseline.

Parameter	Category	WB1 N=4	WB2 N=9	WB3 N=9	WB4 N=11	Overall N=33
Sex	Male Female	2 2	2 7	6 3	6 5	16 (48%) 17 (52%)
Age (months)	Mean (SD)	7.2 (4.7)	18.4 (5.2)	34.5 (7.9)	51.1 (10.3)	32.3 (17.7)
Weight (kg)	Mean (SD)	4.8 (0.6)	8.7 (0.7)	11.7 (1.0)	15.6 (1.5)	11.3 (3.8)
Previous ART	ART naive LPV/r-based	0 4	0 9	0 9	0 11	0 (0%) 33 (100%)
ART duration	< 6 months ≥ 6 months	3 1	4 5	1 8	0 11	8 (24%) 25 (76%)
Viral load (copies/mL)	< 400 >=400	2 2	8 1	8 1	11 0	29 (88%) 4 (12%)
CD4 %	<25 >=25	2 2	1 8	2 7	0 11	5(15%) 28(85%)

Interim results: Overall efficacy (N=33)

The proportion of children with VL<400 cp/mL increased from 88% (29/33) at baseline (the blue box) to 97% (30/31) at the end of the study (the red box). The proportion with VL<50 cp/mL increased from 48% (16/33) to 65% (20/31) , when excluding the missing data.

The median change in CD4 cell count was + 130 (IQR -398, +527) and on average, there was no change in CD4% (IQR -3, +2) between baseline and end of study.

Viral load (copies/ml)		Baseline					
		<50	50 to <400	400 to <1,000	>=1,000	ND/Miss.	Total
End of study	<50	13 (39%)	6 (18%)	1 (3%)	0 (0%)	0 (0%)	**20 (61%)**
	50 to <400	2 (6%)	6 (18%)	1 (3%)	1 (3%)	0 (0%)	**10 (30%)**
	400 to <1000	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>=1000	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	1 (3%)
	ND/Missing	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)
	Total	**16 (48%)**	**13 (39%)**	2 (6%)	2 (6%)	0 (0%)	33 (100%)

10. Review of harms and toxicity: summary of evidence of safety.

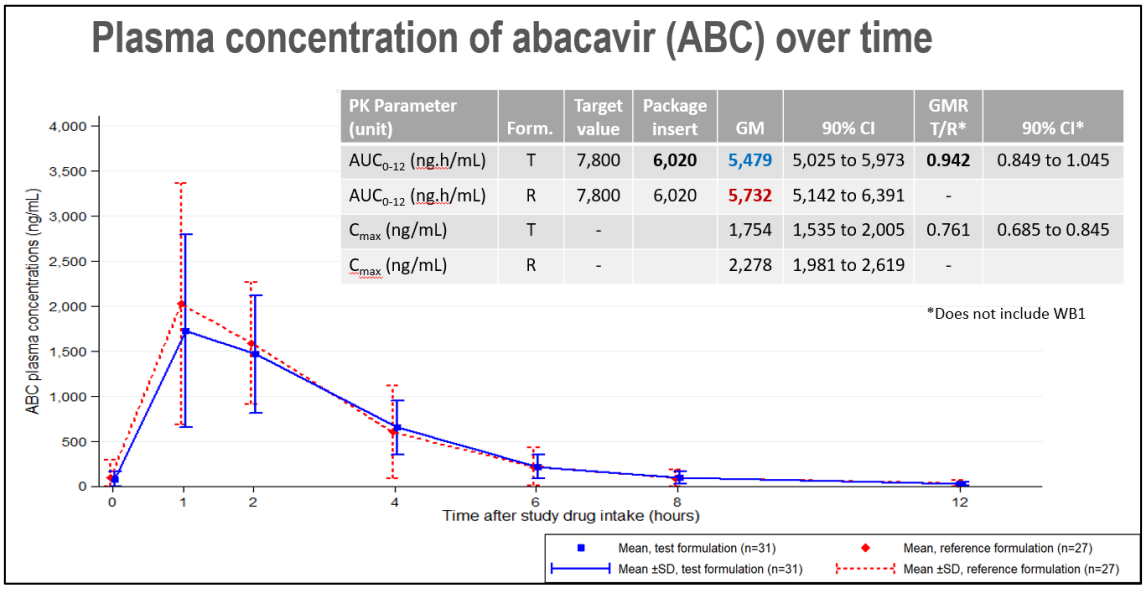
We report here interim data on the first 33 enrolled children in the LOLIPOP study.

Interim Pharmacokinetics results (N=31)

With the 4-in-1, the geometric means (GM) AUC0-12 for ABC, 3TC and LPV were 5,479, 6,059 and 88,398 ng.h/mL, respectively, and GM for Cmax were 1,754, 1,125 and 10,103 ng/mL, respectively;

two children in WB1 (with severe wasting secondary to failure to thrive) had LPV C12 <1,000 ng/mL however one remained virologically suppressed and one became virologically suppressed at the end of the study.

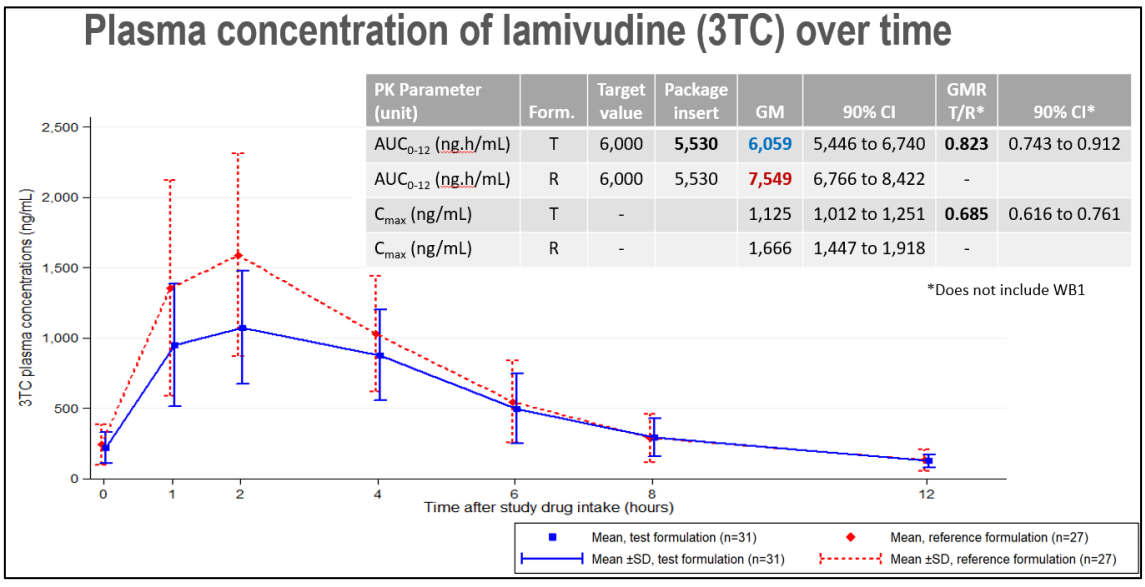
The table below table represents the PK results for Abacavir. The blue curve shows Abacavir in the 4in1 and the red curve shows Abacavir in the reference formulation. These two exposure curves overlap. The AUC target set was extracted from the ARROW study and the Abacavir package insert. The Geometric Mean ratio for the AUC is 94%. The Cmax GMR for Abacavir is 24% lower. The bioequivalence criteria were met for Abacavir AUC.



PK Parameter (unit)	Form.	Target value	Package insert	GM	90% CI	GMR T/R*	90% CI*
AUC_{0-12} (ng.h/mL)	T	7,800	**6,020**	**5,479**	5,025 to 5,973	**0.942**	0.849 to 1.045
AUC_{0-12} (ng.h/mL)	R	7,800	6,020	**5,732**	5,142 to 6,391	-	
C_{max} (ng/mL)	T	-		1,754	1,535 to 2,005	0.761	0.685 to 0.845
C_{max} (ng/mL)	R	-		2,278	1,981 to 2,619	-	

*Does not include WB1

Below are the PK results for 3TC. As before, the blue curve shows 3TC in the 4in1 and the red curve shows 3TC in the reference formulation. The Geometric Mean ratio of the 4in1 for AUC is 82%, and the Cmax is 69%. Neither AUC nor Cmax met bioequivalence criteria but were comparable to historical exposures in adults and children. Interestingly, 3TC exposures with the 4-in-1 were closer to historical values.

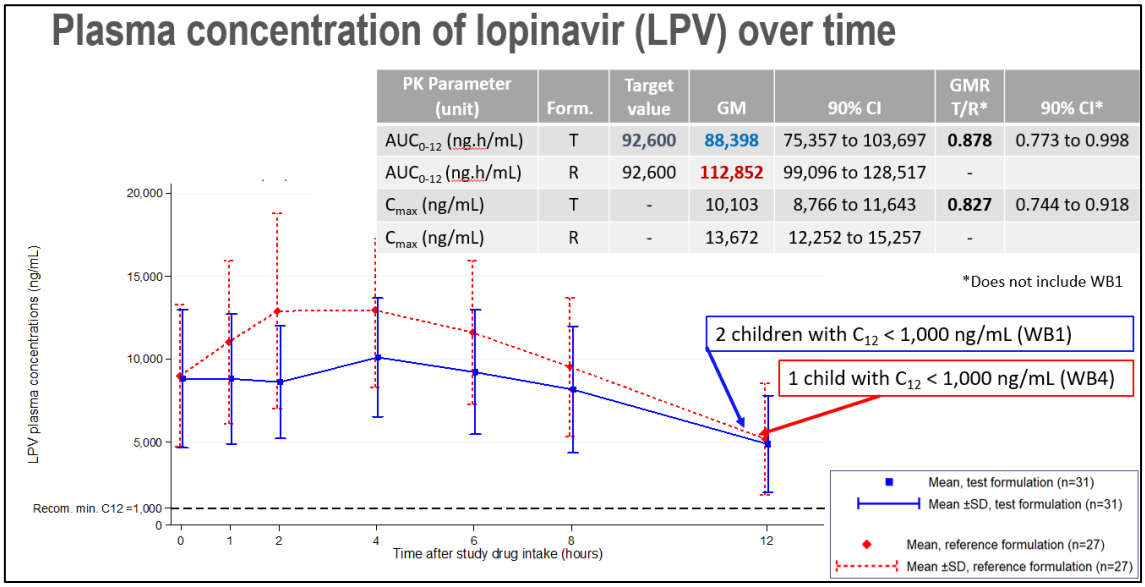


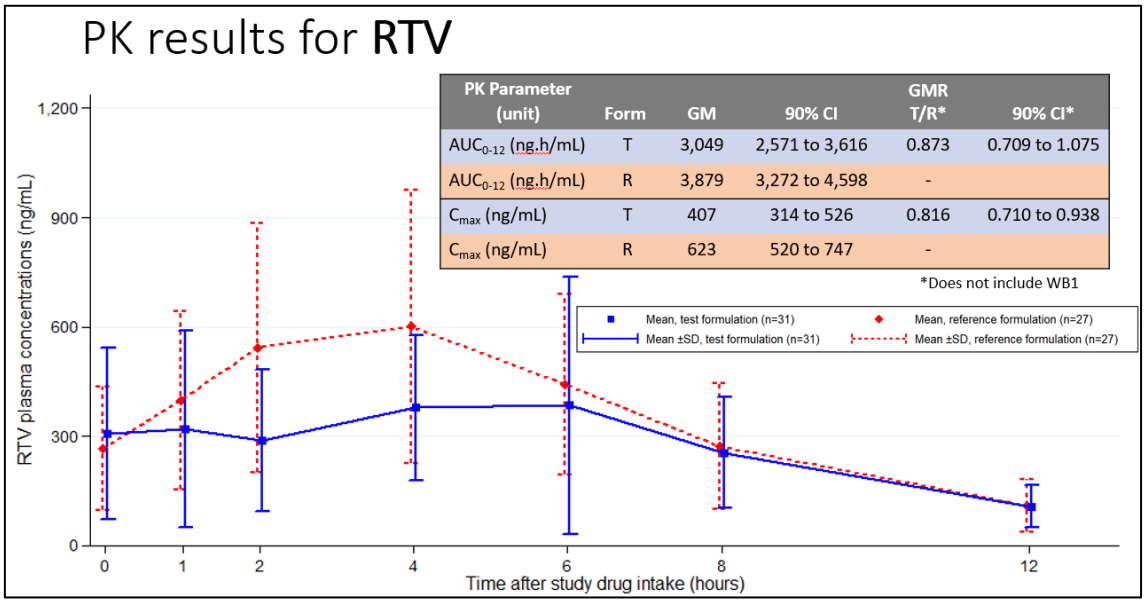
PK Parameter (unit)	Form.	Target value	Package insert	GM	90% CI	GMR T/R*	90% CI*
AUC_{0-12} (ng.h/mL)	T	6,000	**5,530**	**6,059**	5,446 to 6,740	**0.823**	0.743 to 0.912
AUC_{0-12} (ng.h/mL)	R	6,000	5,530	**7,549**	6,766 to 8,422	-	
C_{max} (ng/mL)	T	-		1,125	1,012 to 1,251	**0.685**	0.616 to 0.761
C_{max} (ng/mL)	R	-		1,666	1,447 to 1,918	-	

*Does not include WB1

Below are the PK results for LPV in the 4in1 (blue curve) and in the reference formulation (red curve). The GMR AUC was 12% lower with the 4in1, and the lower confidence interval lay outside the bioequivalence range. The LPV Cmax GMR was 17% lower. Absorption of lopinavir was slower with the 4in1 than with the reference formulation. Overall, the LPV exposure was comparable to historical data in adults and exposures with the 4in1 were closer than those with the reference formulation. Two of four children from Weight band 1 and one child in the weight band 4 had a C_{12} below 1000 ng/ml.

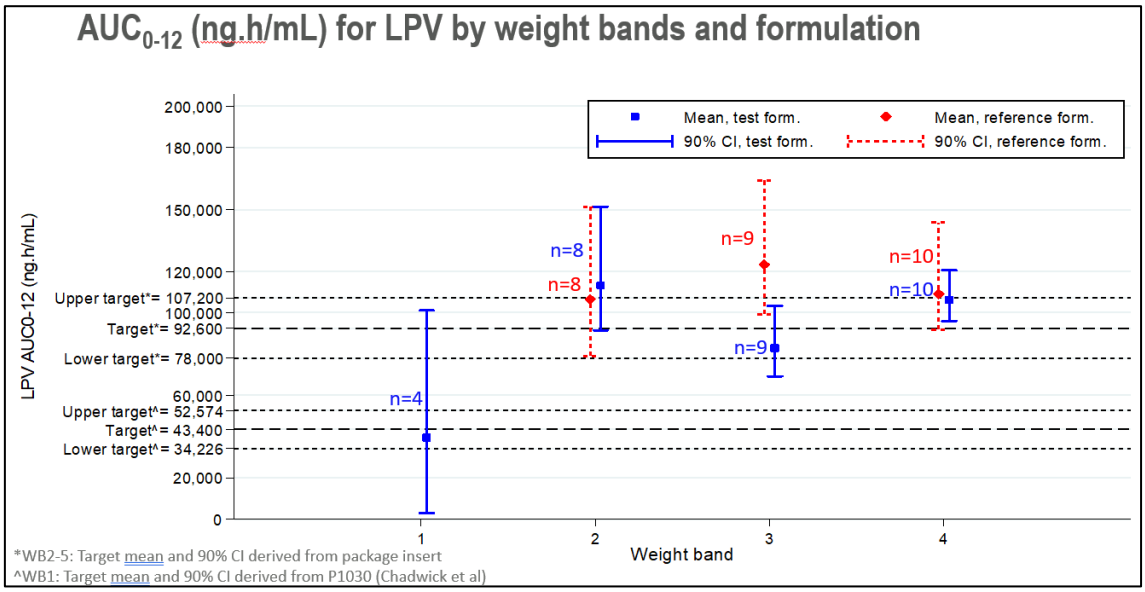
WB1 includes a heterogeneous population of children; more data are needed in this weight band. WB1 includes a child of age less than 5 months at start of the study who had comorbidities and another suspected to have been premature at birth. There were 2 other children aged above 8 months who had a very low weight at screening and failure to thrive/malnutrition. Virological suppression improved on treatment in all these children, including the 2 children who reached the LPV C_{min} starting 8 hours post dose. Food did not appear to impact exposure.





In the graph below, the exposure to lopinavir by formulation according to the expected upper and lower 'target' exposures, stratified by weight band is presented. In Weight Bands 2, 3 and 4, exposure

to LPV is very close to the expected ranges observed in adults. For weight band 1, the target range is based on that observed with the liquid formulation in young children. We see wide variability with the 4 children enrolled to date. Given the small sample size in Weight band 1 we cannot yet draw a firm conclusion and so, more children are being recruited in this weight band.



Interim results: Overall safety and overview of treatment-emergent adverse events (TEAEs) (N=33)

Subjects who experienced…	Reference N=27	4in1 N=31	Overall N=33
Any TEAE	15 (56%) [38]	23 (74%) [63]	25 (76%) [101]
Any TEAE of Grade 1	15 (56%) [35]	23 (74%) [61]	25 (76%) [96]
Any TEAE of Grade 2	1 (4%) [2]	1 (3%) [2]	1 (3%) [4]
Any TEAE of Grade 3 or higher	1 (4%) [1]	0 (0%) [0]	1 (3%) [1]
Any TEAE leading to treatment discontinuation	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]
Any TE serious AE or death	1 (4%) [1]	0 (0%) [0]	1 (3%) [1]
Any treatment-related TEAE	8 (30%) [9]	13 (42%) [25]	17 (52%) [34]
Any treatment-related TEAE of Grade 1	8 (30%) [9]	13 (42%) [25]	17 (52%) [34]
Any treatment-related TEAE of Grade 2 or higher	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]

In square brackets: numbers of TEAEs

101 Treatment-Emergent Adverse Events were reported: 96 were mild, 4 moderate and 1 severe; none led to treatment discontinuation; one was serious (bronchopneumonia), which started while on the reference formulation. The most common TEAEs were vomiting 17 (**52%**), nasopharyngitis 11 (**33%**), Influenza 5 and URTI 5 (both **15%**), and diarrhoea 4 (12%). All treatment related TEAEs were of grade 1.

Acceptability results (N=33)

Of the 31 interviewed caregivers, 30 (97%) reported administering the 4-in-1 as "very easy" or "easy", and 22 (71%) reported that the child had no difficulty in swallowing it.

Question	Answer	4in1 N= 31
Level of difficulty to administer the granules to the child	**Very easy**	**15 (48%)**
	Easy	**15 (48%)**
	Average	1 (3%)
	Difficult	0 (0%)
	Very difficult	0 (0%)
Difficulties of intake of the test formulation by the child	Not difficult	22 (71%)
	Difficult	**9 (29%)**
	Refuses medication	***5 (16%)***
	Spits medication	*1 (3%)*
	Vomits medication	***8 (26%)***
	Chokes	*1 (3%)*
	Coughs	*1 (3%)*
	Gags	*1 (3%)*
	Other	*0 (0%)*

Conclusion on LOLIPOP interim results

In the first 31 CLHIV who completed the study, the 4-in-1 was safe, well-accepted and effective in achieving or maintaining viral suppression. In the first 31 evaluable CLHIV, the 4-in-1 provided comparable drug exposures with the 4-in-1 in WB2-4, but a larger sample size in WB1 is needed to fully evaluate drug exposures in this WB. The final results will be available Q1, 2021.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

This fixed dose combination is not yet marketed thus the final price is not yet available.

The announced price(14) of $1 a day in December 2019 correspond to a treatment cost per year of 10kg child of $360.

Table below summarizes the price per patient per year treatment by WHO weight band of ABC/3TC 60/30mg dispersible tablet with either LPV/r 40/10mg pellets or LPV/r 40/10mg granules in comparison with ABC/3TC/LPV/r 30/15/40/10mg fixed-dose combination(15–17).

Formulations/ WHO weight bands	3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg
ABC/3TC 60/30mg tab + LPV/r (pellets or granules)	260	390	520	650	780
ABC/3TC/LPV/r 30/15/40/10mg granules (capsule)	180	270	360	450	540

REGULATORY INFORMATION

12. Summary of regulatory status and market availability of the medicine.

Dossier of 4-in-1 has been submitted in October 2019 to USFDA and is under review.

Product dossiers has also been submitted to the Regulatory Authorities of Tanzania, Uganda, Kenya, Zambia, Zimbabwe, Mozambique, Rwanda, Malawi, Democratic Republic of Congo and South Africa and are currently under review.

The 4-in-1 is currently not yet approved anywhere globally.

Abacavir, lamivudine, lopinavir and ritonavir have no intellectual property restrictions globally. Since 23rd March 2020, AbbVie committed not to enforce, and has dropped its patent rights globally on all formulations of lopinavir/ritonavir(18).

13. Availability of pharmacopeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

All the individual antiretrovirals abacavir, lamivudine, lopinavir and ritonavir are listed in the United States Pharmacopoeia.

This fixed-dose combination is not included in any of the pharmacopoeias.

14. References

1. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013.

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