



A Novel Chewable Pediatric Fixed-Dose Combination of Stavudine, Lamivudine, Nevirapine: Pharmacokinetics and Safety in HIV-Infected Thai Children

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ABSTRACT

Background: Pediatric FDC are urgently needed to facilitate antiretroviral therapy in children. A novel chewable pediatric FDC has been developed by Thai Government Pharmaceutical Organization (GPO) composed of d4T (7 mg) plus 3TC (50 mg) plus NVP (50 mg), called GPO-VIR® S7. We report the bioavailability, safety and therapeutic adequacy of GPO-VIR® S7 compared to the individual brand name liquid formulations in HIV-infected Thai children.

Methods: The International Maternal Pediatric Adolescent AIDS clinical trials group (IMPAACT) P1056 study was a phase III, 2-arm, randomized, open-label, multiple-dose pharmacokinetic cross-over study. 35 children weighing ≥ 6 to ≤ 30 kg, receiving NVP-based HAART and stable for at least 4 weeks, were enrolled and randomized to receive either: GPO-VIR® S7 tablets or d4T/3TC/NVP original liquid formulations. Children were stratified by weight: Group 1: ≤ 6 kg (n=3), Group 2: $>6-16$ kg (n=9), Group 3: $>16-23$ kg (n=12), and Group 4: $>23-30$ kg (n=12). Dosing was based on body weight. Intensive 12-hour blood sampling for PK was performed on day 14 and day 28, then subjects crossed-over to the alternate formulation at equal doses for 28 days. On Day 56, a second 12-hour sampling for PK was performed. Plasma levels for d4T, 3TC and NVP were determined by HPLC and PK parameters by non-compartmental analysis. Therapeutic inadequacy of GPO-VIR® S7 was based on the location of the 90% CI for the mean area under the curve (AUC). If the 90% CI lay within 70-143% of the target mean, AUC therapeutic adequacy was declared.

Results: 34 children complete the PK sampling. No sequence or carryover effects were observed.

	GPO-VIR® S7 AUC (mcg·h/mL)		Geometric Mean Ratio (GMR) GPO-VIR® S7 /Liquid	
	Geometric Mean	90% CI	Target AUC* (mcg·h/mL)	GMR
d4T	1.54	1.42-1.67	1.28	0.97
3TC	6.39	5.82-7.00	4.43	1.41
NVP	74.1	65.6-83.6	63.6	1.08

*Mean adult AUC (drug package insert)

None of the 3 drug exposures for GPO-VIR® S7 were deemed therapeutically inadequate. The median NVP predose level was 5.4 mg/L for both GPO-VIR® S7 and the liquid formulation; 3/34 (8%) children had a predose level <3.0 mg/L (range: 1.9-2.9 mg/L) with both formulations. No serious drug-related toxicity was reported.

Conclusions: The novel chewable GPO-VIR® S7 FDC was safe and provided therapeutically adequate plasma drug levels in HIV-infected children. Substituting the liquid formulations with GPO-VIR® S7 could be considered to help simplify antiretroviral therapy.

BACKGROUND

- Pediatric FDC are urgently needed to facilitate ART in children.
- A novel chewable pediatric FDC has been developed by Thai Government Pharmaceutical Organization composed of d4T (7 mg) plus 3TC (50 mg) plus NVP (50 mg), called GPO-VIR® S7.
- We report the bioavailability, safety and therapeutic adequacy of GPO-VIR® S7 compared to the individual brand name liquid formulations in HIV-infected Thai children.



Figure 1

METHODS

- Subjects**
- HIV-infected Thai children ≥ 6 months to <13 years of age, clinically stable on a HAART regimen (NVP + 2 NRTIs) and receiving a maintenance dose of NVP for at least 4 weeks.
- Design**
- Two stages, Phase III, two arms, randomized, open-label, multiple-dose pharmacokinetic cross-over study.
 - Stage I: 9 evaluable children, weight 12-30 kg
 - Stage II: 30-44 evaluable children, weight 6-30 kg
- Primary Objectives**
- To compare the bioavailability of d4T/3TC/NVP in GPO-VIR® S7 with the liquid drug formulations
 - To estimate the plasma average exposure to NVP with GPO-VIR® S7, and to compare this to an adult exposure of therapeutically adequate NVP concentration.

Stage III: Study Design

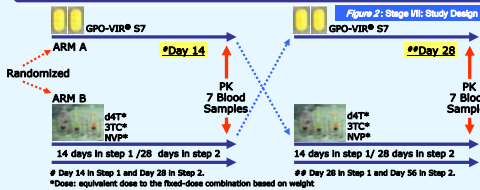
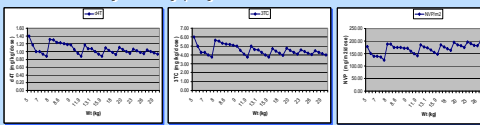


Figure 2: Stage III: Study Design

Table 1: P1056 Weight Band dosing for GPO-VIR® S7 Pediatric tablets

Group	Weight (kg)	GPO-VIR® S7 (tablet per dose)	Liquid Formulations (mL per dose)		
			3TC dose (10 mg/mL)	d4T dose (1 mg/mL)	NVP dose (10 mg/mL)
1	$\leq 6-8$	1.0	6-8	7	5
2	$>6-13$	1.5	8-12	4.5	10.5
3	$>13-18$	2.0	8-12	6	14
4	$>18-23$	2.5	8-12	7.5	17.5
5	$>23-27$	3.0	8-12	9	21
6	$>27-30$	4.0	8-12	10.5	24.5

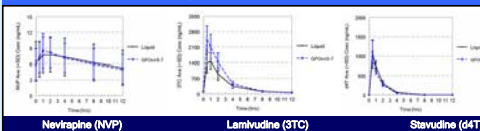
Figure 3: Dosage per kg or m² of GPO-VIR® S7 Pediatric formula



Results of Stage I

- Stage I was performed to provided initial safety and bioavailability data for GPO-VIR® S7
- Nine children were enrolled and therapeutic inadequacy would be declared if the AUC 90% CI lie entirely above 2x or entirely below 1/2 the target mean

Figure 4: Mean concentration vs. time curves for GPO-VIR® S7 and the Individual Liquid formulations in 9 HIV-infected Thai Children



- GPO-VIR® S7 met both safety and therapeutic criteria and subsequently Stage II of the study was opened for enrollment.

Results of Stage II

Demographic Data (n=35)	Mean (SD)	Table 2: Demographic Data	
		Group 1	Group 2
Gender M:F	18:17		
Age Year (SD)	6 (3.7)		
Weight Kg (SD)	19 (6.8)		
CD4 count cells/mm ³ (SD)	1147 (719.1)		
CD4 % (SD)	30 (10.6)		
Median HIV RNA copies/mL	<400		

Figure 5: Mean concentration vs. time curves for the GPO-VIR® S7 Pediatric tablet and Liquid formulations (N=34)

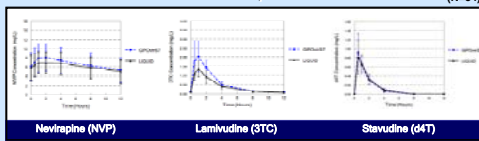


Figure 6: NVP: Individual NVP AUC for both GPO-VIR® S7 & Liquid formulations (by weight group)

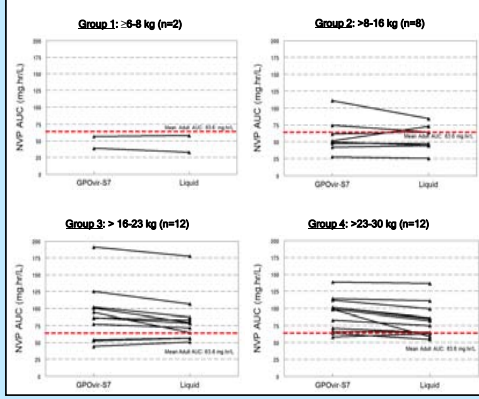


Table 3: Stavudine (d4T), Lamivudine (3TC), and Nevirapine (NVP) pharmacokinetic parameters of GPO-VIR® S7 and Individual liquid formulations in HIV-infected Thai children. Reported values median (range)

	Group 1		Group 2		Group 3		Group 4		All Weight Groups (N=34)	
	≤ 6 kg (n=2)	$>6-16$ kg (n=6)	$>16-23$ kg (n=12)	$>23-30$ kg (n=12)	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2
NVP										
AUC (mcg·h/mL)	47.8 (20.9-87.7)	46.5 (27.6-111)	60.8 (25.4-143)	60.7 (25.4-143)	76.3 (30.3-199)	69.3 (30.3-199)	78.4 (30.3-199)	76.3 (30.3-199)	64.8 (27.9-191)	64.8 (27.9-191)
Cmax (mcg/L)	6.32 (3.0-10.9)	6.06 (3.0-10.9)	6.79 (3.0-10.9)	6.01 (3.0-10.9)	7.53 (3.0-10.9)	6.60 (3.0-10.9)	7.58 (3.0-10.9)	7.58 (3.0-10.9)	7.58 (3.0-10.9)	7.58 (3.0-10.9)
Cmin (mcg/L)	2.21 (1.3-3.7)	2.00 (1.3-3.7)	3.08 (1.3-3.7)	2.79 (1.3-3.7)	3.32 (1.3-3.7)	2.88 (1.3-3.7)	3.36 (1.3-3.7)	3.36 (1.3-3.7)	4.00 (1.3-3.7)	4.00 (1.3-3.7)
3TC										
AUC (mcg·h/mL)	67.2 (44.2-88)	57.5 (34.2-88)	4.44 (1.7-23)	3.51 (1.7-23)	7.58 (3.0-13)	6.28 (3.0-13)	7.70 (3.0-13)	6.92 (3.0-13)	6.93 (3.0-13)	6.93 (3.0-13)
Cmax (mcg/L)	3.99 (1.8-7.4)	3.91 (1.8-7.4)	5.71 (1.8-7.4)	5.71 (1.8-7.4)	5.71 (1.8-7.4)	5.71 (1.8-7.4)	5.71 (1.8-7.4)	5.71 (1.8-7.4)	5.71 (1.8-7.4)	5.71 (1.8-7.4)
Cmin (mcg/L)	0.98 (0.5-1.6)	0.98 (0.5-1.6)	0.98 (0.5-1.6)	0.98 (0.5-1.6)	0.98 (0.5-1.6)	0.98 (0.5-1.6)	0.98 (0.5-1.6)	0.98 (0.5-1.6)	0.98 (0.5-1.6)	0.98 (0.5-1.6)
d4T										
AUC (mcg·h/mL)	1.49 (0.7-2.8)	1.50 (0.7-2.8)	1.19 (0.7-2.8)	1.49 (0.7-2.8)	1.70 (0.7-2.8)	1.70 (0.7-2.8)	1.70 (0.7-2.8)	1.69 (0.7-2.8)	1.67 (0.7-2.8)	1.67 (0.7-2.8)
Cmax (mcg/L)	0.27 (0.1-0.5)	0.27 (0.1-0.5)	0.27 (0.1-0.5)	0.27 (0.1-0.5)	0.27 (0.1-0.5)	0.27 (0.1-0.5)	0.27 (0.1-0.5)	0.27 (0.1-0.5)	0.27 (0.1-0.5)	0.27 (0.1-0.5)

Note: d4T Cmin: median (range) <0.025 mg/L ($<0.025-0.025$) over all weight groups (below lower limit of assay quantification)

Table 4: Geometric Mean Ratio (%) +/- 90% CI for GPO-VIR® S7 /Liquid for AUC and Cmax

	AUC Geometric Mean Ratio (GMR) GPO-VIR® S7/Liquid		Cmax Geometric Mean Ratio (GMR) GPO-VIR® S7/Liquid	
	90% CI	GMR	90% CI	90% CI
d4T	0.97	92-102	108	97-120
3TC	1.41	130-153	159	139-182
NVP	1.08	104-113	114	108-119

- In Stage II therapeutic inadequacy would be declared if the AUC 90% CI lied entirely above 143% or entirely below 70% the target mean.

Table 5: Target AUC ranges for d4T, 3TC and NVP and the AUC +/- 90% CI for GPO-VIR® S7

Target AUC	NVP		3TC		d4T	
	70% - 143% of Target	AUC of GPO-VIR® S7 (90% CI)	70% - 143% of Target	AUC of GPO-VIR® S7 (90% CI)	70% - 143% of Target	AUC of GPO-VIR® S7 (90% CI)
63.6	44.5 to 90.9	44.5 to 83.59	4.43	3.10 to 6.33	0.896 to 1.83	1.28 to 1.67

- GPO-VIR® S7 AUC 90% CI and AUC target threshold did not met the protocol defined therapeutic inadequacy criteria.
- Safety: No serious drug-related toxicity was reported.

Summary

- The GPO-VIR® S7 Pediatric Dose per Body Weight proposed in IMPAACT/PACTG P1056 provided therapeutically adequate plasma drug levels in HIV-infected children of all three drug components.
- The novel chewable GPO-VIR® S7 Pediatric FDC tablet was clinically safe.
- Substituting the liquid formulations with GPO-VIR® S7 Pediatric tablet could be considered to help simplify antiretroviral therapy.

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