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A Chewable Pediatric Fixed-dose Combination Tablet of Stavudine, Lamivudine, and Nevirapine:

Pharmacokinetics and Safety Compared With the Individual Liquid Formulations in Human Immunodeficiency Virus-infected Children in Thailand

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Abstract

Background—Pediatric fixed-dose combinations (FDCs) are needed to facilitate antiretroviral therapy in children. We evaluated the relative bioavailability, safety, and therapeutic adequacy of a novel chewable pediatric FDC tablet of stavudine (7 mg), lamivudine (30 mg), and nevirapine (50 mg), referred to as GPO-VIR S7, and compared it with the individual original brand-name liquid formulations in human immunodeficiency virus-infected Thai children.

Methods—The International Maternal Pediatric Adolescent AIDS Clinical Trials group (IMPAACT) P1056 study was a phase I/II, 2-arm, randomized, open-label, multidose pharmacokinetic cross-over study. Children ≥ 6 to ≤ 30 kg receiving nevirapine-based HAART for at least 4 weeks were randomized to receive GPO-VIR S7 chewable tablets or the equivalent liquid formulations. Children were stratified by weight and dosing was weight-based. Intensive 12-hour blood sampling was performed on day 28, and subjects then crossed-over to the alternate

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formulation at equal doses with identical 12-hour sampling on day 56. Pharmacokinetic indices were determined by noncompartmental analysis.

Results—Thirty-four children completed the study. While taking Government Pharmaceutical Organization (GPO)-VIR S7 the geometric mean (90% CI) area under the curve was $1.54 \mu\text{g} \cdot \text{hr}/\text{mL}$ (1.42–1.67) for stavudine, 6.39 (5.82–7.00) for lamivudine, and 74.06 (65.62–83.60) for nevirapine. Nevirapine drug exposure for GPO-VIR S7 was therapeutically adequate. Geometric mean area under the curve ratios (90% CI) of GPO-VIR S7/liquid formulation for stavudine, lamivudine, and nevirapine were 0.97 (0.92–1.02), 1.41 (1.30–1.53), and 1.08 (1.04–1.13), respectively. No serious drug-related toxicity was reported.

Conclusions—The chewable FDC was safe and provided therapeutically adequate plasma drug exposures in human immunodeficiency virus-infected children. Substituting the FDC for liquid formulations can simplify antiretroviral therapy.

Keywords

pharmacokinetics; antiretrovirals; fixed-dose combinations; children; Thailand

Over the last several years a significant effort has been made toward the development of adult fixed-drug combination (FDC) tablets to help simplify highly active antiretroviral therapy and improve long-term drug adherence. Due in part to lack of affordable pediatric formulations, as well as the convenience of FDC tablets, a large number of HIV-infected children in resource-limited settings have received adult FDCs, which often must be broken in pieces to obtain an appropriate dose.^{1–3} Previous studies in HIV-infected Thai children who were using an adult FDC tablet produced by the Thai Government Pharmaceutical Organization (GPO) composed of stavudine (d4T), lamivudine (3TC), and nevirapine (NVP), named GPO-VIR S-30, (administered as 1/2, 3/4, or 1 tablet to deliver a NVP dose of 120–200 mg/m² every 12 hours), found satisfactory NVP exposure and good clinical response.^{4–6}

The World Health Organization (WHO) released a report in 2008 from their Pediatric Antiretroviral Working Group that high-lighted the need for affordable, safe, high-quality antiretroviral FDC formulations for pediatric use.⁷ To this end, the Thai GPO developed an orange-flavored chewable pediatric FDC scored tablet composed of d4T, 3TC, and NVP, named GPO-VIR S7. The choice of antiretroviral drugs to include in this new pediatric FDC follows the current Thai National Antiretroviral Treatment guidelines⁸ and the d4T:3TC:NVP ratio of 7:30:50 mg was designed to allow for the different maturational rates of the elimination pathways for the individual FDC components. In December 2009, the WHO antiretroviral guidelines for adults and adolescents proposed that countries progressively phase out d4T as the preferred first-line therapy option. However, d4T will remain an important drug in resource limited settings in the immediate future due to its availability, low cost, and good short-term tolerability, especially for children anemic or intolerant to zidovudine and with no immediate access to other nucleoside reverse transcription inhibitors (NRTIs). Pediatric FDCs provide physicians with the option to initiate a simple regimen in children.

Our objective was to assess the relative bioavailability, safety, and therapeutic adequacy of this chewable pediatric FDC tablet in comparison to the individual liquid formulations in HIV-infected Thai children.

METHODS

The International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) P1056 study (NCT00312091; www.clinicaltrials.gov), was a phase I/II, 2 stage, 2 arm, randomized, open-label, comparative pharmacokinetic (PK) study in HIV-infected Thai children ≥ 6 months to < 13 years of age. HIV-infected children clinically stable on a regimen of NVP plus 2NRTIs and receiving a maintenance dose of NVP for at least 4 weeks were recruited from 4 tertiary hospital clinics in Thailand and screened after the parent or legal guardian provided informed consent and assent, when developmentally appropriate, from the child was obtained. Children were excluded if there was a documented history of immunologic failure or any of the following laboratory abnormalities within 14 days before entry: hemoglobin ≤ 8 g/dL (< 2 years of age); hemoglobin ≤ 9 g/dL (≥ 2 years of age); platelets $\leq 75,000$ mm³; aspartate aminotransferase or alanine aminotransferase or alkaline phosphatase (ALP) $> 3 \times$ ULN; creatinine > 1 mg/dL; any other \geq Grade 3 laboratory toxicity; acute hepatitis due to any cause; pregnancy; chemotherapy; vomiting or diarrhea \geq Grade 3 within 30 days prior to entry. The study was approved by the Ethics Committees at the 4 participating hospitals, the Thai Ministry of Public Health, and the University of California, San Diego.

Study Design

Since the new GPO-VIR S7 tablet had never been studied in human subjects, the P1056 study was conducted in 2 stages. Stage I was designed to show early safety and satisfactory dosing and stage II was designed to provide fuller safety, bioavailability, and therapeutic adequacy information. Stage II could only be initiated after satisfactory results from stage I were reported.

Both stages I and II were divided into 2 steps of equal length. In stage I, the duration of each step was 2 weeks but in stage II this was extended to 4 weeks. Only children ≥ 12 kg to ≤ 30 kg could participate in stage I due to the relatively large volume of blood collected in a short period of time. Children 6 to 12 kg were also included in stage II.

Upon entry (Day 0), children were randomized to receive either GPO-VIR S7 tablets or d4T (Zerit by Bristol-Myers Squibb)/3TC (Epivir by GlaxoSmithKline)/NVP (Viramune by Boehringer Ingelheim) original liquid formulations, orally every 12 hours. Dosages were based on body weight as measured at entry. Weight band dosing (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A479>, which shows the GPO-VIR S7 doses per body weight and the corresponding liquid formulation doses) was designed to achieve d4T and 3TC dosing as close as possible to the recommended mg/kg doses, while maintaining the NVP dose within daily 240 to 400 mg/m² range that was recommended by the manufacturer. To allow valid comparisons between formulations the amount of each liquid drug used was equal to that contained in the GPO-VIR S7 tablets administered to that subject. On the morning of Day 14 in Stage I or Day 28 in Stage II, a predose blood sample was drawn, after which the study drugs were administered using directly observed therapy, and blood samples (2 mL each) were collected 0.5, 1, 2, 4, 8, and 12 hours later. Immediately following the PK sampling, children were crossed-over to the alternate formulation at equal doses and identical blood sampling was performed on the morning of Day 28 (stage I) or 56 (stage II). Adherence to the study drugs was measured by pill count. To ensure 100% drug adherence directly observed therapy was performed during the 72 hours prior to the PK assessment. After the second PK sampling visit, the children resumed the same antiretroviral drugs they had received prior to enrollment and were followed for an additional 6 weeks for safety. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1.0, dated December 2004; available at: <http://rcc.tech-res.com>) was used to grade all adverse events.

For stage I, therapeutic inadequacy would be declared if the GPO-VIR S7 regimen-based 90% CI for geometric mean AUC for any of the 3 components lay either entirely less than 50% or entirely more than 200% of the target mean AUC. These stage I boundaries were chosen with the intent to ensure that if the GPO-VIR-S7 tablet was producing unacceptably high or low drug exposures the study would be stopped, while at the same time, and in view of the known variability of NVP exposure in children, allowing the study to continue into stage II, where exposure boundaries were more stringent but the sample size was larger. The target values for the AUC were 1.28, 4.46, and 63.6 $\mu\text{g h/mL}$ for d4T, 3TC, and NVP, respectively.

For stage II, the emphasis was on detecting the therapeutic inadequacy of nevirapine: therapeutic inadequacy would be declared if the 90% CI for NVP AUC lay either entirely below 70% of the NVP target AUC (ie, 44.5 $\mu\text{g h/mL}$, a drug exposure equivalent to obtaining an average NVP concentration of 3.4 $\mu\text{g/mL}$, the recommended minimum trough level¹³ or entirely above the symmetrical upper boundary on a \log_{10} scale (equivalent to 90.9 $\mu\text{g h/mL}$).

Antiretroviral Drug Level Measurement and Analysis

Blood samples were centrifuged, the plasma removed, then aliquoted and stored at -70°C . All plasma samples were sent to the Program for HIV Prevention and Treatment, IMPAACT Laboratory at the Faculty of Associated Medical Sciences, Chiang Mai University for drug level measurement. D4T and 3TC plasma drug concentrations were measured using a validated high performance liquid chromatography assay (average accuracy: 92% to 107%; precision (inter- and intra-assay): $<7\%$ for the coefficient of variation). The lower limit of assay quantification for d4T and 3TC was 0.025 $\mu\text{g/mL}$. NVP plasma concentrations were measured using a previously published high performance liquid chromatography assay,¹⁴ with a lower limit of assay quantification of 0.050 $\mu\text{g/mL}$. External quality controls for these assays were provided by the AIDS Clinical Trial Group, USA, Pharmacology Quality Control program.¹⁵ Pharmacokinetic analysis was performed with WinNonLin (Version 5.2, Pharsight, United States) using noncompartment methods.

Statistical Methods

For stage I, a sample size of 8 was chosen to observe initial safety and desired drug dosing, but no formal power calculations were used. For stage II, a greater emphasis was placed on NVP in determining the sample size since the plasma concentrations of NRTIs are not precise surrogates for intracellular NRTI-triphosphate concentrations and low NVP plasma concentrations are associated with poor virologic suppression.¹⁶ Fixing type I error rate at 5%, accrual of 30 children would provide an 85% probability that the estimated 90% CI for NVP mean concentration lay completely within $\pm 15\%$ of the target mean on the \log_{10} scale. On the basis of this estimate, the sample size for Stage II was a minimum of 30 children, stratified by weight: Group 1: ≥ 6 to 8 kg ($n = 6-8$), Group 2: >8 to 16 kg ($n = 8-12$), Group 3: >16 to 23 kg ($n = 8-12$), and Group 4: >23 to 30 kg ($n = 8-12$). To test for formulation carryover effects, for each study participant, the sum of natural logarithm (\ln) of the GPO-VIR S7 AUC and the \ln of the liquid formulation AUC were obtained. Using a t test values were compared between subjects who received GPO-VIR S7 first and those who received the liquid formulation first. PK parameters were compared between the 2 formulations using paired t tests. The correlations between PK parameters and dosing weight bands for GPO-VIR S7 tablet and the liquid formulations, respectively, were expressed using the Pearson correlation coefficients.

RESULTS

Stage I

Nine children (8 female) were enrolled. Four were randomized to receive the GPO-VIR S7 tablet first and then the liquid formulations and 5 children received the liquid first followed by the tablet. At baseline, the median (range) characteristics were as follows: age 8 (6–11) years, weight 21 (17–29) kg, absolute CD4 cell count 1179 (248–2159) cells/mm³, CD4% 35 (21–44), and HIV RNA <400 copies/mL (<400–668). The geometric mean (90% CI) AUCs while taking GPO-VIR S7 for d4T, 3TC, and NVP were 1.55 (1.44–1.68), 6.83 (5.87–7.96), and 73.93 (58.28–93.77) $\mu\text{g h/mL}$, respectively. Two children had notably high NVP AUC values but the exposures were similar between the GPO-VIR S7 tablet (133.2 and 140.33 $\mu\text{g h/mL}$) and the liquid (144.9 and 149.9 $\mu\text{g h/mL}$). The 90% CIs of the geometric mean AUCs for all 3 components were within the predefined range of 50% to 200% of target AUC, and Stage II was subsequently opened.

Stage II

A total of 35 subjects were enrolled. Eighteen were randomized to receive the GPO-VIR S7 tablet first and then the liquid formulations and 17 children received the liquid first followed by the tablet. Enrollment in the weight strata was as follows: Group 1 (≥ 8 –8 kg) n = 3; Group 2 (>8–16 kg) n = 8; Group 3 (>16–23 kg) n = 12; and Group 4 (>23–30 kg) n = 12. Enrollment to group 1 was difficult due to the lack of subjects who were older than 6 months and also under 8 kg. Eighteen of the 35 participants were male. At baseline, the median (range) characteristics were age 7 (0.5–11) years, weight 21 (7–29) kg, absolute CD4 cell count 980 (158–3014) cells/mm³, CD4% 29 (6–52), and HIV RNA <400 copies/mL (<400–41,217). Thirty-four of the participants completed the study requirements (one subject in Group 1 was lost-to-follow-up prior to the PK visit). The plasma concentration time curves for each drug when administered using both formulations are shown in Figure, Supplemental Digital Content 2, <http://links.lww.com/INF/A480>. No differential carryover effects between formulations were found.

The geometric means and 90% CI for AUC, C_{max}, and C_{min} for GPO-VIR S7 tablet and the liquid formulations, and within-subject geometric mean ratios (GMR) (GPO-VIR S7/liquid formulation) are shown in Table 1. The nevirapine exposure was therapeutically adequate, as defined by the prespecified protocol criteria: the 90% CI of the geometric mean NVP AUC was within the predefined target AUC range (44.5–90.9 $\mu\text{g h/mL}$). Individual NVP AUCs for both formulations, separated by weight group, are shown in Figures, Supplemental Digital Content 3, <http://links.lww.com/INF/A481>. A trend toward lower NVP exposure in the lower weight bands was observed. The median (range) daily NVP dose received by children in each weight band was Group 1, 277 mg/m² (276–278); Group 2, 289 mg/m² (246–358); Group 3, 352 mg/m² (322–376); and Group 4, 379 mg/m², (342–392) respectively. While using the GPO-VIR S7 formulation, 7 children (1 in Group 1, 4 in Group 2, and 2 in Group 3) had a minimum NVP concentration lower than 3.0 $\mu\text{g/mL}$, 16 with levels ranging between 1.4 and 2.9 $\mu\text{g/mL}$. All children had >97% adherence during the study, and 100% adherence 72 hours before the PK blood sampling. Four of these children also had a NVP concentration <3.0 $\mu\text{g/mL}$ while using the liquid formulation, with levels ranging between 1.6 and 2.7 $\mu\text{g/mL}$. For these 7 children, the median daily NVP dose was 286 mg/m² (246–367) and 5 of them received a dose under 300 mg/m² per day. In comparison, for the children with a minimum NVP concentration above >3.0 $\mu\text{g/mL}$, the median daily NVP dose was 353 mg/m² (277–392) and only 2 of 27 children received a dose under 300 mg/m² per day. All 7 children with a NVP minimum concentration <3.0 $\mu\text{g/mL}$ maintained an HIV-RNA viral load <400 copies/mL throughout the study.

For NVP, there was a significant positive linear relationship between AUC and weight bands ($P = 0.002$) and between C_{min} and weight bands ($P = 0.004$) (Fig., Supplemental Digital Content 4, <http://links.lww.com/INF/A482>, which shows the correlations between NVP AUC and C_{min} and dosing weight bands for the GPO-VIR S7 Pediatric tablet). Using regression analysis, with ln AUC of the NVP component in GPO-VIR S7 as the outcome and controlling for dose (mg), there was no significant effect of age ($P = 0.73$) or weight ($P = 0.84$). Likewise, when such an analysis was done controlling for dose in mg/m², there was also no significant effect of age ($P = 0.08$) or weight ($P = 0.11$). For d4T and 3TC, linear relationships were found between AUC and weight bands, but not between C_{max} or C_{min} and weight bands (data not shown).

Tolerance and Safety

The GPO-VIR S7 FDC was well tolerated by children of all ages in the study. In stage I, adverse events were reported in 7 of 9 patients, all were grade 1 or 2 and not related to treatment. In stage II, adverse events were reported in 19 of 35 participants. Three participants experienced grade 3 events: fever (2 patients) and low absolute neutrophil count (1 patient). All other adverse events were grade 1 or 2. All the events were classified as unrelated to the study drugs. CD4 and plasma HIV RNA values did not significantly change during the study.

DISCUSSION

Pediatric FDCs are urgently needed, particularly in resource limited settings where liquid formulations may not be readily available and refrigerated storage facilities are limited. In this study, we found that the new FDC tablet of d4T/3TC/NVP was safe and well tolerated, and nevirapine drug exposure was therapeutically adequate. In fact, the majority of children reported their preference for the tablet when compared with the large volumes of liquid required for 3-drug therapy. GPO-VIR S7 had significantly higher AUCs and C_{max} values than the liquid formulations for NVP and for 3TC but not for d4T. The C_{min} for the 2 formulations were not significantly different. NVP and d4T exposure with the GPO-VIR S7 tablets was very similar to the liquid formulations and provided comparable levels to those reported in adults (AUCs: d4T 1.28 $\mu\text{g h/mL}$ ¹⁷ and NVP 63.6 $\mu\text{g h/mL}$ ¹¹). However, 3TC in GPO-VIR S7 produced higher AUCs than the liquid formulation. Of interest, the AUC of 3TC in children taking GPO-VIR S7 (AUC 6.39 $\mu\text{g h/mL}$) was closer to that of adults taking GPO-VIR S-30 (6.56 $\mu\text{g h/mL}$)¹⁸ or to the 6.30–8.54 $\mu\text{g.hr/mL}$ reported in adult studies using 150 mg twice daily as an individual tablet or part of an FDC.^{19–21} Recently, a study of a pediatric FDC (d4T 6 mg, 3TC 30 mg, and NVP 50 mg) produced by Cipla and approved by WHO also found 3TC plasma concentrations comparable to those reported in adults,²² with mean 3TC AUC ranging from 4.14 to 6.76 $\mu\text{g h/mL}$ for children up to 30 kg. A study of the original formulation of lamivudine (8 mg/kg/d, twice daily) in children <6 years of age,²³ showed that the median AUC and C_{max} were 43% and 47% lower, respectively, compared with older children. The authors speculated that this difference may have been partly due to the lower bioavailability of the oral solution used by the younger children compared with the tablets used by the older children; the bioavailability of the oral solution is lower and more variable, 67% \pm 26% versus 87% \pm 13%, respectively. The target AUC level for 3TC in our study protocol was based on the published data from a study using the liquid formulation.¹⁰ These observations suggest that although the FDC tablet in the current study produced higher than target AUC levels for 3TC, this level of exposure is appropriate. Perhaps in future studies assessing 3TC containing-FDC tablets the 3TC target exposure should be set closer to those reported in adults using the tablet formulation, rather than those from pediatric studies where the liquid formulation was administered.

Several studies have reported that a predose NVP concentration less than 3.0 $\mu\text{g/mL}$ is associated with a higher risk of virologic failure.^{24,25} Among the children with NVP concentrations below this threshold the majority were in the lower weight bands. At the time this study was designed, the recommended daily NVP dose was 240 to 400 mg/m^2 , and the weight band dosing was based on this guideline. Subsequently, a cohort study in the United Kingdom suggested that a NVP dose of $>300 \text{ mg/m}^2$ per day results in better virologic outcomes.²⁶ Among the children with low NVP concentrations in our study, 5 of 7 were receiving a daily NVP dose $<300 \text{ mg/m}^2$. Also, as smaller children can have a larger body surface area relative to body weight when compared with older children/adults, the weight band dosing of NVP could inadvertently be lower when converting the dose to mg/m^2 . All children in weight bands $>13 \text{ kg}$ achieved a daily NVP dose $>300 \text{ mg/m}^2$.

A linear association between the weight bands and NVP parameters was observed. Additional data on NVP exposure in infants weighing $<8 \text{ kg}$ using GPO-VIR S7 are needed; however, recent studies have suggested that young infants, particularly <5 months old, have low NVP exposure.²⁷⁻²⁸ This observation is supported by early PK studies showing NVP clearance to be more rapid in younger children.²⁹ Thus, both age and weight-band dose determination of NVP may play a part in the lower NVP exposure observed in some children in our study. Although these children maintained HIV RNA viral suppression, a higher NVP dose could help reduce the risk of virologic failure. One option would be to adjust the weight band dosing in the smaller group ($<13 \text{ kg}$), to achieve a daily NVP dose of 300 to 400 mg/m^2 , (an increase by a maximum of 25%). This would require caution as it would also result in increases of d4T and 3TC doses. Data in adults showed that daily d4T doses of 4 mg/kg or more increased the chance of neuropathy and/or hepatotoxicity.³⁰ However, our study also found that lower weight bands had less exposure to d4T and 3TC than higher weight bands. For d4T, on average, a subject's AUC was 0.10 $\mu\text{g h/mL}$ lower than that of a subject from one weight band higher ($P = 0.01$). For 3TC, on average, a subject's AUC was 0.47 $\mu\text{g h/mL}$ lower than that of a subject from one weight band higher ($P = 0.01$). Therefore the d4T and 3TC dose increases resulting from a NVP dose adjustment are likely to be safe. On the basis of this logic, our results suggest that if the weight-band dosing for this FDC is used in young children it should be 1 tablet for children 6 kg to $<7 \text{ kg}$, 1.5 tablets for those between 7 and 10 kg, and 2 tablets for those >10 to 16 kg. Such a change will bring the weight-band dosing of GPO-VIR S7 closer to that recommended by the WHO.⁷

Despite the recent WHO proposal that countries progressively phase out d4T as the preferred first-line therapy option, it is expected that d4T will still have a role in resource limited settings. For anemic children or those who are unable to tolerate zidovudine pediatric FDCs that contain d4T can provide physicians with the option to initiate a simple regimen in children. Also, this d4T containing FDC will primarily be used in prepubertal children, the age group who is less prone to fat redistribution than postpubertal adolescents.³¹

In conclusion, our study demonstrated that GPO-VIR S7 has satisfactory PK and is safe. Compared with liquid formulation, it provided similar exposure for d4T and NVP and 3TC exposure comparable to exposure in both children and adults receiving tablet forms of the drug. The weight band doses used in this study provided adequate NVP therapeutic drug levels in older children, but may need to be adjusted for younger children to achieve a higher dose of NVP. It is expected that this novel chewable FDC will help simplify antiretroviral treatment for HIV-infected children who require a d4T regimen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Stage II Stavudine (d4T), lamivudine (3TC), and Nevirapine (NVP) Pharmacokinetic Parameters After Ingestion of GPO-VIR S7 or the Individual Liquid Formulations (Geometric Means and 90% CI) in HIV-infected Thai Children

TABLE 1

	All Weight Groups (N=34)		P [†]	GMR (90% CI) [‡] GPO-VIR S7/ Liquid
	GPO-VIR S7*	Liquid*		
d4T [§]				
AUC (μg h/mL)	1.54 [¶] (1.42–1.67)	1.59 [¶] (1.49–1.71)	0.25	0.97 [¶] (0.92–1.02)
Cmax (μg/mL)	0.94 [¶] (0.84–1.05)	0.87 [¶] (0.79–0.95)	0.21	1.08 [¶] (0.97–1.20)
3TC				
AUC (μg hr/mL)	6.39 [¶] (5.82–7.00)	4.52 [¶] (4.14–4.94)	<0.0001 [¶]	1.41 [¶] (1.30–1.53)
Cmax (μg/mL)	2.16 [¶] (1.90–2.45)	1.35 [¶] (1.23–1.50)	<0.0001 [¶]	1.59 [¶] (1.39–1.82)
Cmin (μg/mL)	0.07 [¶] (0.06–0.07)	0.07 [¶] (0.06–0.07)	0.69	0.98 [¶] (0.90–1.06)
NVP				
AUC (μg h/mL)	74.06 [¶] (65.62–83.60)	68.40 [¶] (61.36–76.25)	0.005 [¶]	1.08 [¶] (1.04–1.13)
Cmax (μg/mL)	7.80 [¶] (7.01–8.67)	6.86 [¶] (6.20–7.58)	<0.0001 [¶]	1.14 [¶] (1.08–1.19)
Cmin (μg/mL)	4.68 [¶] (4.04–5.43)	4.48 [¶] (3.94–5.10)	0.21	1.05 [¶] (0.99–1.11)

* Reported values are geometric mean (90% CI).

[†] The p values are from paired t tests comparing the 2 formulations.

[‡] GMR (90%): Geometric mean ratio and 90% confidence interval.

[§] d4T Cmin was below lower limit of assay quantification (<0.025 μg/mL) over all weight groups.

[¶] P < 0.05 are bolded.