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CYP2B6 Genotype-directed dosing is required for optimal efavirenz exposure in children 3 to 36 months with HIV infection

Carolyn Bolton MOORE, MD^{1,2}, Edmund V. CAPPARELLI, PharmD³, Pearl SAMSON⁴, Mutsa BWAKURA-DANGAREMBIZI⁵, Patrick JEAN-PHILIPPE⁶, Carol WORRELL⁷, Barbara HECKMAN⁸, Lynette PURDUE⁶, Stephen A. SPECTOR³, Alex BENNS⁸, William BORKOWSKY⁹, Amy LOFTIS¹⁰, Elizabeth HAWKINS¹¹, Carole WALLIS¹², and Ellen G. CHADWICK¹³ for the IMPAACT P1070 team

¹Centre for Infectious Disease Research in Zambia, Lusaka, Zambia

²University of Alabama at Birmingham, Birmingham Alabama, USA

³University of California San Diego, La Jolla, California and Rady Children's Hospital, USA

⁴Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

⁵University of Zimbabwe, Harare, Zimbabwe

⁶National Institutes of Allergy and Infectious Diseases, National Institutes of Health,, Bethesda, Maryland, USA

⁷Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA

⁸Frontier Science and Technology Research Foundation, Amherst, New York, USA

⁹New York University's School of Medicine, New York, New York, USA

¹⁰UNC Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Corresponding Author and request for reprints: Dr Carolyn Bolton Moore, PO box 34681, Lusaka, Zambia, 10101, Carolyn.bolton@cidrz.org, +260966841034.

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¹¹Social and Scientific Systems Inc, Silver Springs, Maryland, USA

¹²BARC-SA and Lancet Laboratories, Johannesburg, South Africa

¹³Northwestern University's Feinberg School of Medicine, Chicago, Illinois, USA

Abstract

Objectives—To determine safety, efficacy and genotypic-specific dose requirements of EFV in children aged 3 – < 36 months of age with HIV infection with or without TB co-infection.

Design—IMPAACT P1070 was a 24 week prospective cohort trial of EFV (as open capsules) plus two nucleoside reverse transcriptase inhibitors in children with HIV infection 3–<36 months without tuberculosis (Cohort 1).

Methods—CYP2B6 G516T genotype was determined and intensive PK's were performed at week 2. EFV dose was adjusted if outside the target area under the curve (AUC) 35–180 mcg*hr/mL. PK and CYP2B6 G516T genotype data were used to model EFV exposures based on FDA-approved doses.

Results—Forty-seven participants, median age 19 months, initiated the study regimen with 24 weeks median follow up; 38 516GG/GT and 9 516TT genotypes. Initially, median EFV AUC was higher in 516TT versus 516GG/GT (median 490 vs 107 p =0.0001) with all 516TT above AUC target. Following an amendment that reduced the 516TT EFV dose by 75%, PK modeling predicted that 83% of participants met the AUC target (31/38 516GG/GT, 8/9 516TT). In contrast, modeling using P1070 data predicted that FDA-approved doses would produce sub-therapeutic AUCs in almost one third of participants with 516GG/GT and excessive AUCs in >50% with 516TT genotypes.

Conclusion—CYP2B6 G516T genotype strongly influences EFV exposures in this age group. Genotype-directed dosing yields therapeutic EFV concentrations and appears to out-perform other dosing approaches.

Background

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with a relatively narrow therapeutic window and serum concentrations showing high inter- and intra-patient variability [1, 2]. EFV is recommended by the World Health Organization (WHO) as first-line treatment for HIV-infected adults and children.[3] Significant pharmacokinetic (PK) variability of EFV is related to a single nucleotide polymorphism in the cytochrome (CYP) P450 2B6 gene (G516T, rs3745274).[4–6] The CYP 2B6 isoform has been found to be almost exclusively responsible for EFV metabolism to its primary inactive metabolite [7, 8]. The prevalence of CYP 2B6 516TT (TT) genotype varies across geographic regions and ethnicities but has been reported in 9–23% of South Africans [9, 10]. Persons having 516TT genotype, also referred to as poor metabolizers, have slower clearance of EFV in comparison with 516GG (GG) or 516GT (GT) genotypes (extensive metabolizers), who exhibit more rapid clearance [8, 11]. Furthermore, liquid formulations have shown erratic absorption and even higher variability [12].

Dose-finding for children <3 years of age or weighing <10 kg has been particularly challenging, as pharmacokinetic studies have shown a greater effect of genotype on EFV metabolism in young children due to high clearance, especially among extensive metabolizers [8]. Dutch HIV-infected children with the GG genotype and treated with WHO-approved EFV doses had only a 30–50% probability of achieving a therapeutic trough level of efavirenz [13]. This study aimed to determine the genotype-specific dose requirements of EFV, administered as opened capsules, in HIV-infected children aged 3 – < 36 months with or without TB co-infection, and the 24-week safety and efficacy.

Methods

Study Design

IMPAACT Protocol P1070 was a prospective, Phase I/II open-label 24-week trial implemented in five tuberculosis-endemic countries. Children with HIV infection (Cohort I) or HIV/TB co-infection (Cohort II, reported separately), aged 3 months to less than 36 months, initiating antiretroviral therapy (ART) were eligible to enroll. Exclusion criteria included: prior treatment with or exposure to EFV, infants less than 24 months of age with prior receipt of nevirapine (NVP), or whose mothers received NVP or EFV during gestation or in labor; severe malnutrition, active opportunistic or central nervous system infections which required therapy; or liver enzymes Grade 2 using the Division of AIDS (DAIDS) toxicity tables: (<http://www.niaid.nih.gov/labsandresources/resources/daidsclnrsrch/documents/daidsaegradingtable.pdf>). Participants were stratified into two age groups, 3–<24 months and 24 to <36 months and treated with an antiretroviral regimen consisting of two NRTIs and weight-band based EFV dosing (Table 1) given as capsules opened into porridge, formula or expressed breast milk. Safety and efficacy were judged by clinical examinations and laboratory testing at study entry, weeks 2 and 4 and then monthly, with HIV RNA level at study entry, weeks 4, 8, 16 and 24 weeks. Toxicities were graded using the DAIDS toxicity tables and an expanded study specific table was developed to grade neuro-toxicities.

EFV Dosing Approach

The starting EFV dose was modeled using data from two previous Pediatric AIDS Clinical Trials Group studies of EFV pharmacokinetics in children (P382 and P1021). [8, 14] In Version 1 (V1) of the study, an initial dose of EFV [$\sim 1600 \text{ mg} \times (\text{weight in Kg}/70)^{0.7}$] rounded for weight band dosing] was chosen for all participants to produce a target AUC of 35–180 mcg*h/mL, a systemic exposure similar to that shown to be effective and safe in older children and adults. At the week 2 study visit, real time intensive EFV PK was performed and individual participants' doses were adjusted accordingly. Real-time CYP 2B6 516 (rs3745274) genotype was also assessed. Extremely high EFV exposures in the first 7 TT participants (see Results) led to a protocol amendment, Version 2 (V2), which introduced genotype-guided dosing and incorporated an approximate 75% reduction in EFV dosage for TT participants, [$\sim 400 \text{ mg} \times (\text{weight in Kg}/70)^{0.7}$]. EFV dosing for participants with 516GG/GT genotype remained unchanged in V1 and V2.

Pharmacokinetic Assessments

At study week 2, intensive pharmacokinetic sampling was performed prior to the observed dose and at 2, 4, 8, 12 and 24 hours post-dose. Plasma and dried blood spots (DBS) were prepared from each sample. Individual dose adjustments were made if necessary, based on AUC results and according to pre-determined dosing tables. Repeat intensive pharmacokinetics pre-dose and 4, 8, and 24 hours post-dose were performed two weeks after any dose adjustment; if target AUC was not achieved, participants were discontinued from the study and started on locally prescribed antiretrovirals. The target AUC range (35–180 mcg*h/mL) corresponds to a drug concentration at 24 hours (C24) range of ~0.7 to 4.0 mcg/mL. While both AUC and C24 are highly correlated ($r^2>0.95$), we used AUC to guide dosing since it is less sensitive to deviations in sample collection and prior dosing intervals.

Dose Finding Guidelines

To establish a dose for each age group, the first 8 GG/GT participants were evaluated based on their week two AUC plasma PK results and safety data through week 4. The dose was considered safe for the age group if no participants experienced a Grade 4 life-threatening toxicity or a Grade 4 toxicity accompanying any serious adverse event (SAE) judged to be at least possibly related to EFV. At least 6 of 8 participants were required to achieve a plasma AUC within the target range to deem the dose acceptable.

Determination of Efavirenz Concentration

Efavirenz AUC was determined by non-compartmental methods. Dried blood spot samples from intensive PK collections were assayed in real-time and used to determine immediate EFV exposure for potential individual dose adjustments. Plasma samples were batched for final PK analysis. The plasma AUC was determined either by direct measurement of the plasma samples or from the DBS samples multiplied by the plasma/DBS ratio (1.30) observed from the first 246 plasma-DBS pairs.

Estimation of EFV exposure based on FDA recommended dosages

PK modeling, using P1070 pharmacokinetic data, was used to estimate the percentage of participants, according to genotype, likely to attain therapeutic EFV target concentrations as per FDA-indicated dosages. The predicted EFV exposures (AUC or C24) were calculated and compared with actual exposure from dosing strategies used in P1070. Assuming a linear PK, the observed AUC and C24 from P1070 were multiplied by the ratio of the alternative/actual received doses and were used to generate predicted AUC and C24 for FDA dosing. This was also done to determine differences between V1 and V2 for the TT genotype. The frequency of AUC and C24 in the target ranges of 35–180 mcg*h/mL and 1–4 mcg/mL, respectively, among the three dosing strategies was then compared.

Safety, Virology and Immunology

DBS and plasma samples for resistance mutation genotypes were drawn at Entry and at Weeks 4 and 24, and batched for correlation with virologic responses. In addition, resistance genotypes were collected if a confirmed virologic endpoint was met (defined as $<1 \log_{10}$ decrease from entry quantitative HIV RNA and RNA > 400 copies/ml at week8). A safety

endpoint was defined as any treatment-related Grade 3 or Grade 4 toxicity requiring permanent discontinuation of EFV.

Statistical Methods

Safety, pharmacokinetic and efficacy analyses included only participants enrolled in Cohort I (non-TB infected) aged 3 to 36 months. Analyses are presented in aggregate. Several are further stratified by genotype. Descriptive statistics were used to summarize study entry demographic data. Proportions of participants experiencing adverse events deemed at least possibly treatment-related were bounded by 95% exact confidence intervals (CIs). Median, interquartile ranges (IQR) were calculated for AUC, C24 (trough), clearance, maximum concentrations (C_{max}) and the amount of time the drug was present at maximum concentrations (T_{max}). The proportion of participants falling within the AUC and C24 targets was estimated bounded by 95% exact confidence intervals. Virologic response was analyzed at weeks 4, 8, 16, 24 using an ‘intent-to-treat’ (ITT) approach (children who discontinued study treatment for any reason were considered failures). Rates of virologic success and on treatment at the time when the response was evaluated are presented with the corresponding 95% exact confidence intervals. Median log₁₀ HIV-RNA changes from study entry were calculated in an ‘as-treated’ analysis’ such that only participants who remained on study drug and who had evaluable data were included in this analysis.

Ethical Review

The protocol, amendments, informed consent forms, and relevant study-related documents were reviewed and approved by the ethics committee of each of the participating sites. The study was performed in accordance with Good Clinical Practice and in accordance with country-specific laws and regulations governing clinical studies of investigational products. Written, informed consent was obtained from all participants’ legal guardians. ClinicalTrials.gov identifier NCT00802802.

Role of the Funding Source

The funder representatives were involved in study design, data collection, data analysis, data interpretation, and writing of the report. However the corresponding author had full access to all the data in the study and had final responsibility for the content of the manuscript and the decision to submit for publication.

Results

Forty-seven infants without TB (median age 19 months (13–27 IQR)) were enrolled with 24 weeks median follow up (18–24 IQR), 28 of whom were 3–<24 months. Twenty-two children aged 3 months to 24 months were found to have 516GG/GT and 6 had 516TT genotypes. Among the 24–36 month age group, 16 had a 516GG/GT genotype and 3 had 516TT. Baseline characteristics by genotype are summarized in Table 2.

Pharmacokinetic Results

Median EFV concentrations rose significantly 3 to 8 hours after dosing for participants with the 516GG/GT genotype (Figure 1). The EFV concentrations in participants with 516TT

genotype had EFV concentrations approximately four times greater than those with 516GG/GT genotypes with version 1 dosing. While the majority of participants were in the 7.0–13.99 kg weight bands, there was no indication that those near the lower threshold of 7 kg, who received nearly double the mg/kg dose, had higher EFV exposures than those near the upper weight band threshold of 13.99 kg (Figure 2).

Thirty one of 38 (82%) participants with 516GG/GT genotypes achieved the PK target range with starting dose of $\sim 1600 \text{ mg} \times (\text{weight in kg}/70)^{0.7}$ QD, or approximately 40 mg/kg/day. Three of four with AUCs below target met the target with a 50% dose increase but only one of three with AUCs above target reached the target with a 50% dose reduction. Both age groups with 516GG/GT genotypes met the study's dose-finding criteria, so this dose was accepted.

Nine participants had 516TT genotypes. All 7 (100%) taking V1 EFV dosing ($\sim 40 \text{ mg/kg}$ QD) had significantly elevated EFV exposures, whereas 2/2 taking V2 dosing ($\sim 10 \text{ mg/kg}$ QD) achieved the target range. Three of seven (43%) V1 516TT participants discontinued the study prematurely because the protocol-directed 50% dose reduction either failed ($n=2$) or was predicted to fail ($n=1$) to bring their EFV levels within the target range.

Figure 3 shows the percent of participants achieving the targeted AUC according to genotype and dosing (P1070 version 1 or 2 vs FDA). The P1070 genotype-based dosing results in approximately 80% of 516GG/GT and 90% of 516TT participants receiving the V2 dose achieving the desired AUC. In contrast, FDA-approved dosing recommendations would result in only 63% of 516GG/GT and 44% of the 516TT participants achieving the target AUC (Supplemental Appendix Table 1). Importantly, using FDA dosing, one-third of 516GG/GT participants would have sub-therapeutic EFV exposures and more than half of 516TT participants would have AUCs above the target, including 33% with excessively high AUCs, i.e. $>290 \text{ mcg}\cdot\text{h/mL}$ (Supplemental Appendix Table 1).

Safety Outcomes

Fifteen of 47 participants (32%, 95% CI 19, 47) experienced non-life threatening toxicities that were deemed at least “possibly related to ARV treatment” regardless of grade (11 516GG/GT and 4 516TT). Six participants (6/47, 13%), consisting of all 3 CYP2B6 genotypes, reported neurologic toxicities of lethargy, sleepiness or sleep disturbances. There were no deaths, hospitalizations, or other SAEs that accompanied any of the Grade 4 toxicities deemed at least “possibly related” to treatment.

Virologic Outcomes

Two of 47 enrolled participants were excluded from virologic analysis after developing TB at week 4 (both). Among participants with evaluable virologic data, 89% (95%CI [76,96]) at week 4 and 82% (95% CI [68,92]) at week 8 achieved virologic. At week 16 and 24, 73% (95%CI [58,85]) achieved virologic success: 28/36 (78%; 95%CI [61,90]) with 516GG/GT and 5/9 (56%; 95%CI [21,86]) with 516TT genotypes. All failures by ITT analysis were due to early treatment discontinuation without virologic failure. All participants who completed treatment through week 24 had HIV RNA levels < 400 copies/ml.

Study Discontinuations

Thirty-four of 47 participants (72%) completed 24 weeks of treatment per protocol. Thirteen discontinued early: six (13%) participants were withdrawn for failure to achieve target EFV concentrations despite protocol-defined dose adjustments (5 with AUC > 180 mcg*h/mL and 1 with AUC < 35 mcg*h/mL); three (6%) experienced a protocol defined toxicity (1 Grade 4 lipase, deemed on subsequent review, to be probably not related to EFV; 1 Grade 3 lethargy possibly related to EFV; and 1 Grade 4 absolute neutrophil counts possibly related to EFVTT with AUC >180 mcg*h/mL); two were withdrawn by their guardians; and two were unable to attend follow-up study visits.

Discussion

This study has demonstrated that significant pharmacokinetic variability, largely dependent on CYP2B6 G516T genotype, prohibits recommendations for a uniform efavirenz dosing strategy for children 3 to 36 months of age. Consistent with previous estimates in this setting, over 80% of our participants were extensive metabolizers [516GG/GT genotype] with rapid EFV clearance, thus requiring a high EFV dose of open capsules to achieve therapeutic exposures. However, this high dose was excessive for the 19% who were poor metabolizers [516TT genotype] with EFV approximately 4 times higher than extensive metabolizers, making genotype-directed dosing particularly important in this age group.

Our findings suggest that FDA-approved dosing, which does not consider genotype, is too low for extensive metabolizers and too high for poor metabolizers. PK modeling anticipates that the FDA EFV dose for children <3 years of age would produce sub-therapeutic AUCs in 32% of extensive metabolizers whereas only 11% would be sub-therapeutic with P1070 dosing. Young children often present with very high viral loads and under-dosing risk the development of EFV resistance mutations, as illustrated by a recent study of 37 EFV-treated children ages 3 months-6 years in whom 6/14 (43%) with sub-target EFV levels acquired resistance to EFV during the study [12]. A Thai study of 188 school-age children following FDA-approved weight band dosing correlated EFV concentrations and probability of HIV replication and reported that odds of viral load >400 copies/ml increased by 2.1 (odds ratio: 2.1, 95% CI: 1.4–3.0; p=0.03) for each 0.5 mg/L decrease in EFV C24.[15] Similarly, Ren et. al. reported 6/15 (40%) South African children ages 3–15 years had sub-therapeutic EFV troughs (<1 mg/L), and virologic failure (viral load >200 copies/ml) was observed in 3/6 (50%) with low levels vs. 2/9 (22%) with EFV troughs >1 mg/L.[16]

In a single-site study of 33 children 2.1–16.7 (median 8.2) years of age, Wintergerst et. al. reported a trend for a higher incidence of viral load blips in children with sub-therapeutic EFV plasma concentrations.¹⁷ Virologic responses of the children in P1070 were encouraging. While 73% achieved a plasma RNA <400 copies/ml by week 24 by ITT and all 32 (100%) participants completing 24 weeks were virologically suppressed. Median viral load decrease was 2.7 log at week 4 and 3.3 log at week 24.

The P1070 EFV dose of ~40 mg/kg that proved necessary for extensive metabolizers produced excessive EFV exposures in 100% of the poor metabolizers in protocol Version 1. Reducing the dose by 75% projected that 89% of those with the 516TT genotype would

attain the target AUC. In contrast, the FDA-approved EFV dose would generate only 44% in the target range and 56% would have excessive levels. Van de Wijer and colleagues recently expressed concern that the risk of CNS toxicity (primarily effects on neurocognitive development) in infants may be substantial and should be considered when assessing the risk-benefit ratio of using EFV in HIV-infected infants and children.[17] A trend for higher EFV concentrations in children who experienced CNS-related adverse events was also reported by Wintergerst et. al.[18] While there are presently no long-term data available, it is likely that excessive EFV levels would contribute more significantly to CNS side effects than therapeutic levels.

EFV was well tolerated overall, with only 2/47 participants (one GG/one TT) discontinuing due to toxicities possibly related to EFV and no life threatening or grade 4 SAE's. We did not see disproportionate CNS toxicity in children with excessive levels, but this may be related to the early dose adjustment based on EFV concentrations and the young age of our participants who may be unable to report subjective complaints.

While CYP2B6 516 is the most frequently encountered polymorphism influencing EFV metabolism, the effects of other minor frequency mutant alleles remain unclear. The only three extensive metabolizers with AUCs over the target range had 516GT genotypes, two of whom had EFV AUCs >400 mcg*h/mL. It is possible that the assumed "functional" 516 G allele in these participants possesses a less prevalent, alternative CYP 2B6 mutation associated with reduced activity such as CYP2B6 T983C. This may explain the EFV metabolism in these two participants mimicking the CYP2B6 516TT phenotype group.

Fillekes and colleagues reported significant inter-participant variability in 41 3–12 year old HIV-infected Ugandan children with 17% below therapeutic concentrations and 29% with very high EFV levels.[19] A genotype-directed dosing strategy is likely to minimize excessive exposures yet yield adequate concentrations to ensure viral suppression and avoid possible contributions of ongoing viremia to neurocognitive effects. While the routine use of genotypic screening remains a challenge in resource-limited settings, HLA-B*5701 screening has been used routinely in mid-and high-income settings to determine appropriateness of using abacavir for many years. These tests can now be processed within Africa, although genotyping costs are relatively high (approximately \$60 per polymorphism, personal communication). An increase in demand and subsequent economies of scale will likely result in a significant decrease in cost, making tests more available to resource-limited populations. Given the scarcity of antiretroviral drugs suitable for the treatment of infants and young children, and the need for formulations which can be used concomitantly with anti-tuberculosis treatment, the use of genotypic testing should be required in children under 3 years of age to ensure that optimal drug levels are achieved. Our study demonstrated that this approach achieved excellent target exposures with favorable safety and virologic outcomes, paving the way for the use of a simple dosing algorithm and suggests that this one-time investment is likely to prove cost effective over time.

Conclusion

EFV remains an important treatment option in resource-limited settings with high TB co-infection. Significant inter-participant PK variations, largely dependent on CYP2B6 G516T genotype, challenge the use of uniform EFV dosages for children <3 years of age. CYP2B6 genotype-directed EFV dosing can mitigate this challenge by improving therapeutic EFV exposures in children with the more common 516GG and 516GT genotypes and avoiding excessive drug levels in those with 516TT genotypes. The increased proportion of 516TT genotypes in many resource-limited settings makes this approach particularly important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
24 Hour Plasma PK at Week 2

Figure 2. Percentage of AUC's in Target Range (Observed Dosing and Simulated Dosing)
 GG/GT – v1&2 and TT – v1 represent data obtained from P1070 Version 1. GG/GT – FDA and TT – v2 represent use of P1070 Version 1 pharmacokinetic data modeled to estimate the AUC if Version 2 dosing was applied.; and TT – FDA, if the FDA dosing was applied.

Table 1

Comparison of P1070 and FDA Recommended Dosages

Weight (kg)	P1070 516GT/GG* (mg)	P1070 516TT (Version 2) (mg)	FDA (mg)
3–3.5	200	50	-
3.5–5	200	50	100
5–7	300	50	150
7–7.5	400	100	150
7.5–10	400	100	200
10–14	400	100	200
14–15	500	150	200
15–17	500	150	250

* Version 1 and 2 dosages remained the same throughout the study for GG/GT.

Table 2

Baseline Characteristics By CYP2B6 516 Genotype

		CYP2B6 516 genotype		
Characteristic		516GG/GT (N=38)	516TT (N=9)	Total (N=47)
Gender	M	24 (63%)	4 (44%)	28 (60%)
	F	14 (37%)	5 (56%)	19 (40%)
Race	Asian	9 (24%)	2(22%)	11 (23%)
	Black or African American	28 (74%)	7 (78%)	35 (74%)
	Unknown	1 (3)	0 (0%)	1 (2%)
CYP2B6 516 Genotype	GG	21 (55%)	0 (0%)	21 (45%)
	GT	17 (45%)	0 (0%)	17 (36%)
	TT	0 (0%)	9 (100%)	9 (19%)
Age (mos)	Median	19	20	19
	Q1, Q3	13, 27	18,26	13, 27
Log10 Baseline RNA	Median	5.79	5.83	5.80
	Q1, Q3	5.29, 5.96	5.76, 5.88	5.31, 5.94
Baseline CD4 Count	Median	1,252	1,217	1,241
	Q1, Q3	845, 1,719	1,041, 1,309	953, 1,647
Baseline CD4 Percent	Median	20.60	17.90	19
	Q1, Q3	15, 27.10	12, 21	14, 26

Table 3**Week 2 PK Parameters By Age and Genotype**

Characteristic		516GG/GT 3-24 mos, (N=22)	516GG/GT 24-36 mos, (N=16)	516TT (V1) (N=7)	516TT (V2) (N=2)
Dose amount (mg)	Median	400	400	400	100
	Q1, Q3	400, 400	400, 400	300, 400	100, 100
AUC (mcg* _h /mL)	Median	108.58	106.84	490.20	83.11
	Q1, Q3	58.85, 135.92	35.55, 132.17	339.48, 650.25	63.71, 102.50
Trough*(mcg/mL)	Median	1.80	2.63	20.78	3.11
* 24 hour	Q1, Q3	1.01, 2.48	0.83, 3.74	12.29, 24.25	2.18, 4.03
Clearance (L/h/kg)	Median	0.42	0.36	0.09	0.16
	Q1, Q3	0.34, 0.68	0.24, 1.06	0.06, 0.13	0.09, 0.23
C _{max} (mcg/mL)	Median	9.19	7.53	21.85	4.78
	Q1, Q3	6.02, 10.72	3.49, 10.25	18.37, 33.39	4.48, 5.07
T _{max} (h)	Median	2.05	2.35	4.10	2.15
	Q1, Q3	2.00, 4.10	2.00, 4.05	4, 8	2.00, 2.30
AUC classification	AUC < 35	1 (5%)	3 (19%)	0 (0%)	0 (0%)
	AUC [35,180]	20 (91%) [71%,99%]	11 (69%) [41%,89%]	0 (0%) [0%,41%]	2 (100%) [16%,100%]
	AUC > 180	1 (5%)	2 (13%)	7 (100%)	0 (0%)
Trough classification	Trough < 1	5 (23%)	5 (31%)	0 (0%)	0 (0%)
	Trough [1,4]	14 (64%) [41%,83%]	8 (50%) [25%,75%]	0 (0%) [0%,41%]	1 (50%) [1%,99%]
	Trough > 4	3 (14%)	3 (19%)	7 (100%)	1 (50%)