CLINICAL PHARMACOLOGY REVIEW

NDA: 20-636 SE5 027 & 20-933 SE5 017	Submission Date(s): December 20, 2007
Brand Name	VIRAMUNE
Generic Name	Nevirapine
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	DAVP
Sponsor	Boehringer Ingelheim
Formulation; Strength(s)	Tablet (200 mg) and Oral suspension (10 mg/mL)
Indication	Treatment of HIV-1 infection

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I. Executive Summary

Recommendations

The applicant submitted this supplemental NDA to support the proposed labeling changes to expand the pediatric use of nevirapine from 2 months – 16 years of age to - - days – 16 years of age, to add dosing recommendation based on body surface area across entire pediatric age range (the current recommendation is based on body weight), and to provide dosing recommendations in patients with hepatic impairment. In addition, this submission addresses two post marketing commitments (PMCs):

- To provide additional information to determine the appropriate dosage of VIRAMUNE for chronic treatment of neonates and infants younger than two months of age
- To evaluate and attempt to determine appropriate dosing recommendations in patients with hepatic impairment

The Office of Clinical Pharmacology (OCP) reviewed the information submitted and concluded the information is adequate for the labeling revisions including removal of body weight-based dosing regimens.

Phase IV Commitments

None.

Summary of Clinical Pharmacology Findings

1. Evaluation of Nevirapine in Pediatric Patients

Nevirapine is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 and is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The current labeled dose for nevirapine in children is 7 mg/kg BID if age two months to eight years and 4 mg/kg BID if age ≥ 8 years, following a lead-in dose of 4 mg/kg QD for 14 days regardless of age. Reasons for lead-in phase are to allow the occurrence of auto-induction and to decrease the incidence of rash. This dose scheme was developed to compensate for the changing clearance of nevirapine with age during childhood (Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of nevirapine tablet and oral suspension (NDAs 20-636 and 20933), Study 1100.882). This dosing regimen is simple to calculate, but at eight years will require a change in the dosing sequence due to the change in the weight adjusted dose.

The applicant evaluated a dosing regimen based on body surface area because that method may allow a consistent dose across entire age range. The dose of 150 mg/m^2 was predicted to produce an average steady state concentration of 5.3 µg/mL in children for all age groups, similar to the 4 – 6 µg/mL seen in adults dosed at 200 mg BID.

Study 1100.1368 in this submission addresses the appropriateness of the dosing recommendation based on body surface area in pediatric patients 3 months to 16 years. Study 1100.1368 was a randomised open-label multi-center study to evaluate the pharmacokinetics, safety and efficacy of nevirapine dosed on body surface area (BSA) 150 mg/m^2 and body weight (BW) (4 or 7 mg/kg), in combination with ZDV and 3TC, in patients aged 3 months to 16 years. The primary objective was to evaluate steady state pharmacokinetic parameters of nevirapine 150mg/m^2 BID (not to exceed 200 mg BID) in antiretroviral drug naïve pediatric patients, as well as efficacy and safety of nevirapine 150 mg/m^2 and nevirapine 4 or 7mg/kg (not to exceed 200 mg BID) after 24 and 48 weeks of treatment.

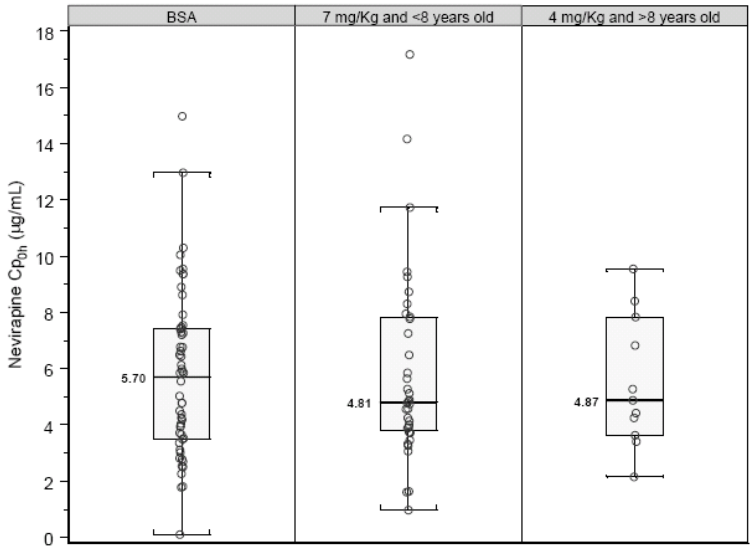
The results of the 48 Week analysis confirmed that 150 mg/m^2 and the 4 or 7 mg/kg NVP doses were well tolerated and effective in treating antiretroviral naive pediatric patients.

At steady-state (Day 28, Week 4), both dose groups attained nevirapine concentration levels comparable to the adult range of 4-6 µg/mL and the proportion of patients whose HIV RNA went below the limit of quantification (< 400 copies/mL) were similar. Approximately 30% of the patients from each dose group were below the HIV RNA limit of quantification at Week 4. However, a difference in the virologic response rate between the 4 or 7 mg/kg and 150 mg/m^2 NVP dose groups was observed at Week 8 and continued through Week 48. The virologic response rate was slightly higher in the 150 mg/m^2 NVP dose group than in the 4 or 7 mg/kg NVP dose group. At Week 48, 61% of patients in 150 mg/m^2 NVP dose group were below the limit of quantification (RNA < 400 copies/mL) compared to 44% in the 4/7 mg/kg NVP dose group. The reason why the 150 mg/m^2 NVP dose group performed better than the 4 or 7 mg/kg NVP dose group in sustained virologic response could be the higher lead-in dose (150 mg/m^2 QD, half of the maintenance dose, 150 mg/m^2 BID) compared to the lead-in dose (4 mg/kg QD, about one quarter of maintenance dose, 7 mg/kg BID) in the two months to eight years age group. Lower lead-in dosing may impact efficacy because resistance develops rapidly for NNRTIs if exposure is suboptimal. Thus we proposed that the lead-in dose for children two months to eight years of age be changed from 4 mg/kg to 7 mg/kg because of the inconsistency between the proposed BSA dosing recommendations and the labeled weight-based dosing recommendations (e.g., lead-in dose is half of the maintenance dose across all recommended dosing regimens).

Pharmacokinetic data demonstrated that the body surface area algorithm for dose administration yielded comparable trough nevirapine concentrations (n=56 patients; 0.33 – 13.69 years) to the approved body weight algorithm (n=47 patients; 0.28 – 11.50 years) presented in the prescribing information for

nevirapine. Dosing of nevirapine at 150 mg/m^2 BID (after a two-week lead in at 150 mg/m^2 QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 µg/mL (as targeted from adult data) without an abrupt change in dosing schedule at age 8 years. The variability observed in the observed trough nevirapine concentrations was comparable between the two methods and reflects the population being treated rather than the dosing method.

Figure 1. Median trough nevirapine concentrations observed using the BSA algorithm (n=56 patients) and the body weight algorithm (n=11 for >8 year old patients and n=36 for <8 year old patients)

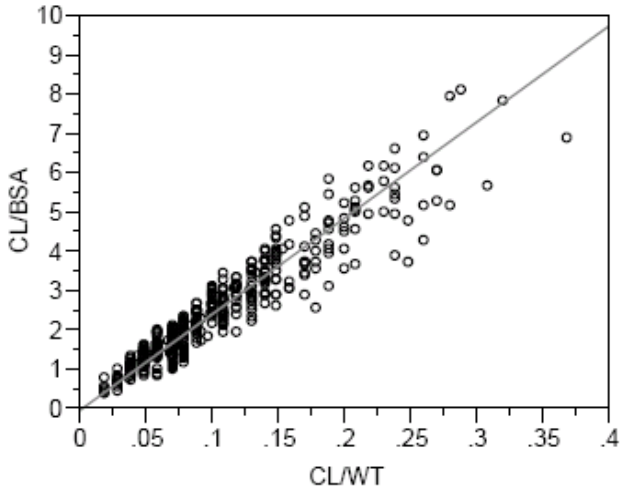


A pharmacokinetic meta-analysis was also included in the submission. The purpose of this meta-analysis was to extend pediatric age group to less than 2 months of age with the same dosing recommendations and to further support that the BSA and BW-based dosing regimens are comparable.

The pharmacokinetic meta-analysis was conducted by combining pharmacokinetic data of the above-mentioned pediatric 48-week safety and efficacy study (1100.1368) with all available historical PACTG data. Five Pediatric AIDS Clinical Trials Group (PACTG) protocols (245, 356, 366, 377, and 403) comprising 495 patients aged 1 month to 19 years. There were 17 subjects <2 months old in PACTG 356.

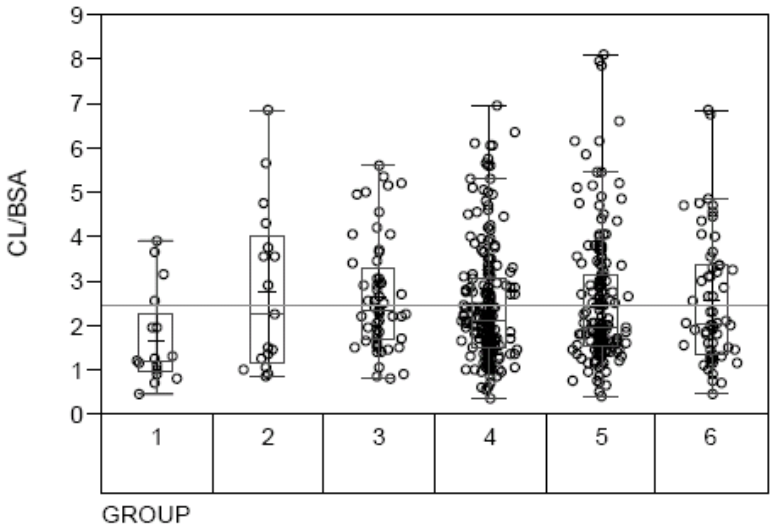
A direct comparison of the two dosing methods demonstrated an orthogonal fit (an empirical line of identity) with a correlation of 0.95 with minor scattering. This demonstrates that either dosing method for nevirapine suspension will produce similar plasma nevirapine concentrations at steady state.

Figure 2. Orthogonal bivariate comparison of CL/BSA by CL/WT for all pediatric patients



A subgroup of interest is patients less than 2 months of age. There were 17 patients that were 2 months of age or less when they initiated nevirapine suspension therapy. Comparing these patients (Group 1 in Figure 3) to the other pediatric patients revealed the majority of the infants' (group 1) individual values and the median clearance value obtained were less than the group (1 to 6) mean of 2.5 L/h/m^2 however there was an overlap with other age groups at lower end.

Figure 3. Box plots of the body surface area-corrected nevirapine clearance sorted by age group (group 1: 0-2 months; group 2: 2-6 months; group 3: 0.5-2 years; group 4: 2-7 years; group 5: 7-12 years; group 6: 12+ years)



The data from PACTG 356 demonstrated that for the subset of pediatric patients (n=17) less than 2 months of age, the plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the pediatric population. However, the majority of the young infants' individual clearance values and their median clearance value obtained (1.5 L/h/m^2) were less than the overall group mean of 2.5 L/h/m^2. Considering the lower clearance in this age group, the proposed nevirapine dose, 150 mg/m^2 BID after the lead-in phase is acceptable (In Trial 356, the dose was 200 mg/m^2 BID after

lead-in phase). The 150 mg/m^2 dose in the 2 week to 2 month age group will provide nevirapine exposure at least as high as exposure in children > 2 months of age who receive the same dose. The safety data for the 2 week to 2 month infants who received 200 mg/m^2 cover the exposure this age group will achieve at 150 mg/m^2.

The meta-analysis confirmed the BSA and BW-based dosing regimens are comparable.

Overall Dosing Recommendations:

Initially we proposed dosing recommendations using [redacted] BSA [redacted] based dosing regimens in pediatric patients of [redacted] days – 16 years of age (not to exceed [redacted] mg adult dose) as following:

1. Dosing Based on Body Surface Area: 150 mg/m^2 BID after 150 mg/m^2 QD for 14 days:

[redacted]

* The current lead-in dose is 4 mg/kg QD regardless of age. Based on similar safety profile and better efficacy results observed in 150 mg/m^2 dose cohort, [redacted]

We then offered another approach [redacted] by eliminating the weight-based regimen and including only the BSA dosing recommendations in the label. BIPI supports the proposal that the VIRAMUNE label only contain the BSA dosing recommendation.

We and BIPI contend that the weight-based dosing regimens require physicians to change dose in patients at age of 8 years old (7mg/kg to 4mg/kg), but there is no corresponding age adjustment when dosing using the BSA regimen. [redacted]

Thus the final proposed dosing recommendations only uses BSA based dosing regimen in pediatric patients of [redacted] days – 16 years of age (not to exceed [redacted] mg adult dose): 150 mg/m^2 BID after 150 mg/m^2 QD for 14 days.

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2. Hepatic impairment

Nevirapine belongs to the class of non-nucleoside reverse transcriptase inhibitors and is metabolized through the cytochrome P450 system (predominantly by 3A4 and 2B6 isoenzymes). Autoinduction of CYP3A4 and CYP2B6 mediated metabolism leads to an approximately 1.5 to 2-fold increase in the apparent oral clearance of NVP as treatment continues from a single dose to 2-to-4 weeks of dosing with 200-400 mg/day. As a result, one 200 mg tablet of NVP is administered daily for the first 14 days, followed by one 200 mg tablet twice daily thereafter.

We requested Boehringer Ingelheim to conduct a post-marketing study to determine whether nevirapine dosing requires adjustment in patients with hepatic impairment. A previous study (U00-3125) in patients with mild and moderate hepatic impairment showed elevated single-dose nevirapine PK parameters in one of the 10 patients studied. This patient's liver disease was classified as Child-Pugh B and moderate to severe ascites was present. This patient, with decreased clearance, had an increased volume of distribution, raising the possibility of ascites causing the delay in clearance. This study concluded that patients with moderate-to-severe hepatic dysfunction may be at risk of accumulating NVP in their systemic circulation. The current trial aimed to build upon and to clarify this finding by examining steady-state trough levels in a larger group of patients, including those with ascites, whose degree of hepatic fibrosis was determined by biopsy.

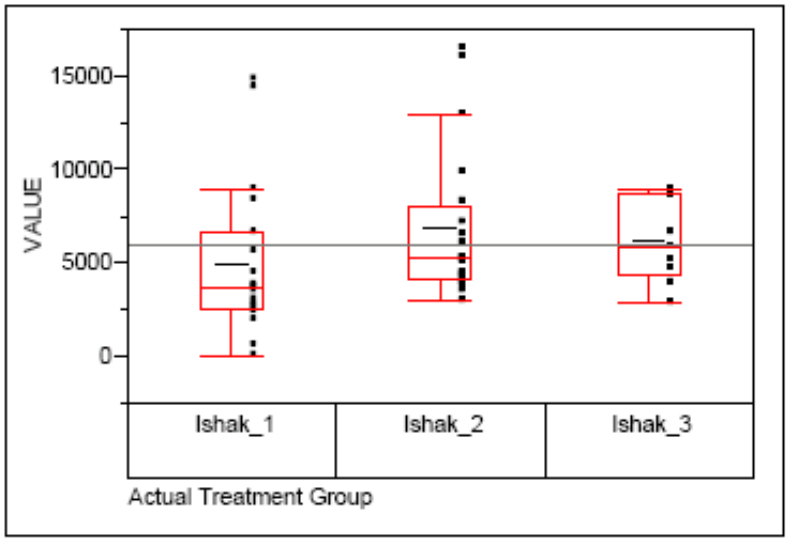
This study was an open-label trial to determine steady-state clearance of nevirapine among HIV-1 positive patients with hepatic fibrosis, for whom nevirapine (200 mg, BID) was part of a stable ARV regimen.

Fifty-one HIV-1 infected patients (male or female subjects ≥18 years of age) with chronic liver disease (confirmed by the finding of fibrosis on liver biopsy) receiving NVP as part of a stable ARV regimen for at least six weeks were entered in this study. All patients had a morning NVP trough level drawn and a subset of thirty-six patients also had extended pharmacokinetics with NVP levels drawn at intervals of 1 hour, 2 hours, and 4 hours post morning dose of NVP.

The study was designed using the Ishak Fibrosis Grading System as a surrogate marker for hepatic impairment. Liver biopsies were performed prior to study enrollment and then analyzed by a central pathologist upon enrollment. Based on the Ishak score, patients were placed into one of 3 groups: Group 1-mild impairment (Ishak score of 1 or 2); Group 2-moderate impairment (Ishak score of 3 or 4); and Group 3-severe impairment (Ishak score of 5 or 6). The latter group had the most significant degree of fibrosis and included pre-cirrhotic and cirrhotic patients. However no control (normal hepatic function) HIV patients were enrolled in this study.

Patients were required to take 200 mg of NVP twice daily as part of their current ARV treatment regimen. Patients who were taking 400 mg of NVP once daily (off-label dose) for a minimum of six weeks and who agreed to change to NVP 200 mg twice daily for a minimum of 14 days prior to trough collection were eligible.

Figure 4. Steady state trough concentrations (ng/mL) of nevirapine for the 48 patients in the three Ishak groups



Nevirapine trough concentrations (ng/mL)

Based on the study results, we conclude that the steady-state nevirapine PK profile (trough concentration levels and calculated CL values) is similar across hepatic impairment groups studied and is comparable to the historical data.

A total of 14.6% of the patients (7 of 48) had a nevirapine trough concentration level ≥9000 ng/mL (two-fold the historical median nevirapine trough). The proportion of patients with a trough ≥ 9000 ng/mL was 15.8% (3 of 19) for Ishak group 1, 20% (4 of 20) for Ishak group 2, and 0% (0 of 9) for Ishak group 3. However there were no serious adverse events observed for patients who had elevated trough nevirapine levels > 6000 ng/mL.

Overall, there was no clinically important effect of hepatic insufficiency on NVP pharmacokinetic profile and no dosage adjustment is indicated in patients with hepatic fibrosis or hepatic cirrhosis with mild hepatic impairment (The Ishak group 3 in this study is equivalent to Child-Pugh A). No information is available for patients with Child-Pugh B or C. Label will indicate these patients should not receive nevirapine.

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II. Question Based Review

A. General Attributes of the Drug

i. What is the proposed therapeutic indication?

Nevirapine is currently approved for the treatment of HIV-1 infection in adults and in children of 2 months – 16 years of age in combination with other antirectroviral agents. This supplement is seeking the approval for use in pediatric patients from ---days – 16 years of age and for adding a body surface area dosing regimen across all pediatric ages.

ii. What is the proposed dosage and route of administration?

The data provided in this efficacy supplement support the Applicant's proposed dosing recommendations for pediatric patients from ---days – 16 years of age.

The proposed dosing recommendations only using BSA based dosing regimen in pediatric patients of --- days – 16 years of age (not to exceed ----mg adult dose): 150 mg/m^2 BID after 150 mg/m^2 QD for 14 days.

iii. What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

For pediatric dosing instructions for HIV drugs, safety and PK are required. The proposed dose in pediatric provide exposures similar to observed in adult patients with no new safety concerns. Efficacy data are only used as supporting evidence.

Study 1100.1368 and five PACTG studies provided relevant safety, PK and efficacy data.

B. General Clinical Pharmacology

i. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The surrogate efficacy endpoints for HIV-1 infection are

1. plasma HIV viral load
2. CD4 cell counts.

The viral load tends to be more predictive of the progression of HIV infection than CD4 cell counts. The primary efficacy endpoint for the submitted pediatric studies is the proportion of subjects with a treatment response (HIV RNA < 400 c/mL) through Week 48.

ii. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The plasma concentrations of nevirapine were determined by a validated LC/MS/MS method. See section F below.

iii. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

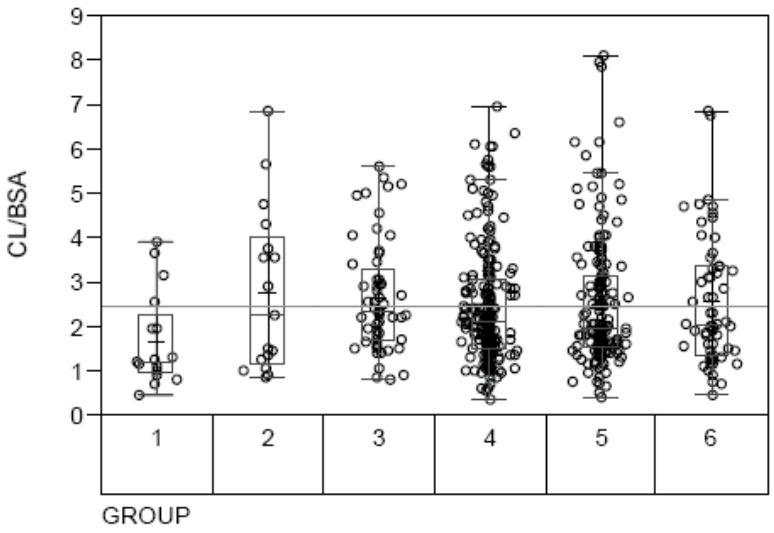
Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of nevirapine tablet and oral suspension (NDAs 20-636 and 20933).

C. Intrinsic Factors

i. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, & organ dysfunction) influence exposure &/or response and what is the impact of any differences in exposure on the PDs? What dosage regimen adjustments, if any, are recommended for each of these subgroups

Age effect

Figure 1. Box plots of the body surface area-corrected nevirapine clearance sorted by age group (group 1: 0-2 months; group 2: 2-6 months; group 3: 0.5-2 years; group 4: 2-7 years; group 5: 7-12 years; group 6: 12+ years)



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Hepatic impairment

The steady-state nevirapine PK profile (trough concentration levels and calculated CL values) is similar across hepatic impairment groups studied and is comparable to the historical data. Overall, there was no clinically important effect of hepatic insufficiency on NVP pharmacokinetic profile and no dosage adjustment is indicated in patients with hepatic fibrosis or hepatic cirrhosis with mild hepatic impairment (The Ishak group 3 in this study is equivalent to Child-Pugh A).

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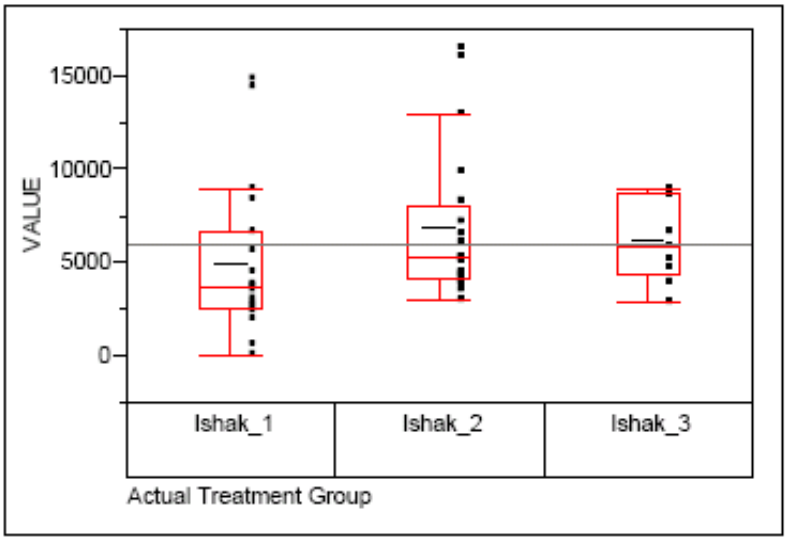

Nevirapine trough concentrations (ng/mL)

Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of nevirapine tablet and oral suspension (NDAs 20-636 and 20933) for information other than age effect and hepatic impairment.

D. Extrinsic Factors

Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of nevirapine tablet and oral suspension (NDAs 20-636 and 20933).

E. General Biopharmaceutics

Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of nevirapine tablet and oral suspension (NDAs 20-636 and 20933).

F. Analytical Section

A validated LC/MS/MS assay for nevirapine was developed at [redacted] The calibration curves were over the range of 60.1 – 30741 [redacted] ecision were <15% and <10%, respectively.

A validated HPLC/UV assay was used for plasma NVP concentrations by [redacted] The calibration range was 0.0025 to 10.0 μg/mL. The average accuracy at two different concentration ranges was within 5% of the

true value. Within- and between-day precisions were within 10% for quality control samples over both ranges.

The analytical methods are acceptable.

III. Labeling Recommendations

The Proposed Labeling Changes Pertinent to Clinical Pharmacology

[redacted]

[redacted]

The above-mentioned changes are acceptable.

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DCP4
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Concurrence:

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IV. Individual Clinical Pharmacology Reports (4)

1100.1368

TITLE: A randomised open label multi-centre trial to evaluate the pharmacokinetic, efficacy and safety parameters of nevirapine 150mg/m^2 and nevirapine 4 or 7mg/kg when administered in combination with ZDV

BACKGROUND: The current labeled dose for nevirapine in children is 7 mg/kg BID if age two months to eight years and 4 mg/kg BID if age ≥ 8 years, following a lead-in dose of 4mg/kg QD for 14 days, regardless of age. This dose scheme was developed to compensate for the changing clearance of nevirapine with age during childhood. This dosing regimen is simple to calculate, but at eight years will require a change in the dosing sequence due to the change in the weight adjusted dose.

Alternatively dosing recommendation can be based on body surface areas across entire age range. The dose of 150 mg/m^2 is predicted to produce an average steady state concentration of 5.3 µg/mL in children for all age groups, similar to the 4 – 6 µg/mL seen in adults dosed at 200 mg BID.

OBJECTIVES: The primary objective was to evaluate steady state pharmacokinetic parameters of nevirapine 150mg/m^2 BID (not to exceed 200 mg BID) in antiretroviral drug naïve pediatric patients, as well as efficacy and safety of nevirapine 150 mg/m^2 and nevirapine 4 or 7mg/kg (not to exceed 200 mg BID) after 24 and 48 weeks of treatment.

SUBJECTS AND STUDY DESIGN:

This was a randomised open-label multi-center study to evaluate the pharmacokinetics, safety and efficacy of nevirapine dosed on body surface area (BSA) 150 mg/m^2 and body weight (BW) (4 or 7 mg/kg), in combination with ZDV and 3TC, in patients aged 3 months to 16 years.

A total of 123 HIV-1 positive, antiretroviral drug naïve patients (3 months to 16 years of age) were enrolled. 66 were in NVP 150 mg/m^2 BSA dose regimen and 57 were in 4 or 7 mg/kg BW dose regimen.

Dose regimens:

1. 150 mg/m^2 BSA BID after 150 mg/m^2 BSA QD for 2 weeks
2. 4 or 7 mg/kg BW BID depending on patient age (7 mg/kg if age two months to eight years and 4 mg/kg if age > 8 years) following a lead-in dose of 4 mg/kg QD for 14 days

Patients were stratified by age into the following 4 age groups:

1.) ≥3 months to < 2 years (n=33)
2.) ≥ 2 years to < 7 years (n=42)
3.) ≥7 years to < 12 years (n=42)
4.) ≥12 years to ≤16 years (n=6)

Plasma nevirapine concentrations were assessed at four weeks of nevirapine therapy after steady state was achieved (Study Day 28).

Efficacy endpoints included virologic response (HIV-1 RNA < 400 copies/ml) and changes from baseline in CD4+ cell count.

Safety was assessed by physical examination, vital sign monitoring, clinical laboratory evaluations and adverse event monitoring.

Table 1. Subject Demographics

	Treatment Group		
	4/7 mg/kg N(%)	150 mg/m^2 N(%)	Total N(%)
Total treated	57 (100)	66 (100)	123 (100)
Gender			
Male	33 (57.9)	27 (40.9)	60 (48.8)
Female	24 (42.1)	39 (59.1)	63 (51.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Race			
White	7 (12.3)	16 (24.2)	23 (18.7)
Black	50 (87.7)	50 (75.8)	100 (81.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Age			
3 months to <2	17 (29.8)	16 (24.2)	33 (26.8)
≥ 2 to <7	19 (33.3)	23 (34.8)	42 (34.1)
≥ 7 to <12	21 (36.8)	21 (31.8)	42 (34.1)
≥ 12 to ≤16	0 (0.0)	6 (9.1)	6 (4.9)

FORMULATION: Viramune Oral suspension (50 mg/5 ml)

PK SAMPLE COLLECTION: Blood samples for the determination of nevirapine concentrations in plasma were assessed at four weeks of nevirapine therapy after steady state was achieved (Study Day 28).

Intensive PK patients: The first 10 patients in each age group were to receive nevirapine based on BSA regimen. The patients in this group had samples taken at 1 hour, 3 hours and 6 hours following their scheduled morning dose.

Non-intensive PK monitoring: Once the first 10 patients per age group were enrolled further patients recruited, in that age group, were randomized in a 2:1 manner to receive nevirapine based on BW or BSA. These patients had trough levels measured on day 28 of treatment.

BIOANALYTICAL ASSAYS: A validated LC/MS/MS assay for nevirapine was developed at [redacted] The calibration curves were over the range of 60.1 – 30741 ng/mL for nevirapine. The accuracy and precision were <15% and <10%, respectively.

PHARMACOKINETIC DATA ANALYSIS: The pharmacokinetics of nevirapine were characterized using non-compartmental methods with the pharmacokinetic and statistical software programs WinNonlin version 4.1 [redacted] Primary pharmacokinetic parameters of interest

included the area under the concentration-time curve over one dosing interval (AUCτ), maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), and oral clearance (Dose/AUC) at steady state (4 weeks) over the age range studied (3 months to 16 years) for nevirapine administered as 150 mg/m^2 BID, and C_{min} for non-intensive PK samplings.

PHARMACOKINETIC RESULTS:

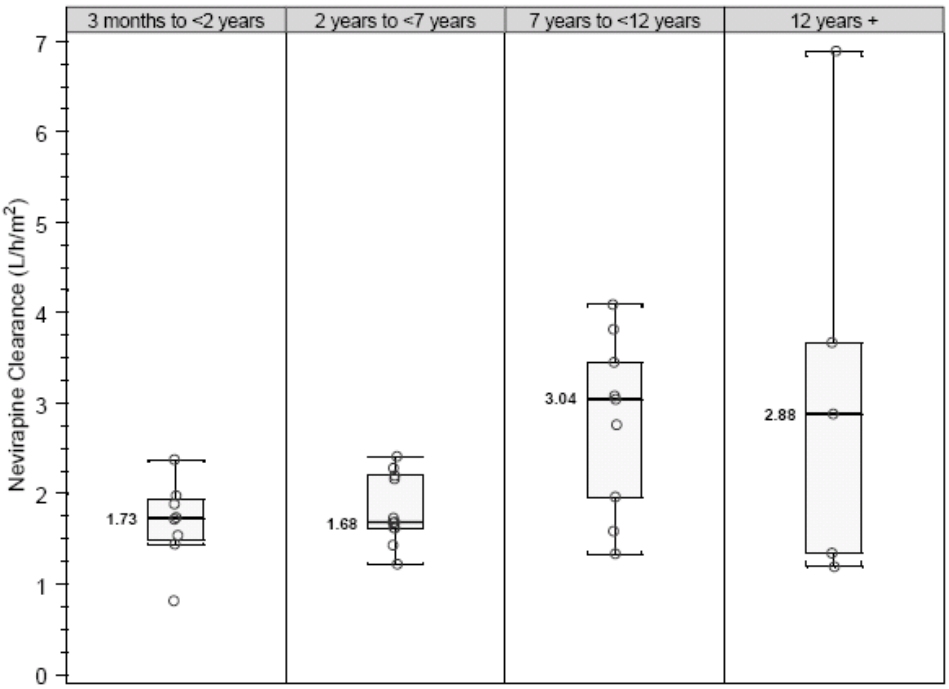
Table 2. Nevirapine Pharmacokinetics Following Dosing of nevirapine at 150 mg/m^2 BID (After a Two-Week Lead In at 150 mg/m^2 QD) (Intensive PK Sampling)

Age Range (y)	n	Geometric Mean (Mean±SD) AUC (µg•h/mL)	Geometric Mean (Mean±SD) C_{max} (µg/mL)	Geometric Mean (Mean±SD) Clearance (L/h/m^2)
<7	19	87.6 (90.7±27.6)	8.76 (9.04±2.46)	1.71 (1.76±0.41)
7-12	9	57.7 (62.0±26.6)	5.80 (6.15±2.38)	2.61 (2.79±0.97)
>12	5	57.1 (69.1±43.8)	5.89 (6.71±3.67)	2.59 (3.19±2.32)

Table 3. Comparison of Trough Steady State Nevirapine Concentrations Observed Following administration using the BSA and BW Dosing Algorithms

Patient Group	Dosing Method	Age Range (y)	n	Geometric Mean Trough NVP Concentration (µg/mL)	Mean ± SD Trough NVP Concentration (µg/mL)
Intensive PK	Body Surface Area	0.77-13.69	32	4.68	5.83 ± 3.14
Non-Intensive PK	Body Surface Area	0.33-11.64	24	5.03	5.59 ± 2.65
Non-Intensive PK: Age>8 yr	Body Weight 4 mg/kg	8.11-11.50	11	5.05	5.51 ± 2.33
Non-Intensive PK: Age <8 yr	Body Weight 7 mg/kg	0.28-7.76	36	5.03	5.87 ± 3.40

Figure 1. Median oral clearances (CL/F) of nevirapine observed in the intensive pharmacokinetic patient group stratified by age of the patients



The box plots identify the median (line at middle of the box) and quartiles (top and bottom limit for each box that correspond to the 25th and 75th percentiles) connected to whiskers that are drawn to the nearest value not beyond a standard span (1.5 x interquartile range) from the quartiles; points beyond this value (outliers) are drawn individually)).

Figure 2. Oral clearances (CL/F) (L/hr/m^2) of nevirapine observed in the intensive pharmacokinetic patient group by body surface area of the patients

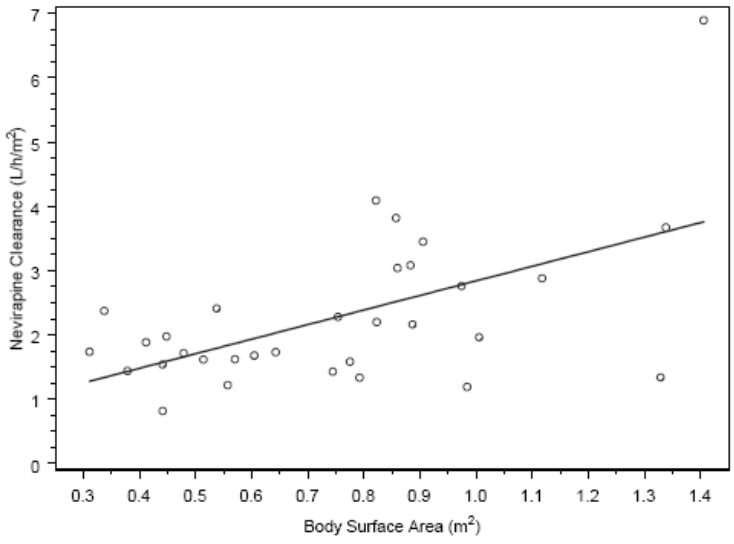
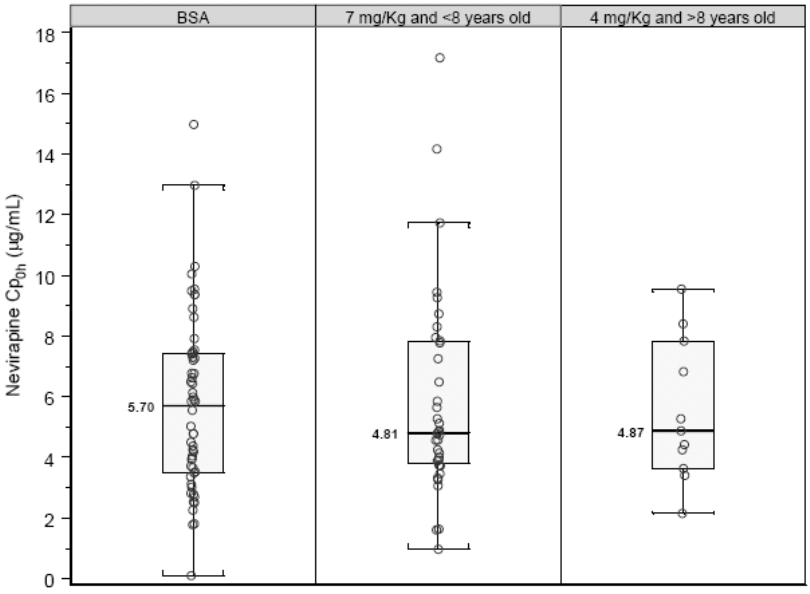


Figure 3. Median trough nevirapine concentrations observed using the BSA algorithm (n=56 patients) and the body weight algorithm (n=11 for >8 year old patients and n=36 for <8 year old patients)



The box plots identify the median (line at middle of the box) and quartiles (top and bottom limit for each box that correspond to the 25th and 75th percentiles) connected to whiskers that are drawn to the nearest value not beyond a standard span (1.5 x interquartile range) from the quartiles; points beyond this value (outliers) are drawn individually)).

EFFICACY RESULTS:

At steady-state (Day 28, Week 4), both dose groups attained nevirapine concentration levels comparable to the adult range of 4-6 µg/mL. The proportion of patients whose HIV RNA went below the limit of quantification (< 400 copies/mL) were similar. Approximately 30% of the patients from each dose group were below the limit of quantification at Week 4.

A difference in the virologic response rate between the 4 or 7 mg/kg and 150 mg/m^2 NVP dose groups was observed at Week 8 and continued through Week 48. The virologic response rate was slightly higher in the 150 mg/m^2 NVP dose group than in the 4 or 7 mg/kg NVP dose group. At Week 48, 61% of patients in 150 mg/m^2 NVP dose group were below the limit of quantification (RNA < 400 copies/mL) compared to 44% in the 4 or 7 mg/kg NVP dose group. See details in Medical Officer's review.

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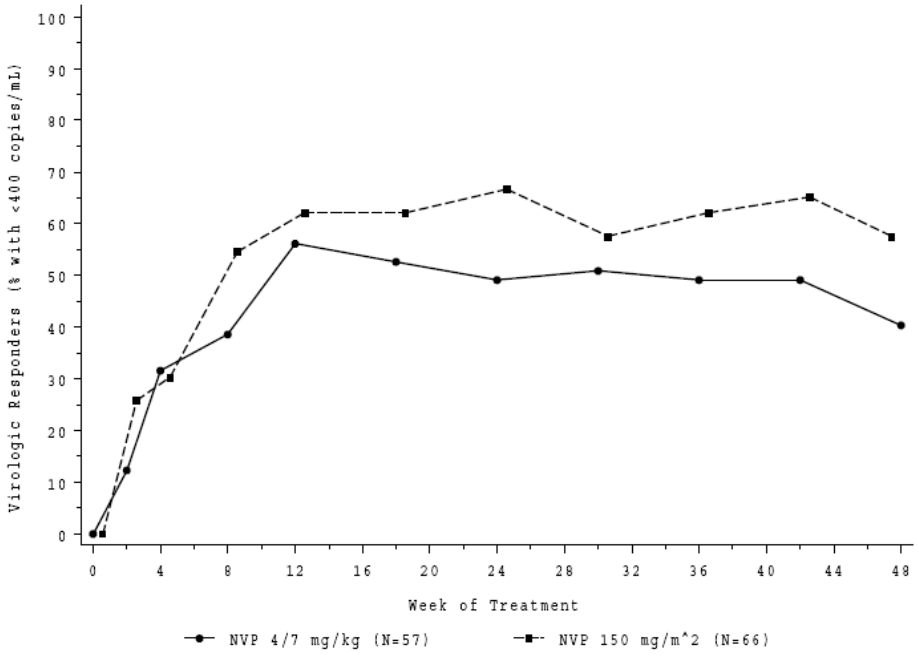
Figure 4. Percentage of patients below the limit of quantification (HIV-1 RNA< 400 copies/mL) through Week 48



SAFETY RESULTS:

There were no drug related deaths in this group of pediatric patients treated for 48 weeks with nevirapine. Discontinuation of nevirapine due to drug related events was limited to nevirapine related rash in 4 (3%) of patients. Skin manifestations occurred within 4 weeks of initiating therapy in all 4 cases and resolved after nevirapine withdrawal. 3 other patients developed a mild related rash which resolved without withdrawing drug. No patients in this group discontinued therapy because of liver related abnormalities. There were no unexpected safety findings in this group of patients. See details in Medical Officer's review.

DISCUSSION AND CONCLUSIONS:

Pharmacokinetic data on 33 patients (age range 0.77 – 13.7 years) in the intensive sampling group demonstrated that oral clearance of nevirapine increased with increasing age in a manner consistent with increasing body surface area. The precision of the body surface area algorithm for dose administration was evaluated by comparing the trough nevirapine concentrations obtained using the body surface area method (n=56 patients; 0.33 – 13.69 years) to the conventional body weight algorithm (n=47 patients; 0.28 – 11.50 years) presented in the prescribing information for nevirapine. The trough nevirapine concentrations observed were comparable between the two methods. Dosing of nevirapine at 150 mg/m^2 BID (after a two-week lead in at 150 mg/m^2 QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 µg/mL (as targeted from adult data) without an abrupt change in dosing schedule at age 8 years. The variability observed in the observed trough nevirapine concentrations was comparable between the two methods.

The reason why the 150 mg/m^2 NVP dose group performed better than the 4 or 7 mg/kg NVP dose group in sustained virologic response could be the higher lead-in dose (150 mg/m^2 QD, half of the maintenance dose, 150 mg/m^2 BID) compared to the lead-in dose (4 mg/kg QD, about one quarter of maintenance dose, 7 mg/kg BID) in the two months to eight years age group. Lower lead-in dosing may impact efficacy

because resistance develops rapidly for NNRTIs if exposure is suboptimal. Based on similar safety profile observed in 150 mg/m^2 dose cohort, [redacted]

The results of the 48 Week analysis confirmed that the 4 or 7 mg/kg and 150 mg/m^2 NVP dose groups were well tolerated and effective in treating antiretroviral naive pediatric patients.

After deliberations with BIPI, we and BIPI contend that the weight-based dosing regimens require physicians to change dose in patients at age of 8 years old (7mg/kg to 4mg/kg), but there is no corresponding age adjustment when dosing using the BSA regimen. [redacted]

Thus the final proposed dosing recommendations only uses BSA based dosing regimen in pediatric patients of [redacted] days – 16 years of age (not to exceed [redacted] mg adult dose): 150 mg/m^2 BID after 150 mg/m^2 QD for 14 days.

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Pharmacokinetic Meta-analysis

TITLE: Evaluation of Nevirapine in Pediatric Patients

OBJECTIVES: The purpose of this meta-analysis was to further support that the BSA and BW-based dosing regimens are comparable and to extend pediatric age group to less than 2 months of age

METHODS: Pharmacokinetic exposure in HIV-infected children was assessed by modeling plasma nevirapine concentrations obtained following dosing using either body surface area (BSA) and age adjusted body weight (WT) regimens.

Nevirapine pharmacokinetic data derived from two major sources:

1. Five Pediatric AIDS Clinical Trials Group (PACTG) protocols (245, 356, 366, 377, and 403) comprising 495 patients aged 1 month to 19 years.

    - PK Data were derived from sparse pharmacokinetic sampling (sampled at 1 - 7 visits generating 2163 plasma nevirapine concentrations) and population pharmacokinetic modeling.

    - The dosing regimen for Trials 245, 366, 377, and 403 was NVP suspension 120 mg/m^2 QD for 14 days followed by BID.

    - For Trial 356, subjects enrolled <30 days old received NVP 5 mg/kg QD for 14 days followed by 120 mg/m^2 QD for 14 days followed by 200 mg/m^2 BID. Subjects >30 days received NVP 120 mg/m^2 QD for 14 days followed by 200 mg/m^2 BID.

    - 17 subjects <2 months old were from Trial 356.

2. Study 1100.1368 (104 HIV-1 positive, antiretroviral naïve patients aged 3 months to 16 years) (Intense pharmacokinetic sampling)

The population PK model fitting described the data well. The method is acceptable.

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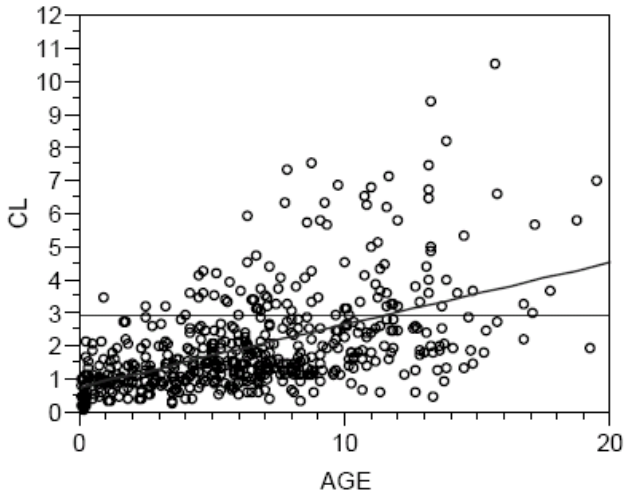
RESULTS:

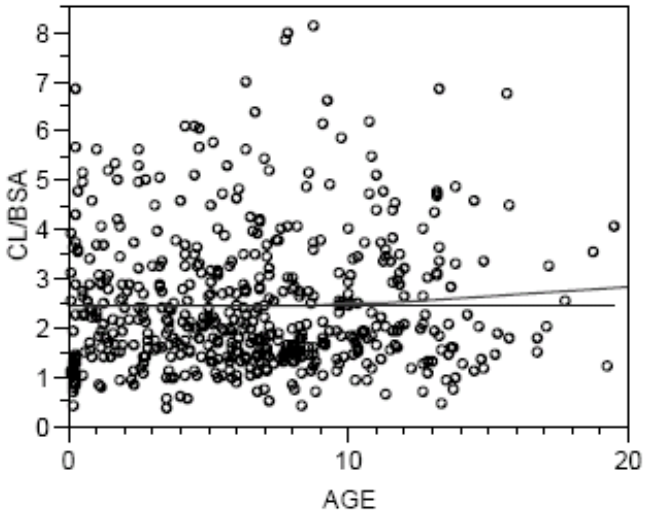
If clearance is not corrected for body weight or body surface area, systemic clearance increases during childhood reaching an adult steady state estimate of 3 L/h at 12 years of age.

Figure 1. Oral systemic clearance of nevirapine at steady state observed with age in the six studies conducted with nevirapine suspension. The trend line can be described by the equation CL = 0.79 + 0.19(AGE) with only an R^2-adjusted of 0.278. The adult clearance for nevirapine at steady state is approximately 3 L/hr



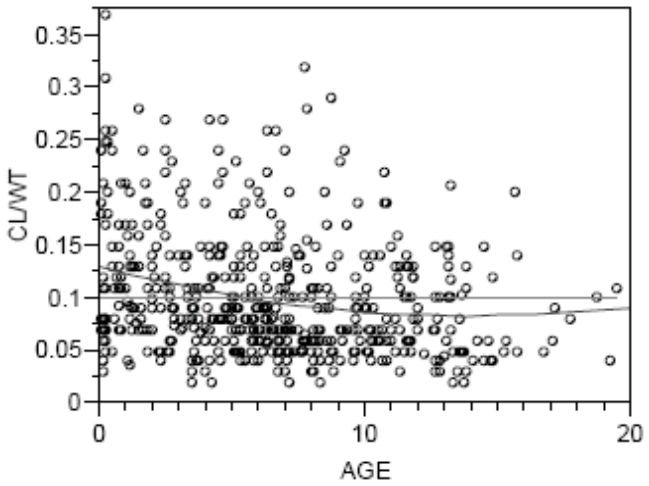
If the oral systemic clearance estimate at steady state for nevirapine is normalized for either body surface area (Figure 2) or body weight (Figure 3), the trend that CL increases with age is not clear any more.

Figure 2. Oral systemic clearance of nevirapine at steady state observed with age in the six studies



The oral systemic clearance of nevirapine was corrected for body surface area (CL/BSA, L/h/m^2) to produce an overall mean clearance of 2.5 L/h/m^2 or a non-significant improved quadratic fit of CL/BSA = 2.42 + 0.009(AGE)+0.001(AGE-6.53)^2.

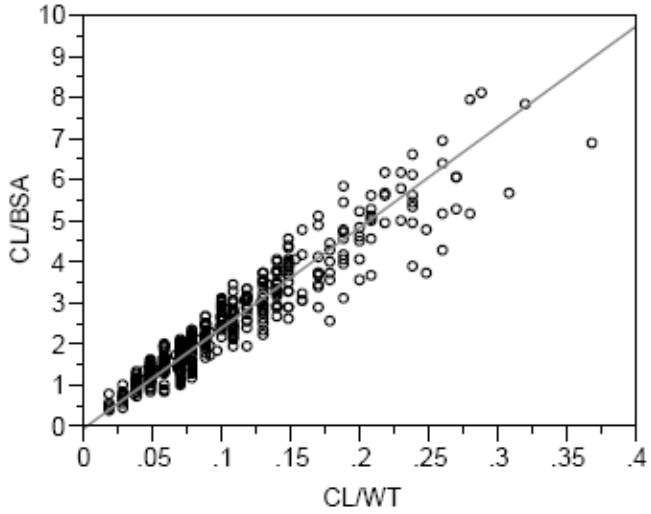
Figure 3. Oral systemic clearance of nevirapine at steady state observed with age in the six studies



Correcting the oral systemic clearance of nevirapine for body weight (CL/WT, L/h/kg) produced an overall mean clearance of 0.10 L/h/kg or an improved quadratic fit of CL/WT = 0.12 + 0.004(AGE)+ 0.0002(AGE-6.53)^2.

A direct comparison of the two dosing methods demonstrated an orthogonal fit (an empirical line of identity) with a correlation of 0.95 with minor scattering. This demonstrates that either dosing method for nevirapine suspension will produce the desired result of predictable plasma nevirapine concentrations at steady state.

Figure 4. Orthogonal bivariate comparison of CL/BSA by CL/WT for all pediatric patients



A subgroup of interest is patients less than 2 months of age. There were 17 patients that were 2 months or less of age when they initiated nevirapine suspension therapy. Comparing these patients (Group 1 in

Figure 5) to the other pediatric patients revealed the majority of the infants' (group 1) individual values and the median clearance value obtained were less than the group (1 to 6) mean of 2.5 L/h/m^2 however there was an overlap with other age groups at lower end.

Figure 5. Box plots of the body surface area-corrected nevirapine clearance sorted by age group (group 1: 0-2 months; group 2: 2-6 months; group 3: 0.5-2 years; group 4: 2-7 years; group 5: 7-12 years; group 6: 12+ years)

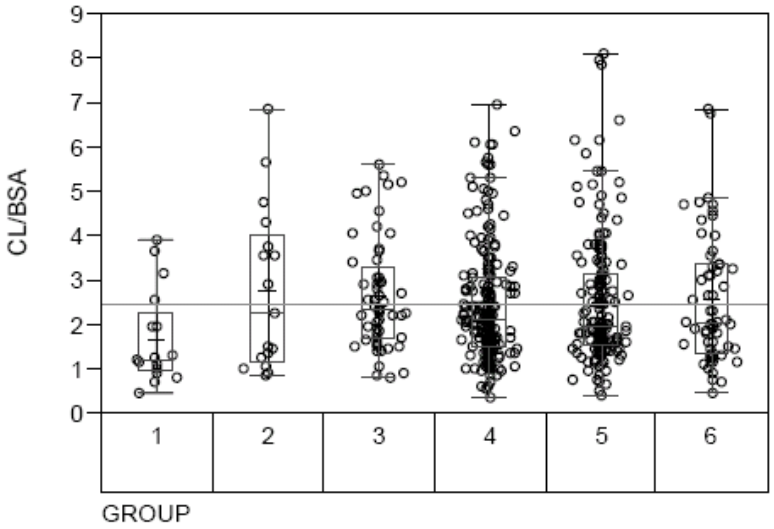


Table 1. Population pharmacokinetic estimates of CL from NONMEM based on the observed plasma nevirapine concentrations for the 17 patients entering the PACTG 356 trial within the first two months of life (Age based on first dose)

PT	Age (y)	BSA (m2)	WT (kg)	CL (L/h)	CL/BSA (L/h/m2)	CL/WT (L/h/kg)
79	0.1	0.225	3.5	0.265	1.18	0.08
369	0.1	0.265	4.4	1.037	3.92	0.24
382	0.1	0.194	2.8	0.497	2.56	0.18
398	0.1	0.236	3.9	0.261	1.11	0.07
486	0.1	0.270	4.6	0.854	3.16	0.19
85	0.2	0.236	3.8	0.318	1.34	0.08
86	0.2	0.250	4.1	0.230	0.92	0.06
87	0.2	0.284	5.0	0.347	1.22	0.07
97	0.2	0.227	3.5	0.239	1.05	0.07
167	0.2	0.238	3.8	0.469	1.97	0.12
198	0.2	0.246	4.1	0.112	0.46	0.03
368	0.2	0.252	4.1	0.324	1.28	0.08
370	0.2	0.297	5.3	0.585	1.97	0.11
381	0.2	0.227	3.4	0.192	0.84	0.06
392	0.2	0.304	5.6	0.223	0.73	0.04
400	0.2	0.290	5.1	1.066	3.67	0.21
487	0.2	0.296	5.2	0.338	1.14	0.07

DISCUSSION AND CONCLUSIONS:

The meta-analysis confirmed the BSA (150 mg/m^2 BID) and BW (4 or 7 mg/kg BID)-based dosing regimens provide comparable nevirapine exposure.

The data from PACTG 356 demonstrated that for the subset of pediatric patients (n=17) less than 2 months of age, the plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the pediatric population. However, the majority of the young infants' individual clearance values and their median clearance value obtained (1.5 L/h/m^2) were less than the overall group mean of 2.5 L/h/m^2. Considering the lower clearance in this age group, the proposed nevirapine dose, 150 mg/m^2 BID after the lead-in phase is acceptable (In Trial 356, the dose was 200 mg/m^2 BID after lead-in phase). The 150 mg/m^2 dose in the 2 week to 2 month age group will provide nevirapine exposure at least as high as exposure in children > 2 months of age who receive the same dose. The safety data for the 2 week to 2 month infants who received 200 mg/m^2 cover the exposure this age group will achieve at 150 mg/m^2.

U06-3702

TITLE: A pharmacokinetic study to assess nevirapine levels in HIV-infected patients with impaired hepatic function

BACKGROUND: Nevirapine belongs to the class of non-nucleoside reverse transcriptase inhibitors and is metabolized through the cytochrome P450 system (predominantly by 3A4 and 2B6 isoenzymes). Autoinduction of CYP3A4 and CYP2B6 mediated metabolism leads to an approximately 1.5 to 2-fold increase in the apparent oral clearance of NVP as treatment continues from a single dose to 2-to-4 weeks of dosing with 200-400 mg/day. As a result, one 200 mg tablet of NVP is administered daily for the first 14 days, followed by one 200 mg tablet twice daily thereafter.

The FDA requested that Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) conduct a post-marketing study to determine whether nevirapine dosing requires adjustment in patients with hepatic impairment. A previous study (U00-3125) in patients with mild and moderate hepatic impairment showed elevated single-dose nevirapine PK parameters in one of the 10 patients studied. This patient's liver disease was classified as Child-Pugh B and moderate to severe ascites was present. This patient, with decreased clearance, had an increased volume of distribution, raising the possibility of ascites causing the delay in clearance. This study concluded that patients with moderate-to-severe hepatic dysfunction may be at risk of accumulating NVP in their systemic circulation. The current trial aimed to build upon and to clarify this finding by examining steady-state trough levels in a larger group of patients, including those with ascites, whose degree of hepatic fibrosis was determined by biopsy.

OBJECTIVES: To evaluate the steady-state clearance of nevirapine among HIV-1 positive patients with hepatic fibrosis and to examine whether the degree of hepatic impairment influences clearance

SUBJECTS AND STUDY DESIGN: This study was a Phase IV, open-label trial to determine steady-state clearance of nevirapine among HIV-1 positive patients with hepatic fibrosis, for whom nevirapine (200 mg, BID) was part of a stable ARV regimen.

Fifty-one HIV-1 infected patients (male or female subjects ≥18 years of age) with chronic liver disease (confirmed by the finding of fibrosis on liver biopsy) receiving NVP as part of a stable ARV regimen for at least six weeks were entered in this study. All patients had a morning NVP trough level drawn and a subset of thirty-six patients also had extended pharmacokinetics with NVP levels drawn at intervals of 1 hour, 2 hours, and 4 hours post morning dose of NVP.

This study was designed using the Ishak Fibrosis Grading System as a surrogate marker for hepatic impairment. Liver biopsies were performed prior to study enrollment and then analyzed by a central pathologist upon enrollment. Based on the Ishak score, patients were placed into one of 3 groups: Group 1-mild impairment (Ishak score of 1 or 2); Group 2-moderate impairment (Ishak score of 3 or 4); and Group 3-severe impairment (Ishak score of 5 or 6). The latter group had the most significant degree of fibrosis and included pre-cirrhotic and cirrhotic patients. However no control (normal hepatic function) HIV patients were enrolled in this study.

Patients were required to take 200 mg of NVP twice daily as part of their current ARV treatment regimen. Patients who were taking 400 mg of NVP once daily for a minimum of six weeks and who agreed to change to NVP 200 mg twice daily for a minimum of 14 days prior to trough collection were eligible.

Summary of Baseline Demographics of Patients

	Ishak Group 1	Ishak Group 2	Ishak Group 3	Total
Number of Patients	20	22	9	51
Age				
Mean	48.7	47.5	50.4	48.5
Min-Max	32-70	34-76	40-65	32-76
Sex				
Male (%)	18 (90.0)	14 (63.6)	8 (88.9)	40 (78.4)
Female (%)	2 (10.0)	8 (36.4)	1 (11.1)	11 (21.6)
Race				
White (%)	18 (90.0)	19 (86.4)	8 (88.9)	45 (88.2)
Black (%)	2 (10.0)	3 (13.6)	1 (11.1)	6 (11.8)
BMI (kg/m^2)				
Mean	25.9	24.7	27.4	25.7
HIV RNA (log_{10} copies/mL)				
Median	2.05	2.27	1.87	2.03
Range	1.23-4.3	1.23-2.83	1.70-3.80	1.30-4.30
CD4+ Count ($cells/mm^3$)				
Median	404.5	394.5	376.0	400.0
Range	141-835	149-161	211-602	141-861

INVESTIGATORS AND STUDY LOCATIONS: Multicenter

FORMULATION: Viramune® 200 mg

SAMPLE COLLECTION: In addition to a morning trough level, a subset of thirty-six patients also had NVP levels drawn 1 hour, 2 hours and 4 hours after NVP dosing.

ASSAYS: A validated HPLC/UV assay was used for plasma NVP concentrations by [redacted] The calibration range was 0.0025 to 10.0 µg/mL. The average accuracy at two different concentration ranges was within 5% of the true value. Within- and between-day precisions were within 10% for quality control samples over both ranges.

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Bioanalytical assay summary for nevirapine

Analyte	Nevirapine	
Internal Standard	[redacted]	
Matrix / Anticoagulant	Human plasma/ heparinized or EDTA	
Assay Volume Required	250 µL	
Extraction Method	[redacted]	
% Recovery	111%	
Detection Method	HPLC-UV	
Standard Curve Range	25.0 ng/mL to 10,000 ng/mL	
Regression Type	1/concentration^2 weighted linear regression	
Quantitation Method	Peak height	
Parameters	**Intra-day**	**Inter-day**
Accuracy		
LLOQ QC (RE%)	<4.76	<3.61
High QC (RE%)	<1.64	<-0.613
Precision		
LLOQ QC (%CV)	<6.18	<9.56
High QC (%CV)	<2.31	<1.61
Stability in plasma after 3X freeze-thaws (% difference from theory)	-2.00% to -0.09%	
Stability in plasma at room temperature for 24 hours (% difference from theory)	2.20% to 3.08%	
Autosampler extract stability for 31 hours at room temperature (% difference from theory)	-3.60% to -3.09%	
*Long-term freezer stability in plasma for 1084 days at -20°C (% difference from theory)	≤ to 9.0%	
Nevirapine Stock Solution Stability [redacted]	[redacted]	
Internal Standard Stock Solution Stability [redacted]	[redacted]	

In addition, a bioanalytical method for the analysis of NVP oxidative metabolites: 2-hydroxy NVP, 3-hydroxy NVP, 8-hydroxy NVP, 12-hydroxy NVP, and 4-carboxynevirapine in human plasma was also developed at [redacted]

PHARMACOKINETIC DATA ANALYSIS: Plasma concentrations of NVP were used to calculate pharmacokinetic parameters using WinNonlin® Version 5.0.1 [redacted] Pharmacokinetic variables of area under the concentration-time curve over one dosing interval (AUC), maximum observed concentration (C_{max}), minimum observed concentration (C_{min}) at steady state by the Ishak Score studied (1-6) for nevirapine and its metabolites were analyzed.

PHARMACOKINETIC RESULTS:

Table 1. Geometric means and 95% confidence intervals for nevirapine pharmacokinetic parameters

Parameter	Algorithm	Population	Ishak Grp 1§ Gmean / CI	Ishak Grp 2 Gmean / CI	Ishak Grp 3 Gmean / CI
C_{minSS} (ng/mL)	observed C_{minSS}	n=46	4583 [3351, 6268]	6021 [4786, 7574]	5854 [4337, 7901]
$AUC_{SS(t,1,2,4)}$ (h•µg/mL)	$[C_{minSS} + C_1]/2 + [C_1 + C_2]/2 + \{8•[C_4 + C_{minSS}]/2\}$	intensive only (n=33)	69.0 [48, 99]	74.7 [58, 95]	75.1 [53, 107]
$CL_{SS(t,1,2,4)}$ (L/h)	200 mg / $AUC_{SS(t,1,2,4)}$	intensive only (n=33)	2.90 [2.0, 4.2]	2.68 [2.1, 3.4]	2.66 [1.9, 3.8]
C_{maxSS} (ng/mL)	observed C_{maxSS}	intensive only (n=33)	7117 [5146, 9844]	7087 [5679, 8846]	7262 [5163,10215]

§ without patients 131 and 301

Table 2. The proportion of patients with trough nevirapine concentration levels ≥ 6000 ng/mL and < 6000 ng/mL

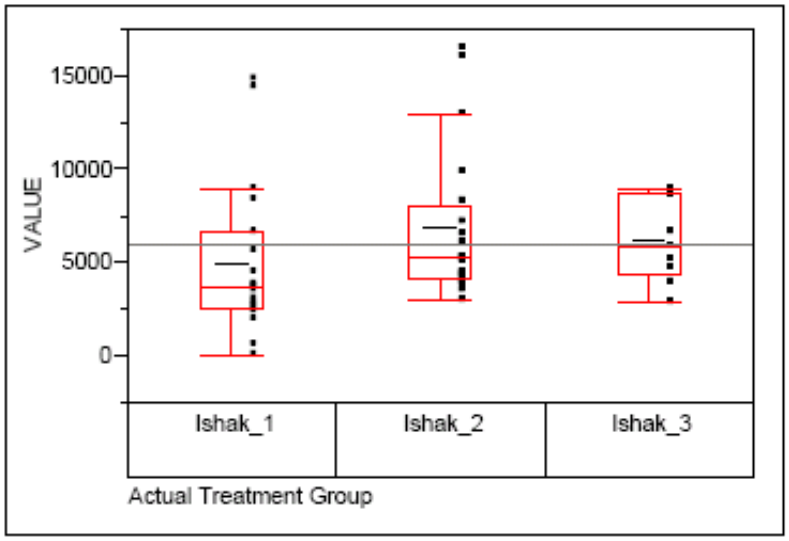
Trough Elevation	**Ishak Grp 1**	**Ishak Grp 2**	**Ishak Grp 3**	**Overall**
Total	19 (100.0)	20 (100.0)	9 (100.0)	48 (100.0)
Cmin < 6000 ng/mL	14 (73.7)	12 (60.0)	5 (55.6)	31 (64.6)
Cmin ≥ 6000 ng/mL	5 (26.3)	8 (40.0)	4 (44.4)	17 (35.4)

Table 3. The proportion of patients with elevated trough nevirapine levels ≥ 6000 ng/ml) by Ishak group

Thresholds	Trough Elevations	Ishak Grp 1	Ishak Grp 2	Ishak Grp 3	Overall
Total treated		19 (100.0)	20 (100.0)	9 (100.0)	48 (100.0)
One to two std dev. above the historical mean*	≥ 6000 -7500 ng/mL	1 (5.3)	3 (15.0)	1 (11.1)	5 (10.4)
Two to three std dev. above the historical mean*	>7500 - 9000 ng/mL	1 (5.3)	1 (5.0)	3 (33.3)	5 (10.4)
Three to four std dev. above the historical mean*	>9000 ng/mL	3 (15.8)	4 (20.0)	0 (0.0)	7 (14.6)
	Total	5 (26.3)	8 (40.0)	4 (44.4)	17 (35.4)

*Historical mean and standard deviation among patients without pronounced hepatic impairment were 4500 ± 1500 ng/mL.

Figure 1. Steady state trough concentrations (ng/mL) of nevirapine for the 48 patients in the three Ishak groups



Nevirapine trough concentrations (ng/mL)

Horizontal line (black) is the grand mean of each NVP. Box plot representation of the data where the box represents the 25th through 75th percentile, the bar inside the box is the median, and the whiskers extend to 1.5 interquartile ranges.

Historical Data

In the 1100.1090 study, NVP clearance was estimated, using a population PK model, to be 3.3 L/h (95% confidence interval 2.9-3.7 L/h) for 43 patients (U98-3203). Historical data (i.e., NVP Trials: 1100.1224, 1100.1203 and 1100.1031) revealed that the average trough levels at steady-state (C_{minSS}) was approximately 4.5 μg/mL among patients without pronounced hepatic impairment.

Table 4. Historical mean nevirapine trough levels at steady state (C_{minSS})

Trial	1100.1224	1100.1203	1100.1031
N	22	23	156
Mean C_{minSS} (mcg/mL) +/- std. dev.	4.6 +/- 1.6	4.4 +/- 1.3	4.6 +/- 2.0

SAFETY RESULTS: No serious adverse events (SAEs) or deaths occurred related to NVP in patients entered into the trial. There were no serious adverse events observed for patients who had elevated trough nevirapine levels >6000 ng/mL. A total of 8 (15.7%) patients experienced adverse events while participating in this study. The intensity of the adverse events ranged from mild to moderate in intensity. None of the adverse events (AE) were defined as drug-related and no patients discontinued participation due to an adverse event. See details in Medical Officer, Dr. Connelly's review.

DISCUSSION AND CONCLUSIONS: Based on the study results, we conclude that the steady-state nevirapine PK profile (trough concentration levels and calculated CL values) is similar across hepatic impairment groups studied and is comparable to the historical data.

A total of 14.6% of the patients (7 of 48) had a nevirapine trough concentration level ≥9000 ng/mL (two-fold the historical median nevirapine trough). The proportion of patients with a trough ≥ 9000 ng/mL was 15.8% (3 of 19) for Ishak group 1, 20% (4 of 20) for Ishak group 2, and 0% (0 of 9) for Ishak group 3. However there were no serious adverse events observed for patients who had elevated trough nevirapine levels > 6000 ng/mL.

Overall, there was no clinically important effect of hepatic insufficiency on NVP pharmacokinetic profile and no dosage adjustment is indicated in patients with hepatic fibrosis or hepatic cirrhosis with mild hepatic impairment (The Ishak group 3 in this study is equivalent to Child-Pugh A). In addition, this study report fulfills PMC #2.

ACTG A5093

TITLE: An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions between Depo Medroxyprogesterone Acetate (DMPA,DEPO-PROVERA) and Selected Protease Inhibitor (PI) and Nonnucleoside Reverse Transcriptase Inhibitor (NNRTI) Therapies among HIV-Infected Women

OBJECTIVES: To evaluate the effect of selected ARV therapies (nelfinavir [NFV], efavirenz [EFV], indinavir in combination with ritonavir, and nevirapine on the PK of DMPA and to determine the effect of DMPA on the PK of selected ARV therapies among HIV-infected subjects

SUBJECTS AND STUDY DESIGN: This was a 12 week open-label, non-randomized, steady-state study of pharmacokinetic (PK) interactions between Depo-Medroxyprogesterone Acetate (DMPA) and selected antiretrovirals in women whose current antiretroviral (ARV) regimens corresponded to one of the five treatment arms. Subjects were required to be on stable ARV regimens for a minimum of 30 days prior to DMPA administration to achieve adequate steady-state plasma trough levels of ARV agents.

Subjects were enrolled into one of the five arms based on their current ARV regimen:

73 subjects were enrolled and 71 were included in the final analysis.

Arm A (n=16): DMPA and no current PIs or nnRTIs; NRTIs allowed
Arm B (n=21): DMPA and NFV (1250 mg b.i.d. or 750 mg t.i.d.) with or without NRTIs
Arm C (n=17): DMPA and EFV (600 mg q.d.) with or without NRTIs
Arm D (n=1): DMPA and IDV (800 mg b.i.d)/RTV (100 mg b.i.d. or 200 mg b.i.d.) with or without NRTIs
Arm E (n=16): DMPA and NVP (200 mg b.i.d.) with or without NRTIs

PK SAMPLE COLLECTION: Blood samples for DMPA concentration levels were taken at baseline (day 0) prior to the DMPA injection and at weeks 2, 4, 6, 8, 10, and 12 after DMPA was administered. For subjects on arms B, C, D, and E, study ARV concentrations were measured at both week 0 (day 0, prior to DMPA injection) and week 4 (after DMPA injection); intensive PK sampling was performed, with samples collected at 0 (pre-dose), 0.5, 2, 4, 6, 8, and 10 hours post-dose.

PHARMACOKINETIC DATA ANALYSIS: The pharmacokinetics of DMPA and ARVs were characterized using non-compartmental methods. Primary pharmacokinetic parameters of interest included the area under the concentration-time curve over one dosing interval ($AUC\tau$), maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), and oral clearance (Dose/AUC) at steady state.

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PHARMACOKINETIC RESULTS:

Table 1. Descriptive statistics of DMPA PK parameters by treatment arm

	Arm	N	Mean	Median	SD	Range (Min, Max)
AUC_{12} (ng*week/mL)	A	14	11.48	12.38	3.10	(6.03, 15.64)
	B	19	13.88	15.08	4.76	(5.02, 20.72)
	C	14	10.47	9.55	5.34	(3.03, 20.31)
	E	14	11.23	10.63	3.67	(5.14, 17.21)
Cmax (ng/mL)	A	14	1.64	1.74	0.56	(0.88, 2.58)
	B	19	1.94	1.82	0.75	(0.88, 3.70)
	C	14	1.57	1.36	0.92	(0.32, 3.37)
	E	14	1.52	1.43	0.55	(0.69, 2.76)
Cmin (ng/mL)	A	14	0.45	0.43	0.24	(0.04, 0.89)
	B	19	0.58	0.46	0.32	(0.09, 1.31)
	C	14	0.37	0.36	0.21	(0.07, 0.89)
	E	14	0.54	0.47	0.22	(0.33, 1.12)
Tmax (week)	A	14	2.57	2.00	0.94	(2.00, 4.00)
	B	19	3.16	2.00	1.38	(2.00, 6.00)
	C	14	3.57	3.00	1.95	(2.00, 8.00)
	E	14	3.71	2.00	2.33	(2.00, 8.00)
Cl = $Dose/AUC_{12}$ (L/week)	A	14	14193.29	12117.08	4645.24	(9588.34, 24881.39)
	B	19	12538.14	9945.63	5785.51	(7239.13, 29886.86)
	C	14	19384.85	16005.23	12248.92	(7386.36, 49530.64)
	E	14	14919.66	14113.66	5534.57	(8717.67, 29167.88)
$T_{1/2}$ (week)	A	14	9.01	5.37	11.04	(1.54, 44.76)
	B	19	6.54	5.92	3.79	(2.11, 16.63)
	C	14	8.00	4.74	10.36	(1.33, 42.50)
	E	14	10.00	6.48	10.97	(3.08, 45.49)

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Table 2. Week 0 and week 4 NVP PK parameters of arm E

	N	Week	Mean	Median	SD	Range (Min, Max)
$\log(AUC_{12})$	13	0	10.98	10.92	0.32	(10.29, 11.48)
(ng*hour/mL)		4	11.14	11.26	0.34	(10.48, 11.59)
Cmax	13	0	6056.15	6310.00	1619.70	(3010.00, 8680.00)
(ng/mL)		4	7281.54	7020.00	2328.69	(3950.00, 11000.00)
Cmin	13	0	4191.92	810.00	1513.38	(1720.00, 6950.00)
(ng/mL)		4	4966.92	5380.00	1730.64	(2530.00, 8360.00)
Tmax	13	0	4.15	4.00	1.52	(2.00, 8.00)
(hour)		4	3.81	4.00	2.39	(0.50, 8.00)
$CL = Dose/AUC_{12}$	13	0	3.57	3.62	1.23	(2.07, 6.80)
(L/hour)		4	3.07	2.58	1.12	(1.86, 5.64)
$T_{1/2}$	13	0	25.13	21.12	18.99	(5.87, 75.03)
(hour)		4	26.81	29.18	16.00	(6.16, 65.29)

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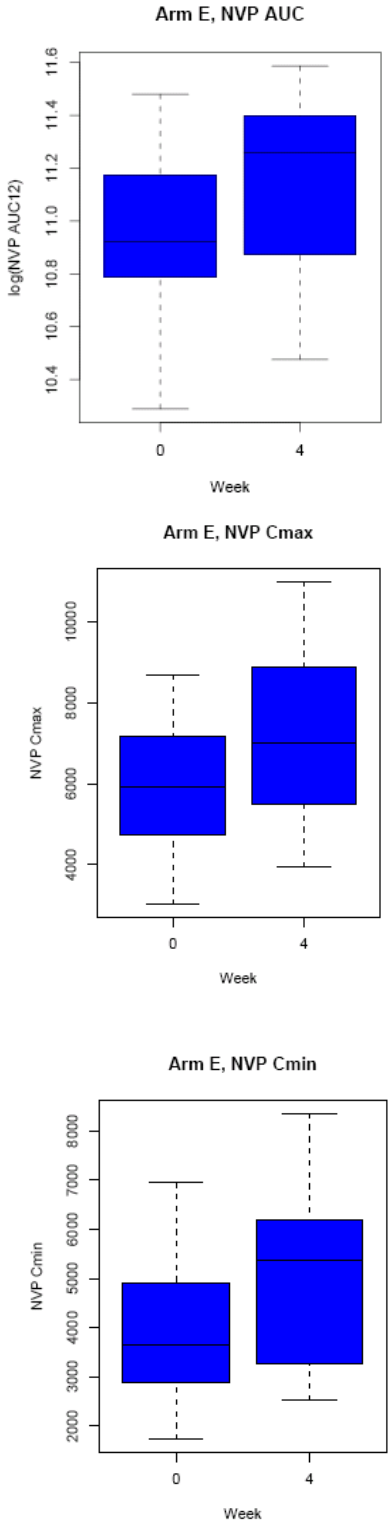
Figure 1. Boxplots of week 0 and week 4 AUC and Cmax and Cmin of NVP arm



CONCLUSIONS:

There were no differences in DMPA PK parameters AUC_{12}, C_{max}, C_{min} between the treatment arm A (Control) and treatment arm E (NVP).

There were slight but not significant increases in NVP PK parameters C_{max}, C_{min}, and AUC_{12} from week 0 to week 4.

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/s/

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