P_10

Bioavailability of Efavirenz Capsule Contents (Sprinkles) Mixed with a Small Amount of Food Compared with Intact Capsules in Healthy Adults

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Background

- The recommended adult dose for efavirenz (EFV) is 600 mg once daily on an empty stomach
- Some patients have difficulty swallowing capsules or tablets, resulting in a need for alternative methods of administration[1]
- The contents of efavirenz capsules ("sprinkles") are granules. Mixing the granules with a food vehicle for a short period of time prior to dosing prevents disintegration and allows the granules to slide down the throat with the vehicle.
- The ability to administer efavirenz capsule contents (sprinkles) with a small amount of food could make dosing more convenient and tolerable for a variety of patients
- Previous studies have shown that administration with food increases exposure to efavirenz[2,3] however, the effect of mixing efavirenz sprinkles with a small amount of food is unknown

Objectives

Primary

- To assess the bioavailability of efavirenz capsule contents when mixed with one of three food vehicles (applesauce, grape jelly, or yogurt) or infant formula, relative to the intact capsule formulation administered under fasted conditions.

Secondary

- To assess the safety associated with this mode of administration

Methods

Study Design

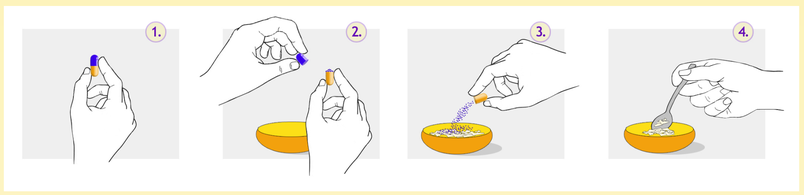
- This was an open-label, randomized, three-period cross-over study, involving 24 healthy adult subjects equally divided into two treatment groups (Groups I and II)
- Group I received Treatments A, B, and C, while Group II received Treatments A, D, and E, as described below (**Figure 1**)

Inclusion Criteria

- Subjects were required to be healthy, HIV-negative, between 18 and 45 years of age, not nursing or pregnant, and using acceptable oral, implanted, or injectable methods of contraception
- Women of childbearing potential were required to have a negative pregnancy test within 24 hours prior to each dose

Description of Food Vehicles for Administration of EFV Sprinkles

- Subjects were admitted to the clinical facility in the evening prior to dosing, and remained in the facility until at least 168 hours (7 days) after dose administration for each treatment period
- On day –1, subjects were randomly assigned to one of 12 different treatment sequences. All subjects fasted for at least 10 hours prior to and 4 hours after dosing
- On the mornings of days 1, 21, and 41, subjects received a single oral 600-mg dose of efavirenz given as three intact 200 mg capsules (Treatment A) with 240 mL of water, or a single 600-mg dose of capsule sprinkles administered by opening three 200 mg capsules and mixing contents with two teaspoons of one of four possible food vehicles:
  - Applesauce [Treatment B; 4 kcal]
  - Grape jelly [Treatment C; 33 kcal]
  - Organic whole milk plain yogurt [Treatment D; 7.5 kcal]
  - Infant formula [Treatment E; 7 kcal])
- The capsule was held vertically with the cap facing up, then the cap was pulled away from the body of the capsule carefully and the contents were sprinkled and mixed with the food in a 100-mL container



- The mixture was administered with a spoon as soon as possible, but no more than 30 minutes after mixing
- After administration of the efavirenz-food mixture, the container was rinsed three times with 50 mL water and the subject swallowed each rinse. Following the three rinses, subjects consumed an additional 90 mL of water

Pharmacokinetic Monitoring

- Serial blood samples were taken prior to and over a 21-day period after dosing at the following approximate times during each of the three study periods: prior to dosing (0 hour), and at 1, 2, 3, 4, 5, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 336, and 480 hours following dose administration
- The last sample in each period (480 hours) also served as the predose sample for the subsequent period

Taste Assessments

- Taste assessments were conducted approximately 5, 30, and 60 minutes after dosing on days 1, 21, and 41
- Subjects were asked to rate the overall taste of the different treatment groups on a 5-point scale: really bad, bad, not sure, good, & really good

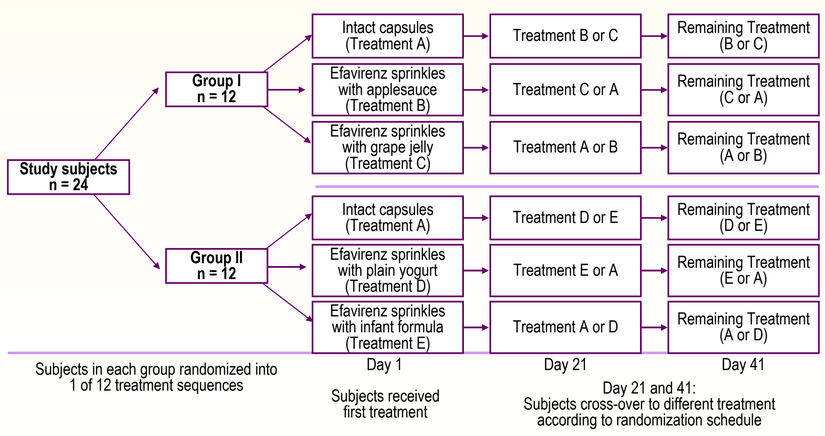
Safety Monitoring

- Subjects were closely monitored for adverse events, and safety assessments were performed at selected times, and prior to discharge

Pharmacokinetic & Statistical Analysis

- Single-dose pharmacokinetic parameters (maximum observed concentration [C_{max}], time of maximum observed concentration [t_{max}], area under the concentration–time curve extrapolated to infinity [AUC_{inf}], and half life [$t_{1/2}$]) were derived from plasma concentration versus time data
- The number of subjects was not based on statistical power considerations; however, 24 subjects (12 subjects/treatment group) provided at least 96% confidence that the estimate of the ratio of the geometric mean of sprinkles mixed with food to the geometric mean of intact capsules would be within 20% of the true value for C_{max} and AUC_{inf}
- For C_{max}, and AUC_{inf}, the 90% confidence intervals for the ratios of population geometric means for sprinkles with food vehicle to intact capsules were constructed from the results of analyses of variance on log(C_{max}) and log(AUC_{inf})

Figure 1. Cross-over Study Design



Results

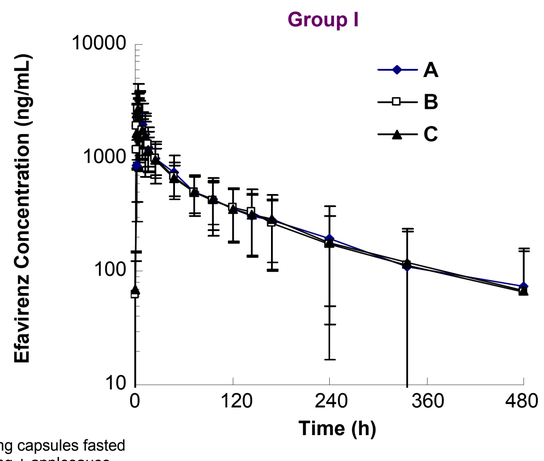
Table 1. Demographic and Patient Characteristics

Characteristic	Group I (ABC)[a]	Group II (ADE)[a]	All Treated (n=24)
Age, years			
Mean	33	33	33
SD	7	7	7
Range	23–45	20–45	20–45
Gender, n (%)			
Male	11 (92)	12 (100)	23 (96)
Female	1 (8)	0 (0)	1 (4)
Race, n (%)			
White	8 (67)	4 (33)	12 (50)
Black/African American	4 (33)	8 (67)	12 (50)
Weight, kg			
Mean	77.8	83.4	80.6
SD	12.0	10.1	11.2
Range	59.6–90.3	61.6–98.1	59.6–98.1
Height, cm			
Mean	175.9	179.4	177.7
SD	7.3	4.6	6.2
Range	159.6–186.0	171.5–184.5	159.6–186.0
Body Mass Index (kg/m²)			
Mean	25.1	25.9	25.5
SD	3.2	2.8	2.9
Range	20.0–29.2	20.3–29.0	20.0–29.2

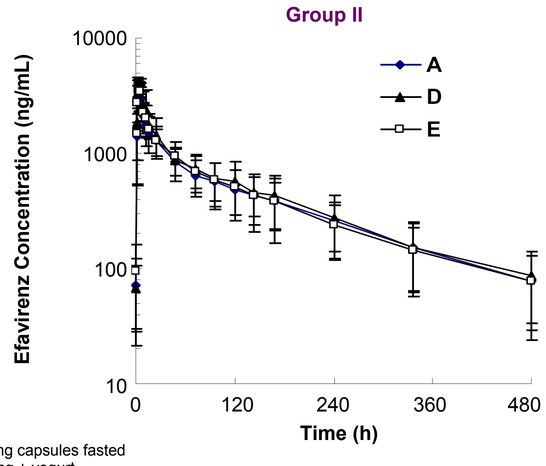
[a] A = 3x200 mg capsules fasted B = 3x200 mg + applesauce C = 3x200 mg + grape jelly D = 3x200 mg + yogurt E = 3x200 mg + infant formula

- 21/24 subjects completed the study; three discontinued early (two due to adverse events and one was lost to follow-up)

Figure 2. Mean Efavirenz Plasma Concentration-time Profiles of Group I and Group II Following Oral Administration



A = 3x200 mg capsules fasted
B = 3x200 mg + applesauce
C = 3x200 mg + grape jelly



A = 3x200 mg capsules fasted
D = 3x200 mg + yogurt
E = 3x200 mg + infant formula

- For Group I, Median (min, max) values for tmax were 4.5 (2.0, 8.0), 4.0 (2.0, 8.0), and 3.0 (1.0, 5.0) hours for treatments A, B, and C, respectively
- For Group II, Median (min, max) values for tmax were 3.0 (2.0, 4.0), 4.0 (1.0, 12.0), and 4.0 (1.0, 12.0) hours for treatments A, D, and E, respectively
- The half-life of efavirenz varied slightly between treatment groups; mean (SD) values for Group I were 117 (53), 125 (69), and 149 (139) hours for treatments A, B, and C, respectively, and for Group II, 122 (40), 127 (41), and 127 (39) hours for treatments A, D, and E, respectively

Table 2. Geometric Means and Ratio of Geometric Means for Oral Administration of a Single 600-mg Efavirenz dose as Intact Capsules (Treatment A) or as Capsule Contents Mixed With Food Vehicles: Applesauce (Treatment B), Grape Jelly (Treatment C), Yogurt (Treatment D), or Infant Formula (Treatment E)

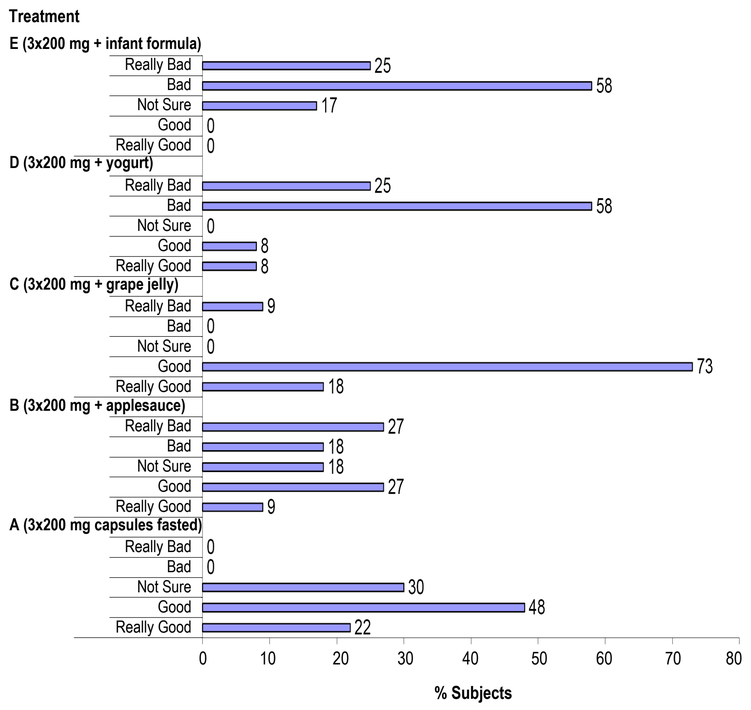
Group: Treatment (Food Vehicle)	C_{max} (ng/mL)		AUC_{inf} (ng•h/mL)	
	Geometric Mean	Ratio of Geometric Mean vs. Treatment A (90% CI)[a]	Geometric Mean	Ratio of Geometric Mean vs. Treatment A (90% CI)[a]
I: A (none)	2625	–	147,408	–
I: B (applesauce)	2461	0.94 (0.76–1.16)	138,930	0.94 (0.81–1.10)
I: C (grape jelly)	2710	1.03 (0.83–1.28)	144,630	0.98 (0.84–1.15)
II: A (none)	3522	–	192,826	–
II: D (yogurt)	4114	1.17 (1.04–1.31)	219,003	1.14 (1.08–1.20)
II: E (infant formula)	3794	1.08 (0.96–1.21)	202,967	1.05 (1.00–1.11)

Comparisons are with Treatment A in each respective Group (I or II).
[a]CI = confidence interval.

- The 90% confidence intervals for efavirenz sprinkles mixed with food vehicles versus intact capsules in each treatment group were within the 0.8-1.25 range for the AUC_{inf}

Results (Cont'd)

Figure 3. Taste Assessment Evaluation (5 Minutes After Dosing): Overall Taste



- Subjects rated efavirenz mixed with grape jelly (Treatment C) as the most palatable of the food vehicle mixtures
- Overall, majority of subjects rated grape jelly as tasting "good" or "really good" when assessed 5 minutes after administration

Table 3. Number (Percent) of Most Frequent Adverse Events Reported in 2 or More Subjects

	TRT A N = 23	TRT B N = 11	TRT C N = 11	TRT D N = 12	TRT E N = 12	All Treated N = 24
Total AE[a]	12	4	3	4	5	25
Total Subjects with AE	8 (34.8)	3 (27.3)	3 (27.3)	4 (33.3)	5 (41.7)	16 (66.7)
Dizziness	3 (13.0)	0	2 (18.2)	3 (25.0)	2 (16.7)	7 (29.2)
Feeling Abnormal	0	0	0	1 (8.3)	1 (8.3)	2 (8.3)
Alanine Aminotransferase Increased	1 (4.3)	1 (9.1)	0	0	0	2 (8.3)
Aspartate Aminotransferase Increased	1 (4.3)	1 (9.1)	0	0	0	2 (8.3)
Euphoric Mood	1 (4.3)	0	0	0	1 (8.3)	2 (8.3)

[a]Total events may include subjects who report more than one event.

- No deaths or serious or unexpected adverse events were reported
- Overall, 25 treatment-emergent AEs were reported in 16 of 24 subjects (66.7%)
- Two subjects discontinued due to investigator reported adverse events
  - One subject had a Grade 1 AST/ALT elevation
  - One subject had a Grade 1 AST and Grade 2 ALT elevation
- The intensity and frequency of adverse events and laboratory abnormalities were similar whether efavirenz was administered as intact capsules or mixed with applesauce, grape jelly, yogurt, or infant formula
- The most frequent treatment-emergent adverse events were dizziness, which occurred in seven subjects (29%), feeling abnormal, increased ALT, increased AST, and euphoric mood, each occurring in two subjects (8%)
- All adverse events were resolved prior to discharge from the study

Conclusions

- The AUC of EFV capsule contents mixed with these food vehicles was bioequivalent to the intact capsule formulation administered under fasted conditions
- All treatments were generally safe and well tolerated
- Grape jelly was the most palatable food vehicle
- These data suggest that EFV capsule contents may be administered with a small amount (2 teaspoons) of applesauce, grape jelly, yogurt, or infant formula

References

1. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. *Expert Opin Drug Deliv.* 2007;4:37–45.
2. Sustiva® (efavirenz) capsules and tablets package insert. Princeton, NJ: Bristol-Myers Squibb Company; 2009 March.
3. Sustiva® (efavirenz) summary of product characteristics. Uxbridge, United Kingdom: Bristol-Myers Squibb Pharmaceuticals Ltd; 2008 August.

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