

## Abstract

**Background:** RDEA806 is a novel NNRTI with potent in vitro activity against both wild-type HIV ( $EC_{50} = 3$  nM or 1.7 ng/mL) and the majority of viruses resistant to the currently approved NNRTIs. The objective of this study was to evaluate the safety and pharmacokinetics (PK) of single ascending doses of RDEA806, and the effect of food on the PK of selected doses.

**Methods:** A randomized, double-blind, placebo-controlled, single ascending oral dose study was conducted in 40 healthy male volunteers. Eight subjects (6 active and 2 placebo) were dosed under fasting conditions at 50 mg, 150 mg, or 300 mg. In addition, eight subjects received a single 300 mg dose under both fed (high-fat breakfast) and fasting conditions. The final dose escalation to 600 mg was conducted under fed conditions (standard breakfast). Samples were collected through 72 hrs post dose for PK assessment. Laboratory safety tests, vital signs, and ECGs were collected throughout the study.

**Results:** RDEA806 was safe and well tolerated at all doses tested. No serious adverse events and no grade 3 or 4 adverse events were reported. No clinically significant laboratory or ECG abnormalities were noted. The systemic exposure of RDEA806 increased linearly from 50 mg to 300 mg under fasted conditions. RDEA806 was readily absorbed with  $T_{max}$  occurring at 1.25–3.0 hr post-dose for the fasted group. The half-life of RDEA806 was approximately 11 hr at the higher doses. Administration of RDEA806 following a high-fat breakfast did not affect the extent of exposure of RDEA806, but led to an increase in  $T_{max}$  to 4.2 hr, a decrease in the  $C_{max}$  and nearly doubling of the  $C_{24h}$  concentration from 146 nM to 260 nM, which are well above the  $EC_{50}$  (3 nM) and  $EC_{50\%}$  (1.3 nM).

**Conclusions:** RDEA806 is safe and well tolerated at the doses evaluated. A multiple-dose study with RDEA806 will be conducted in healthy male volunteers to verify the safety and PK profile.

## Introduction and Methods

RDEA806 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type-1 (HIV-1). Preclinical testing has shown a better resistance profile of RDEA806 over currently marketed NNRTIs against most HIV reverse transcriptase mutations and a much higher barrier to resistance than efavirenz (see Abstract #1622).

Two Phase 1 studies in healthy adult male volunteers have been conducted. RDEA806-101 was a single-dose study which included five segments. RDEA806-102 was a 14-day multiple-dose study with dosing at 300 and 500 mg q12h with an immediate-release capsule, and a 10-day multiple-dose study at 400 mg q12h with a modified-release capsule.

### Key Inclusion Criteria:

- > Healthy adult male subjects  $\geq 18$  and  $\leq 45$  years of age
- > Body mass index within the range of  $\geq 18$  and  $\leq 30$  kg/m<sup>2</sup>
- > All laboratory parameters within normal limits or not clinically significant
- > Non-smokers

### Safety Assessment:

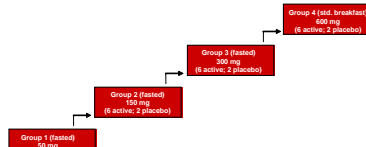
- > Safety was assessed as adverse events, clinical laboratory test results (hematology, chemistry, urinalysis), vital signs, 12-lead electrocardiograms (ECGs), and physical examination

### PK Analysis:

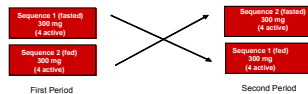
- > Blood samples were collected for the evaluation of RDEA806 PK
- > Concentration of RDEA806 was determined by a validated LC-MS/MS method with a validated LLOQ at 250 pg/mL
- > PK parameters were estimated using non-compartment model (WinNonlin)
- > Statistical analysis was based on the log-transformed PK parameters

## Methods

### RDEA806-101 SAD Segment I: Single Ascending Dose/Immediate-release Capsule



### Segment II: Food Effect (high fat diet)/Immediate-release Capsule



### Segment III: PK Enhancement/Immediate-release Capsule



### Segment IV: Food effect (high fat diet)/Modified-release Capsule



### Segment V: Rantitidine (antacid)/Immediate-release Capsule



### RDEA806-102 MAD Multiple Ascending Dose/Immediate-release Capsule



### Modified-release Capsule



**Table 1. Summary of Adverse Events in RDEA806-101 Occurring in More Than One Subject in Any Treatment Group After Single Ascending Doses of RDEA806 (number of subjects) by Preferred Term**

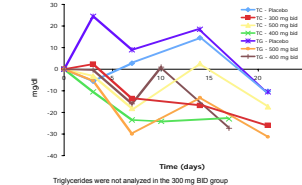
Preferred Term	Placebo (N=8)	50 mg (N=6)	150 mg (N=6)	300 mg (N=6)	600 mg (N=6)
Diarrhea			1	1	
Back pain	1				1

**Table 2. Summary of Adverse Events in RDEA806-102 14-Day Treatment Ascending Dose Study Occurring in More Than One Subject in Any Treatment Group (number of subjects) by Preferred Term**

Preferred Term	Placebo (N=6)	300 mg bid (N=6)	500 mg bid (N=6)	400 mg bid <sup>a</sup> (N=6)	Total RDEA806 (N=18)
Abdominal pain	1 (17%)	2	2	1	3 (17%)
Constipation			1	1	2 (11%)
Diarrhea	1 (17%)		2	2	2 (11%)
Dizziness	1 (17%)	1			1 (6%)
Fatigue	1 (17%)				1 (6%)
Headache	1	1	2	2	3 (17%)
Musculoskeletal stiffness	1 (17%)				1 (6%)
Pruritus	1 (17%)	1	1	1	1 (6%)
Somnolence	1				1 (11%)

<sup>a</sup>The 400 mg group was dosed with a modified-capsule for 10 days. Overall exposures were higher than with the 300 mg or 500 mg group.

**Figure 1. Mean Change in Total Cholesterol (TC) and Triglycerides (TG)**



Triglycerides were not analyzed in the 300 mg BID group

### Clinical Safety Results (Table 1 and 2):

- > Subjects enrolled in both the single- and multiple-dose studies were comparable among dose groups with regards to age, weight, and body mass index.
- > The adverse event data for the placebo-controlled dose escalation segments of the single- and multiple-dose studies are presented in Tables 1 and 2, respectively.
- > There were no serious adverse events or deaths in the study and no discontinuation due to adverse events.
- > Adverse events occurred infrequently in both studies and were all of mild severity except for two non-drug related moderate adverse events in the single-dose study.
- > The safety profile in the single-dose study was not influenced by the dose, standard meals, treatment with ritonavir (Segment III), or rantitidine (Segment V) (data not shown).
- > Dosing with the modified-capsule at 400 mg bid achieved significantly higher exposures than 500 mg bid, without an increase in adverse events.
- > No clinically significant detrimental changes were noted in any laboratory or ECG parameters.
- > Total cholesterol and triglycerides were lower or unchanged during 10-14 days of dosing (Figure 1).

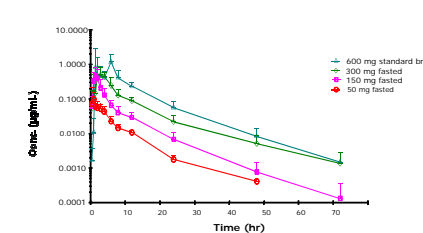
## Results

**Table 3. Selected Mean (%CV) Pharmacokinetic Parameters Following Single and Multiple Doses**

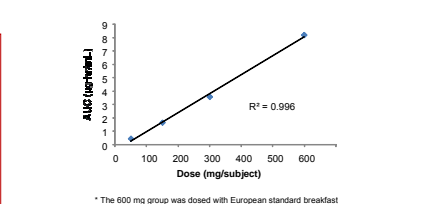
Regimen	Dose Segment	(mg)	Food	N	AUC <sub>0-24</sub> or AUC <sub>0-12</sub> (μg·hr/mL)	C <sub>max</sub> (ng/mL)	C <sub>24h</sub> or C <sub>12h</sub> (hr)	
Single	I	50	Fasted	6	0.465 (23.1)	0.141 (67.2)	0.0101 (116.7)	
			Fed	6	1.66 (55.4)	0.458 (68.5)	0.0277 (40.4)	
		150	Fasted	6	3.59 (35.6)	0.658 (37.2)	0.0831 (26.9)	
			Fed	6	9.21 (35.7)	2.00 (63.1)	0.218 (27.7)	
		300	Fasted	6	4.20 (68.3)	1.44 (85.6)	0.0830 (67.5)	
	Fed <sup>a</sup>		8	3.72 (50.1)	0.467 (47.0)	0.149 (59.1)		
	Fed <sup>b</sup>		6	6.56 (32.9)	2.63 (49.1)	0.0944 (30.0)		
	q12h	IV	300 <sup>a</sup>	Fasted	6	3.33 (37.5)	0.423 (36.0)	0.0574 (159.1)
				Fed <sup>c</sup>	6	5.17 (9.59)	1.97 (41.9)	0.0794 (30.4)
		V	300	Fasted	6	5.07 (29.2)	0.607 (53.3)	0.131 (38.6)
Fed				6	6.87 (27.9)	0.746 (52.1)	0.181 (23.1)	
400 <sup>d</sup>		ES	Fasted	6	10.6 (26.6)	5.56 (31.5)	0.112 (40.9)	
	Fed		6	10.6 (26.6)	5.56 (31.5)	0.112 (40.9)		

- <sup>a</sup> Modified-release capsule
- <sup>b</sup> Standard breakfast
- <sup>c</sup> FDA recommended high-fat, high-calorie diet
- <sup>d</sup> Rantitidine pre-dosing
- ES: Empty stomach

**Figure 2. Concentration-Time Profiles of RDEA806 Following Single Doses of RDEA806**

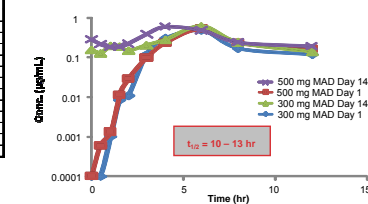


**Figure 3. Exposure Increased Linearly Between 50 and 600 mg Single Doses**

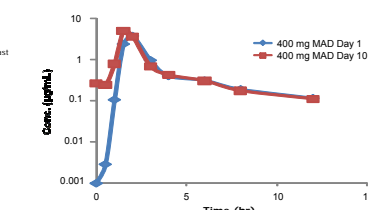


<sup>a</sup> The 600 mg group was dosed with European standard breakfast

**Figure 4. Concentration-Time Profiles of RDEA806 Following q12h Dosing with Immediate-Release Capsules (Fed)**



**Figure 5. Concentration-Time Profiles of RDEA806 Following 400 mg q12h with Modified-Release Capsules (Fasted)**



## Conclusions

- > RDEA806 was safe and well tolerated in single doses up to 600 mg and multiple doses up to 1,000 mg per day for 14 days.
- > The adverse events seen were almost all mild, sporadic and similar to those frequently seen in healthy volunteer studies; no relationship to exposure was observed with multiple dosing.
- > Exposure of RDEA806 increased linearly from 50 to 600 mg single doses, on an empty stomach or following a standard European breakfast.
- > Lower C<sub>max</sub>, AUC, and higher C<sub>24h</sub> were observed when RDEA806 was administered with a high-fat meal.
- > Less inter-subject variability was observed with the modified-release capsule or immediate-release capsule when rantitidine was used to decrease stomach acid.
- > C<sub>24h</sub> was well above the EC<sub>50</sub> (3 nM = 1.7 ng/mL) after a 50 mg single dose.
- > The terminal half-life of RDEA806 was up to 11 hr after single doses and up to 13 hr after multiple dosing, suggesting once daily dosing may be as effective as twice daily, but regimens will be compared in a Phase 2a proof-of-concept study planned to begin 4Q07.