

## Abstract

**Background:** RDEA806 is a novel NNRTI under development with potent *in vitro* activity against both wild-type HIV and the majority of resistant viruses. During a multiple dose study, significant reduction of serum uric acid (sUA) was discovered, which can be beneficial toward the treatment of gout.

**Objectives:** The significant effect of sUA reduction was analyzed and the possible mechanism and active moiety of lowered sUA was investigated.

**Methods:** Analysis of sUA reduction was conducted in a randomized, double-blind, placebo-controlled multiple dose study with 24 healthy male volunteers. Eight subjects (6 active and 2 placebo) were dosed RDEA806 under fasted conditions at 300 mg or 500 mg in immediate-release capsules for 14 days, or at 400 mg in modified-release capsules for 10 days. Correlation of increased uric acid excretion in urine was assessed in a randomized, double-blind, placebo-controlled, single-ascending-dose (SAD) study with 32 healthy male volunteers receiving either 300 mg or 600 mg of RDEA806 or placebo. Laboratory safety tests, vital signs, and ECGs were collected throughout both studies.

**Results:** In the multiple dose study, the mean changes in sUA from baseline were 3.0% (0.47 mg/dL) in the placebo group, -31.6% (-2.04 mg/dL) and -38.1% (-1.88 mg/dL) in the 300 mg and 500 mg groups, respectively, on Day 14; and -47.9% (-2.45 mg/dL) in the 400 mg group on Day 10. Based on an ANCOVA model, the decrease was statistically significant (p-values < 0.001) in all active groups, and the decrease was significantly larger (p-values < 0.001) in the active groups than in the placebo group. Further analysis of sUA reduction reveals that sUA reduction was greatest in subjects with highest sUA baselines. The mean sUA reductions were 7.23 mg/dL to 3.96 mg/dL (-45.3%), 6.40 mg/dL to 4.06 mg/dL (36.6%), 5.40 mg/dL to 3.21 mg/dL (-40.5%), and 4.12 mg/dL to 2.62 mg/dL (-38.2%) in subjects with baseline values of > 7 mg/dL, 6 - 7 mg/dL, 5 - 6 mg/dL, and < 5 mg/dL, respectively. In the SAD study, urinary excretion of RDEA806, RDEA594 (a metabolite of RDEA806), and uric acid was evaluated on DAY1 (0 - 24 hr) and DAY 3 (48 - 72 hr). A significantly higher amount of uric acid was eliminated through urine on DAY 1 than Day 3 (treated at baseline) as determined by a paired t-test. Excretion of uric acid in urine showed a linear correlation ( $r > 0.99$ ) with the amount of RDEA594 but not with RDEA806. RDEA806 and RDEA594 are 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.

**Conclusion:** Despite the well-understood etiology of gout, current treatment options are limited. Approved pharmaceutical agent, allopurinol, has significant limitations. RDEA594 has demonstrated that it can effectively reduce sUA levels in humans through increased urinary uric acid elimination and potentially provides an alternative treatment option for hyperuricemia and gout.

## Introduction

Uric acid has been implicated as a risk factor and a cause of numerous diseases. Some diseases such as gout, hypertension, and cardiovascular disease have been shown to be related to high uric acid levels in the blood. Gout, also known as metabolic arthritis, is a painful and debilitating disease. These abnormally elevated serum uric acid levels lead to the deposition of uric acid crystals in and around the connective tissue of the joints and in the kidneys, leading to inflammation, the formation of disfiguring nodules (tophi), intermittent attacks of severe pain (acute flares), and kidney damage (nephropathy). An estimated greater than 5 million people in the EU and 3-5 million people in the U.S. suffer from gout, where it is the most common form of inflammatory arthritis in men over 40.

RDEA806 is a novel NNRTI in development with potent *in vitro* activity against both wild-type HIV and the majority of NNRTI-resistant viruses. During a multiple dose study in normal healthy volunteers, significant reductions of serum uric acid (sUA) were observed, leading to the discovery of an unexpected effect of the drug. The ability of RDEA806, or more specifically its main metabolite RDEA594, to increase uric acid excretion and lower sUA may be beneficial in the treatment of gout. RDEA594 does not have significant anti-HIV activity.

## Methods

### RDEA806-102 Multiple Ascending Dose Study in Healthy Volunteers

RDEA806-102 was a multiple-dose placebo-controlled study in 24 subjects with dosing at 300 and 500 mg q12h for 14 days with an immediate-release capsule, and at 400 mg q12h for 10 days 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

#### Assessments:

- > Safety was assessed as adverse events, clinical laboratory test results (hematology, chemistry, urinalysis), vital signs, 12-lead electrocardiograms (ECGs), and physical examination
- > Pharmacokinetics of RDEA806 and RDEA594 in plasma

### RDEA806-201 HIV Monotherapy Study in HIV-Infected Patients

RDEA806-201 was a 7-day monotherapy, placebo-controlled study in 24 HIV infected patients naive to antiretroviral therapy with dosing at 400 mg twice daily (BID) and 600 mg once daily (QD) with a modified-release capsule.

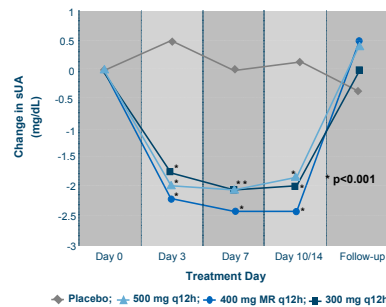
#### Key Inclusion Criteria:

- > HIV-infected male patients  $\geq 18$  and  $\leq 65$  years of age
- > HIV-1 RNA > 5,000 copies/mL; CD4 > 50 cells/mm<sup>3</sup>
- > No prior antiretroviral treatment
- > Serum creatinine > 1.5 x ULN; ALT, AST, or GGT > 5 x ULN; pancreatic amylase or lipase > 1.5 x ULN; platelet count < 75 x 10<sup>9</sup> cells/L; hemoglobin < 5.10 mmol/L

#### Assessments:

- > Safety was assessed as adverse events, clinical laboratory test results (hematology, chemistry, urinalysis), vital signs, 12-lead electrocardiograms (ECGs), and physical examination
- > Serum and urine uric acid
- > Pharmacokinetics of RDEA806 and RDEA594 in plasma and urine

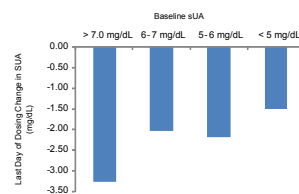
**Figure 1. Mean Change in Serum Uric Acid in RDEA806-102**



◆ Placebo; ▲ 500 mg q12h; ■ 400 mg MR q12h; ● 300 mg q12h

## Results

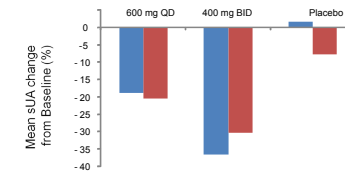
**Figure 2. Mean Change in sUA in RDEA806-102 Stratified by Baseline sUA**



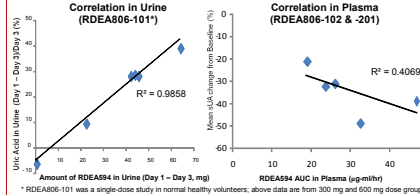
sUA Level	Baseline sUA Range			
	> 7.0 mg/dL	6 - 7 mg/dL	5 - 6 mg/dL	< 5 mg/dL
Baseline (mg/dL)	7.23	6.40	5.40	4.12
Day 14/10 (mg/dL)	3.96	4.06	3.21	2.62
Change (mg/dL)	-3.28	-2.04	-2.19	-1.50
% Change	-45.3	-36.6	-40.5	-38.2
N	2	5	5	6

- > Serum UA reduction in two patients with hyperuricemia at baseline (sUA > 7 mg/dL) was the largest in the study;
- > Every patient met the regulatory criteria of sUA < 6 mg/dL on the last day of dosing.

**Figure 3. Mean Change in sUA in HIV Patients (RDEA806-201)**



**Figure 4. RDEA594 Concentrations are Correlated to UA Excretion and sUA Reduction**



\* RDEA806-101 was a single-dose study in normal healthy volunteers; above data are from 300 mg and 600 mg dose groups.

### Clinical Safety Results for RDEA806-102 and RDEA806-201:

- > Adverse events were generally mild and of short duration, with no severe adverse events.
- > No serious adverse events, deaths or premature discontinuations.
- > No clinically significant changes were noted in any laboratory parameter, including liver and renal function tests.
- > No clinically significant changes were noted in ECG parameters.
- > Dosing with the modified-capsule at 400 mg q12h achieved significantly higher exposures than 500 mg q12h, without an increase in adverse events (Table 1).

**Table 1. Summary of Adverse Events in Multiple Ascending Dose Study (RDEA806-102) Occurring in More Than One Subject by Preferred Term**

Preferred Term	Placebo (N=6)	300 mg bid (N=6)	500 mg bid (N=6)	400 mg bid* (N=6)	Total RDEA806 (N=18)
<b>Number with AEs</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>5</b>	<b>14</b>
<b>Number of AEs</b>	<b>7</b>	<b>9</b>	<b>10</b>	<b>7</b>	<b>28</b>
Abdominal pain	1 (17%)	2	1	3 (17%)	
Constipation			2	1	3 (17%)
Diarrhea	1 (17%)		2		2 (11%)
Dizziness	1 (17%)	1			1 (6%)
Fatigue	1 (17%)		1		1 (6%)
Headache		1	2		3 (17%)
Musculoskeletal stiffness	1 (17%)			1	1 (6%)
Pruritus	1 (17%)		1		1 (6%)
Somnolence		1	1		2 (11%)

\*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.

## Conclusions

- > Despite the well-understood etiology of gout, current treatment options are limited.
- > RDEA806 has demonstrated that it can effectively reduce sUA levels in humans.
- > The reduction of sUA is correlated with baseline sUA, with greater decreases observed in patients with higher baseline values.
- > Reduction in sUA is produced through increased urinary uric acid elimination and this effect is the result of a major metabolite of RDEA806.
- > RDEA594, the metabolite of RDEA806, may potentially provide an alternative treatment option for hyperuricemia and gout, given the limitations of currently available treatments.
- > RDEA594 is currently being developed as a treatment for gout.