

SAFETY, PHARMACOKINETICS, AND SERUM URIC ACID LOWERING EFFECT OF RDEA594, A NOVEL URICOSURIC AGENT, IN HEALTHY VOLUNTEERS

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Abstract

Background: The URAT1 transporter is believed to be largely responsible for the regulation of uric acid elimination in the kidney, and diminished renal clearance is associated with the majority of hyperuricemia and gout, as approximately 90% of hyperuricemic patients are classified as under-excretors of uric acid. Increasing renal excretion of uric acid by moderating URAT1 transporter activity may provide the most physiologically appropriate treatment for gout. RDEA594, a major metabolite of RDEA806, an NNRTI in clinical development for the treatment of HIV, is an inhibitor of the URAT1 transporter in the kidney. RDEA594 is and is believed to be responsible for the uric acid-lowering effects observed with the NNRTI in Phase 1 - 2 clinical trials with over 230 subjects. Based on these observations, RDEA594 is being developed as a new chemical entity for the treatment of hyperuricemia and gout.

Objectives: To evaluate the safety, pharmacokinetics, and serum uric acid (sUA) lowering effect of RDEA594 following single and multiple doses in healthy volunteers.

Methods: Randomized, double-blind, placebo-controlled, single and multiple ascending doses studies of RDEA594 were performed in healthy male volunteers. Panels of 5 subjects (4 active, 1 placebo) received a single oral dose in either the fasted or fed state at dose levels from 5 to 600 mg. Safety was assessed by adverse event reports, laboratory safety tests, vital signs, and ECGs. Serial plasma/serum and urine samples were assayed for RDEA594 and sUA. Panels of 8 subjects (6 active, 2 placebo) received daily doses of 100 mg and 200 mg once daily for up to 10 days, with planned escalations for additional cohorts up to 600 mg once daily.

Results: Following single doses of an oral solution, RDEA594 mean plasma C_{max} was achieved at about 0.7 hour post-dose in the fasted state (5, 25, 100, 200 mg), and was slightly delayed to about 1.2 hours post-dose in the fed state (100, 400, 600 mg). Oral clearance was fairly constant across the dose range indicating that extent of oral absorption was not markedly or consistently altered by the fed/fasted state or by increased dose. Significant amount of RDEA594 was cleared into urine within 24 hours with unchanged RDEA594 ranging from 20 to 50%. After single doses, sUA lowering was detected starting following a 25 mg oral solution dose with 27-31% reduction in 24-hour sUA seen with single doses of 400 mg to 600 mg. Following multiple doses at 100 mg and 200 mg, approximately 15% and 30% reductions of sUA from baseline were achieved at steady-state. At higher dosing, greater sUA lowering is anticipated. Reductions of sUA were accompanied by increases in urinary UA excretion.

RDEA594 was safe and well tolerated at all doses. No serious adverse events and no grade 3 or 4 adverse events were reported. No clinically significant laboratory or ECG abnormalities were noted.

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 approximately 5 million people in the U.S. suffer from gout, where it is the most common form of inflammatory arthritis in men over 40.

RDEA594 is a new chemical entity being investigated for the treatment of hyperuricemia and gout. RDEA594 lowers serum urate (sUA) levels in humans by increasing the renal excretion of uric acid (uricosuric agent), and is believed to act through inhibition of the URAT1 urate transporter in the proximal tubule of the kidney. The pharmacokinetics, sUA lowering effect, and effect on urinary urate excretion following single and multiple ascending doses of RDEA594 with or without food in healthy volunteers were evaluated in healthy male volunteers.

Methods

RDEA594 Single and Multiple Ascending Dose Studies in Healthy Volunteers

RDEA594-101 was a single-dose, placebo-controlled study in 34 subjects of which 28 received ascending single doses of RDEA594 oral solution from 5 mg to 600 mg in a fed (5 mg, 25 mg, 100 mg, 200 mg) or fasted (100 mg, 400 mg, 600 mg) state.

RDEA594-102 was a multiple-dose, placebo-controlled study in 64 subjects of which 48 received multiple doses of RDEA594 once daily (qd) in ascending dose cohorts as an immediate release (IR) dose formulation dosed for 10 days in fasted or fed state from 100 mg to 400 mg:
 > 100 mg oral solution qd (fed)
 > 200 mg IR capsule qd (fasted)
 > 400 mg IR capsule qd (fasted)
 > 200 mg IR capsule qd (fed)
 An experimental extended release (ER) tablet formulation was also evaluated up to 600 mg qd under fed conditions, but did not perform as well as the IR formulation for either pharmacokinetics (PK) or serum urate lowering.

Key Inclusion Criteria:

- > Healthy adult male subjects ≥ 18 and ≤ 45 years of age
- > Body mass index within the range of ≥ 18 and ≤ 30 kg/m²
- > All laboratory parameters within normal limits or not clinically significant
- > Willing to abstain from tobacco, alcohol, caffeine, fruit juice, or sweetened soft drinks
- > Serum uric acid ≥ 5 mg/dL

Assessments:

- > Safety was assessed as adverse events (AEs), clinical laboratory test results, vital signs, 12-lead electrocardiograms (ECGs), and physical examination (PE)
- > Pharmacokinetics (PK) of RDEA594 in plasma and urine and preliminary effect of food
- > Pharmacodynamics (PD) including urate acid lowering effects of RDEA594

Results – Safety and Tolerability

- RDEA594 was well tolerated following single and multiple doses up to 600 mg qd:
 > All AEs were mild to moderate in severity with no serious AEs, deaths or discontinuations due to AEs
 > No clinically significant changes in PE, vital signs, ECGs or laboratory parameters (other than uric acid)
 > Reported AEs were similar between the IR and ER dose forms with no increase in severity or frequency of AEs with increasing dose

Table 1. AEs in Multiple Dose Study Occurring in >1 Subject Receiving RDEA594 IR Capsules

Adverse Event	Number of Subjects with Adverse Events - n (%)					Total Active Subjects (N=24)
	100 mg (N=6)	200 mg (N=6)	200 mg (fasted) (N=6)	400 mg (fasted) (N=6)	Placebo (N=6)	
Abdominal Pain	1 (17)	2 (33)	2 (33)	2 (25)	3 (13)	
Diarrhea	1 (17)	2 (33)	2 (33)	5 (21)	5 (21)	
Nasopharyngitis	1 (17)	1 (17)	1 (17)	2 (8)	2 (8)	
Back Pain	1 (17)	1 (17)	1 (17)	1 (13)	2 (8)	
Pain in Extremity	1 (17)	1 (17)	1 (17)	2 (8)	2 (8)	
Dizziness	1 (17)	2 (33)	2 (33)	1 (13)	3 (13)	
Headache	1 (17)	2 (33)	1 (17)	3 (13)	3 (13)	
Oropharyngeal Pain	2 (33)	2 (33)	1 (17)	1 (13)	5 (21)	

Results – PK and PD

SINGLE ASCENDING DOSE STUDY

Figures 1. Exposures of RDEA594 exhibited dose-proportional increases between 5 and 600 mg regardless of food; however, food reduced the C_{max} of RDEA594

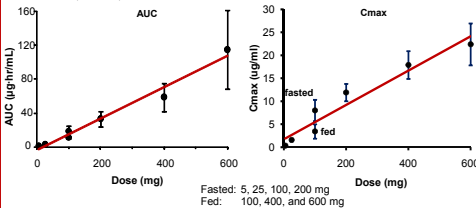
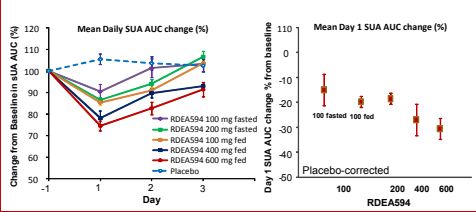


Figure 2. Serum urate lowering was seen following dosing of RDEA594 at 100 mg or higher

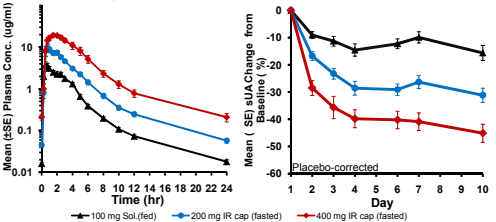


MULTIPLE ASCENDING DOSE STUDY

Table 2. Mean (CV%) pharmacokinetic parameters of RDEA594 following Multiple Dosing of RDEA594

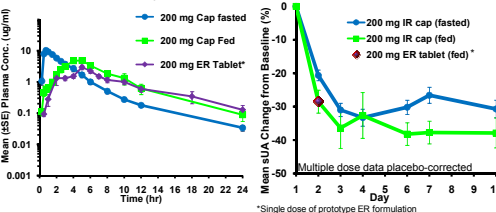
Dose (mg)	Form.	Food	Day	Median T_{max} (hr)	C_{max} (μ g/mL)	AUC_{0-24} (μ g·hr/mL)	Accumulation Ratio $C_{max} / C_{max, AUC}$
100	Sol.	Fed	10	0.625	4.19	12.2	0.875
				(0.50-2.50)	(31.1)	(12.7)	0.867
200	IR cap	Fed	10	4.50	6.59	31.0	1.23
				(3.00-5.00)	(15.6)	(24.9)	1.03
200	IR cap	Fasted	10	0.750	12.0	33.5	1.15
				(0.50-2.00)	(22.2)	(16.4)	1.17
400	IR cap	Fasted	10	2.0	22.2	62.3	1.02
				(1.00-4.00)	(17.3)	(23.7)	1.30

Figure 3. sUA lowering effect (Right) and Day 10 RDEA594 plasma concentration profiles (Left) following multiple doses of RDEA594 in solution of capsule formulation



In order to improve uric acid lowering even further, work was conducted on several experimental extended release tablet formulations, as well as evaluation of the IR capsule given with a standard breakfast

Figure 4. The IR capsule given with a standard breakfast produced the best overall pharmacokinetic profile (Table 1) and the greatest sUA reduction



Conclusions

- > RDEA594 was well tolerated in all subjects tested
- > RDEA594 exhibited linear increases in AUC and C_{max} following single oral doses of solution
- > Increasing sUA reduction was seen with increasing doses of 100 mg to 400 mg QD for 10 days
- > Following multiple dosing of RDEA594, modest accumulation was seen at 400 mg dosing
- > Administration of the IR capsule with a standard breakfast resulted in the best overall plasma concentration profile and the greatest reduction in sUA. This formulation will be used under fed conditions in the Phase 2 program starting 2Q2009