

# RDEA594, a Novel Uricosuric Agent, Significantly Reduced Serum Urate Levels and was Well Tolerated in a Phase 2a Pilot Study in Hyperuricemic Gout Patients

Poster # 1105

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## Abstract

**Purpose:** RDEA594 is in development for the management of hyperuricemia in gout patients. It is a uricosuric agent that acts through inhibition of the uric acid transporter (URAT1) in the proximal tubule of the kidney. RDEA594 was safe and well tolerated and demonstrated dose-dependent reductions in serum urate (sUA) in over 100 healthy volunteers in Phase 1 studies of up to 10 days duration. The primary objective of this pilot study was to compare the proportion of patients whose sUA level was <6.0 mg/dL following 2 weeks of continuous treatment with RDEA594 compared to placebo in gout patients.

**Method:** Twenty-one gout patients with hyperuricemia (sUA ≥ 8.0 mg/dL) were enrolled. Patients were randomized in a 2:1 ratio to the following treatment groups: RDEA594 200 mg once daily (qd) for 1 week followed by 400 mg qd for 1 week, RDEA594 matching placebo for 2 weeks, or placebo for 2 weeks. The study included a 2-week treatment period, a 2-week washout period, and a 1-week follow-up period. To reduce the incidence of gout flares, colchicine (0.6 mg qd) was administered to all patients throughout the 5-week study. An immediate release (IR) capsule formulation was administered under supervision. Serum urate levels were assessed at baseline, Day 1, 5, 8, 14, and 15, and at the end of the follow-up period. Safety was assessed by physical examinations, vital signs, 12-lead ECGs, and ECGs and laboratory examinations. Drug exposure was assessed by measuring concentrations of RDEA594 in plasma and urine.

**Results:** Preliminary results suggest that RDEA594 plasma levels in gout patients were generally consistent with those observed in Phase 1 healthy volunteer studies. A large majority of the patients achieved target sUA concentrations of less than 6 mg/dL after the first week of treatment, which was comparable to patients receiving allopurinol and significantly better than placebo. On average, RDEA594-treated patients achieved a 40% reduction in serum urate levels by the early time point. RDEA594 was well tolerated in this study, with no serious adverse events and no premature discontinuations due to adverse events at the time of this assessment.

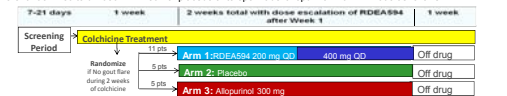
**Conclusion:** Preliminary results in this pilot study show that RDEA594 lowers sUA and is well tolerated after dosing in gout patients with hyperuricemia.

## Introduction

RDEA594 is a selective URAT1 transport inhibitor currently in Phase 2b development for the treatment of hyperuricemia and gout. RDEA594 had a good safety profile in a standard preclinical toxicology program with no significant organ toxicity in long-term studies in rats and monkeys and has been well tolerated in over 100 healthy adult male volunteers at doses from 5 mg to 800 mg per day with substantial decreases in sUA of up to 45%. This Phase 2a study was conducted as a proof-of-concept study in gout patients with hyperuricemia.

## Methods

This pilot, dose titration study was designed to assess the pharmacodynamic activity, tolerability and safety of RDEA594 in gout patients with hyperuricemia. The study includes two cohorts. In the completed cohort 1, 21 subjects were randomized to RDEA594 or placebo in a 2:1 ratio as follows:



In the ongoing Cohort 2, subjects will receive allopurinol 300 mg qd for one week followed by RDEA594 or placebo in a 5:1 ratio for 2 weeks.

Subjects were evaluated on Day 1 (baseline), Day 8 (end of Week 1 dosing), Day 9 (first day of second week of dosing), Day 14 (last dosing day), Day 15 (24 hours after last dosing) and the follow-up visit (~1 week after last dose). To reduce the incidence of gout flares, colchicine 0.6 mg qd was administered to all subjects starting 14 days prior to the baseline visit and continuing through the treatment period and follow-up period.

**Key Entry Criteria (Cohort 1):**  
 > Male healthy gout patients  
 > Mean sUA at baseline ≥ 8.0 mg/dL  
 > Prior urate-lowering therapy (ULT) must have been discontinued due to toxicity or lack of efficacy  
 > Creatinine clearance (CrCl) by Cockcroft-Gault (CG) method not less than 50 mL/min

## Results

This small study was not prospectively stratified for baseline variables. As shown in Table 1, several important baseline characteristics, including distribution of renally impaired patients, baseline creatinine clearance, age, race, and over-producers of uric acid (uric urate (UR) > 800 mg/24 hours) were not balanced between arms. All patients were male in Cohort 1. Due to the small size and important imbalances, statistical comparisons across arms are not informative.

RDEA594 produced robust reductions in sUA, with the majority of patients reaching levels below the target of 6 mg/dL, as presented in Table 2. Since over-producers of uric acid already excrete large amounts of uric acid, they are not considered candidates for initial treatment with a URAT1 inhibitor and are excluded from the ongoing Phase 2b single agent study. Excluding this small group of patients greatly reduces the risk of renal lithiasis<sup>3</sup>. These patients have also been removed from analyses, unless specifically noted.

## Results

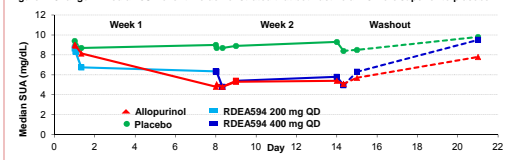
**Table 1. Significant imbalances existed in baseline demographics between groups in this small, pilot study**

Parameter	Placebo	RDEA594	Allopurinol
<b>Age (years)</b>	Mean (SD) 50.2 (9.5)	54.3 (13.7)	43.4 (5.9)
Median	51	57	43
Min, Max	40, 65	27, 72	35, 66
<b>BMI (kg/m<sup>2</sup>)</b>	Mean (SD) 33.4 (4.2)	27.8 (3.1)	31.4 (8.9)
Median	32.2	29.2	32.2
Min, Max	29.3, 39.8	23.5, 34.1	24.3, 41.7
<b>Race</b>	White 5 (100.0%) Asian 0 (0.0%) Black 0 (0.0%)	5 (45.5%) 5 (45.5%) 1 (9.1%)	5 (100.0%) 0 (0.0%) 0 (0.0%)
<b>Over-producers (UR &gt; 800 mg/24 hr)</b>	n/N	3/5	1/5
<b>Baseline sUA &gt; 11 mg/dL</b>	n/N	0/5	2/11
<b>Creatinine Clearance</b>	Mean (SD) C-G method (mL/min)	117.7 (18.6) 128.1 92, 138	92.5 (27.2) 118.2 53, 158
Median	117	109	127
Min, Max	92, 138	53, 158	76, 148

**Table 2. Majority of patients on RDEA594 and allopurinol responded following 2 weeks of treatment (Response < 6.0 mg/dL) with similar reductions from baseline in sUA for both treatment groups**

	RDEA594	Allopurinol
	% (N/N)	% (N/N)
<b>All Randomized Subjects Excluding Over-producers</b>		
Response Week 1	0 (0/2)	40 (4/10)
Response Week 2	0 (0/2)	60 (6/10)
Mean (±SEM) Change in sUA (%) at nadir	-2.6±3.0%	-46.7±2.6%
<b>All Subjects with Mild to Moderate Renal Insufficiency</b>		
Response Week 1	0 (0/0)	50 (3/6)
Response Week 2	0 (0/0)	83 (6/6)
Mean (±SEM) Change in sUA (%) at nadir	-	-47.8±4.2%
<b>All Randomized Subjects</b>		
Response Week 1	0 (0/5)	36 (4/11)
Response Week 2	0 (0/5)	56 (5/11)
Mean (±SEM) Change in sUA (%) at nadir	-2.4±2.4%	-46.2±2.4%

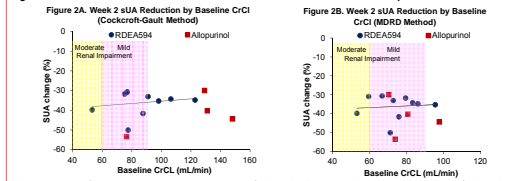
**Figure 1. Change in median sUA over time demonstrated that both active arms were superior to placebo**



Regardless of the baseline imbalances, the study provides evidence that RDEA594 at 200 mg and 400 mg qd are effective at reducing sUA in gout patients. This data also confirm the selection of these two doses for the on-going Phase 2b dose-response study. Of the four patients who did not meet the response criteria on RDEA594 (excluding the over-producer), two were within 0.3 mg/dL of meeting the criteria, and two had baseline values only 11 mg/dL; none of the patients randomized to allopurinol had baseline values this high. Even so, the response rate observed with RDEA594 is still consistent with historical rates of response to both allopurinol and febuxostat. It is also responded at two weeks to 300 mg dose of allopurinol in a recent late Phase 3 study<sup>2</sup> while 56% of patients responded after two weeks of febuxostat 40 mg in Phase 2.<sup>3</sup> The mean reduction in sUA observed with RDEA594 is 42% consistent with published results for allopurinol (~33%) and febuxostat 40-80 mg (~37% and ~42%). The unusually high response rate with allopurinol in this study was likely due to the lack of binding, very small sample size, and significant baseline imbalances.

A large percentage of patients randomized to RDEA594 had mild renal impairment (CrCl = 60-89 mL/min), with 1-2 patients (depending on the calculation method) reaching moderate renal impairment (CrCl = 30-59 mL/min). All patients with renal impairment experienced at least a 30% reduction in sUA by the end of week 2; the patient with the lowest baseline CrCl (63 mL/min) had a 40% reduction in sUA (Figure 2A). Baseline CrCl was calculated by both Cockcroft-Gault and MDRD methods. The MDRD method is more accurate for patients with low CrCl and identified three additional patients with some level of renal impairment (Figure 2B). With both methods, the slope of the linear trend line for sUA reduction with RDEA594 shows an increasing benefit with lower CrCl.

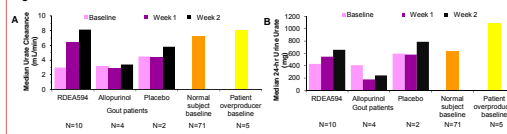
**Figures 2A and 2B. RDEA594 Works Well in Patients with Mild to Moderate Renal Impairment**



Ninety percent of gout patients are under-excretors of uric acid. The lower than normal excretion of uric acid is readily seen at baseline in the RDEA594 and allopurinol groups in Figure 3. This defect in renal excretion leads to elevated blood levels and ultimately gout. Allopurinol decreases sUA by blocking the manufacture of uric acid; this reduction in production and sUA leads to even lower excretion of uric acid. By inhibiting the reabsorption of uric acid in the proximal tubule, RDEA594 increases the amount of uric acid excreted and increases the overall clearance rate of uric acid. In the figures below, the improvement in both 24-hour excretion of uric acid and urate clearance rates match, but don't exceed, the levels seen in healthy volunteers in our Phase 1 program, with 24-hour excretion still well below that seen in over-producers at baseline. Mean unassociated urate was 14 mg/dL in the low risk range.<sup>1</sup>

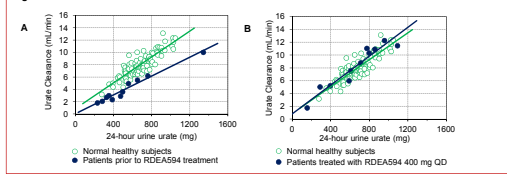
The potential for RDEA594 to increase urate excretion back to normal in patients receiving allopurinol is being evaluated in Cohort 2 of this trial. Raising the urate excretion back to baseline in the allopurinol patients shown in Figure 3A would result in an additional loss of approximately 6 gm of urate from body stores per month, increasing the velocity of tophi resolution. Normalizing urate excretion would increase the speed of tophi clearance even further.

**Figures 3A and 3B. RDEA594 Normalizes 24-Hour Urine Urate Excretion and Urate Clearance**



Comparing gout patients to healthy volunteers in Figure 4A clearly shows that gout patients have diminished urate clearance, which leads to lower than normal excretion of uric acid. With the administration of RDEA594, the gout patients had both clearance rates and total excretion amounts that were virtually identical to normal healthy volunteers (Figure 4B). Because RDEA594 only normalizes the excretion of uric acid in under-excretors, the risk of renal lithiasis from excessive uric acid excretion should be minimized. The one patient who did not meet with RDEA594 had a 24-hour excretion above the normal range at baseline (shown in Figure 4A); RDEA594 increased his clearance modestly and normalized urate excretion, resulting in a 26% reduction in sUA.

**Figures 4A and 4B. Normal Renal Excretion of Uric Acid is Restored with RDEA594**



**Table 3. In contrast to allopurinol, RDEA594 adverse events (AEs) were generally mild in severity with no severe or serious adverse events (SAEs)**

Treatment Group	N	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)	Serious Adverse Event
RDEA594	11	11 (100%)	1 (9.1%)	0	0
Placebo	5	3 (25%)	1 (15%)	0	0
Allopurinol	5	3 (25%)	1 (15%)	1 (15%)	1 (15%)

<sup>1</sup>Acute colic symptoms was both severe and a serious adverse event due to hospitalization

**Table 4. RDEA594 was well tolerated with no consistent pattern in reported AEs**

System / Preferred Term	RDEA594 (n=11)	Placebo (n=5)	Allopurinol (n=5)
Abdominal Distension	0 (0%)	0 (0%)	1 (20%) [2]
Abdominal Pain	0 (0%)	0 (0%)	2 (40%) [2]
Acute Coronary Syndrome	0 (0%)	0 (0%)	2 (20%) [2]
Arrhythmia	0 (0%)	1 (15%) <sup>1</sup>	0 (0%)
Blood Creatinine Increased	0 (0%)	2 (18%)	0 (0%)
Blood Triglycerides Increased	1 (20%) [2]	0 (0%)	0 (0%)
Cough	0 (0%)	1 (15%) <sup>1</sup>	0 (0%)
Diarrhea	0 (0%)	0 (0%)	1 (20%)
Dizziness	0 (0%)	0 (0%)	1 (20%)
Feces Hard	0 (0%)	0 (0%)	1 (20%)
Fatigue	0 (0%)	1 (9%)	0 (0%)
Fluorescence	0 (0%)	0 (0%)	0 (0%)
Gout Flare	1 (20%)	0 (0%)	0 (0%)
Headache	1 (20%)	1 (18%)	0 (0%)
Hypertension	0 (0%)	1 (15%) <sup>1</sup>	0 (0%)
Lower Respiratory Tract Infection	0 (0%)	1 (9%)	0 (0%)
Nausea	0 (0%)	0 (0%)	0 (0%)
Nasopharyngitis	0 (0%)	1 (15%) <sup>1</sup>	0 (0%)
Nausea	1 (20%)	0 (0%)	0 (0%)
Pain in Extremity	0 (0%)	1 (9%) <sup>1</sup>	0 (0%)
Prostatitis	1 (20%)	1 (18%) [2]	0 (0%)
Syncope	1 (20%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	0 (0%)	1 (20%)

<sup>1</sup> N = Subjects studied; (%) = Percentage of subjects with adverse events; [ ] = Severity Grade for Grade 2 or 3 SAEs; all other AEs were mild; Events coded by MedDRA; <sup>1</sup> = subject reported 2 AEs

**Table 5. Few treatment-emergent laboratory abnormalities were reported for RDEA594 and all were mild**

Treatment Group	N	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3/4)
RDEA594	11	Creatinine (2)	-	-
Placebo	5	-	Glucose, ALT, Triglycerides	-
Allopurinol	5	ALT	-	Albustone

There were no patients with treatment-emergent Grade 2, 3 or 4 laboratory abnormalities on RDEA594. There was one Grade 3 laboratory abnormality observed in a patient on allopurinol with hyperaldosteronism. Three patients had increases to Grade 2 abnormal values on placebo, and three patients on RDEA594 had Grade 1 abnormal laboratory values, including two patients with Grade 1 increases in creatinine. The increases in serum creatinine occurred at Day 14, were transient (returned to WNL by the 7-day follow-up visit), and were not associated with increases in BUN levels or with significant abnormalities in the urinalysis (e.g., no increase in protein) in any of these patients. In all three patients, the increase in 24-hour urinary excretion of creatinine. There have been no adverse effects on kidney function with RDEA594 in 48 healthy volunteers in Phase 1 or 25 gout patients who previously received the RDEA594 prodrug, RDEA806, for 28 days.

There were no clinically significant changes on physical exam or in vital signs, or ECGs reported.

## Conclusions

- RDEA594 produced robust reductions in sUA with a majority of patients reaching target at two weeks
- Response rates seen with RDEA594 were consistent with that seen with currently marketed products and supported the selection of the 200 mg and 400 mg qd doses for evaluation in the on-going Phase 2b dose-response study, which also includes 600 mg qd
- RDEA594 also produced excellent reductions in sUA in patients with mild to moderate renal impairment, who comprise about 30% of the gout patient population
- RDEA594 increased both urate renal clearance and the total urate excreted, both increased to levels seen in normal healthy subjects, but below levels seen in over-producers at baseline
- Normalizing urate excretion, while keeping unassociated urate in the normal range in under-excretors of uric acid (90% of the gout patient population) should not increase the risk of renal lithiasis<sup>3</sup>
- RDEA594 was well tolerated with predominantly mild AEs, with no SAEs, no discontinuations due to AEs, and no significant changes in laboratory abnormalities

1. Perez-Ruiz F. 2009 ACR-ARHP Poster #1409. 2. Becker et al. N Engl J Med 2005;353:2482-61. 3. Becker et al. Arthritis and Rheumatism 2005;50:1200-1208. 4. Clinical Trials.gov Study NCT0176497