

EFFICACY AND SAFETY OF RDEA594, A NOVEL URICOSURIC AGENT, AS COMBINATION THERAPY WITH ALLOPURINOL IN GOUT PATIENTS: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 EXPERIENCE

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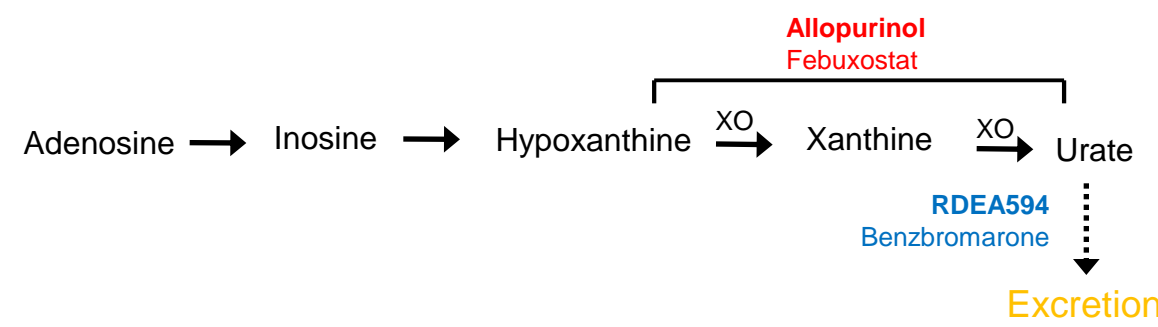
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Introduction

RDEA594 is a uricosuric agent in development for the treatment of gout, which acts through inhibition of the URAT1 uric acid transporter in the proximal tubule of the kidney. In clinical trials, RDEA594 has been well tolerated, with dose-dependent reductions in serum urate (sUA) in gout patients in a recently concluded monotherapy study.¹ Allopurinol is a marketed xanthine oxidase (XO) inhibitor, which is widely used for the treatment of gout; however, recent controlled studies have shown that less than 50% of patients reach target sUA reduction (sUA < 6mg/dL) on standard dose of 300 mg per day.² Targeting of these two sequential mechanisms for sUA lowering (Figure 1) has produced rapid and substantial reductions in sUA in gout patients, which may lead to a greater reduction in flares.

Figure 1. Dual Mechanism of sUA Reduction: Decrease Urate Production by XO Inhibition and Increase Urate Excretion by URAT1 Inhibition



Methods - General

Three pilot clinical studies were conducted with RDEA594 to evaluate serum urate (sUA) lowering, pharmacokinetics (PK), safety and tolerability of RDEA594 once daily (QD) in combination with allopurinol QD in gout patients with hyperuricemia, with varying degrees of renal function (Table 1).

Table 1. Study Designs for RDEA594 Combination Trials with Allopurinol

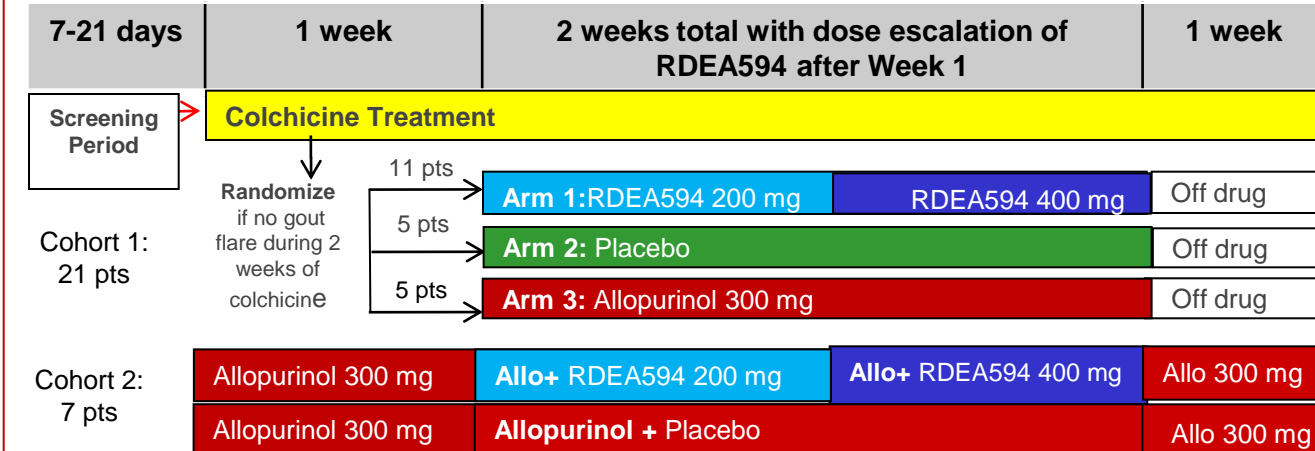
Study Number	201	110	204
Study Description	Combination Dose Titration Study	Combination Dose Ranging Drug-Drug Interaction (DDI) Study	Add-on Study in Renally Impaired
Location	Canada	USA	Belgium
Phase	2a	1b	2a
Design Features	Double-blind, placebo-controlled	Open-label	Open-label
Population	Gout patients not on ULT with hyperuricemia	Gout patients not on ULT with hyperuricemia	Gout patients with hyperuricemia and moderate renal insufficiency
Required sUA level	sUA >9 mg/dL off ULT	sUA >8 mg/dL off ULT	sUA ≥ 6 mg/dL on allopurinol
Required Creatinine Clearance (crCL)	>50 mL/min (MDRD)	>50 mL/min (C-G)	≥30 - <60 mL/min (MDRD)
RDEA594 Doses	200 mg QD 400 mg QD	400 mg QD 600 mg QD	200 mg QD
Allopurinol Dose	300 mg QD	300 mg QD	100-300 mg QD
Duration of Pre-dosing Allopurinol Alone	7 days	Panel 1 (P1): 7 days Panel 2 (P2): 7 days	Patients on stable allopurinol at study entry
Duration of Combination RDEA594 & Allopurinol	7 days at Low Dose then 7 days at Mid dose	P1: 7 days at Mid Dose P2: 7 Days at High Dose	5 days at Low Dose
Colchicine Gout Flare Prophylaxis	0.6 mg QD	0.6 mg QD	0.5 mg QD

MDRD = Modification of Diet in Renal Disease method; C-G = Cockcroft-Gault formula

All patients enrolled in the 201 and 110 studies were male and 50% of the patients enrolled in study 204 were male. Important baseline characteristics were similar for patients randomized to allopurinol alone and to the combination in Study 201, with the exception of baseline sUA > 10 (2/6 patients on allopurinol alone vs. 4/6 on combination).

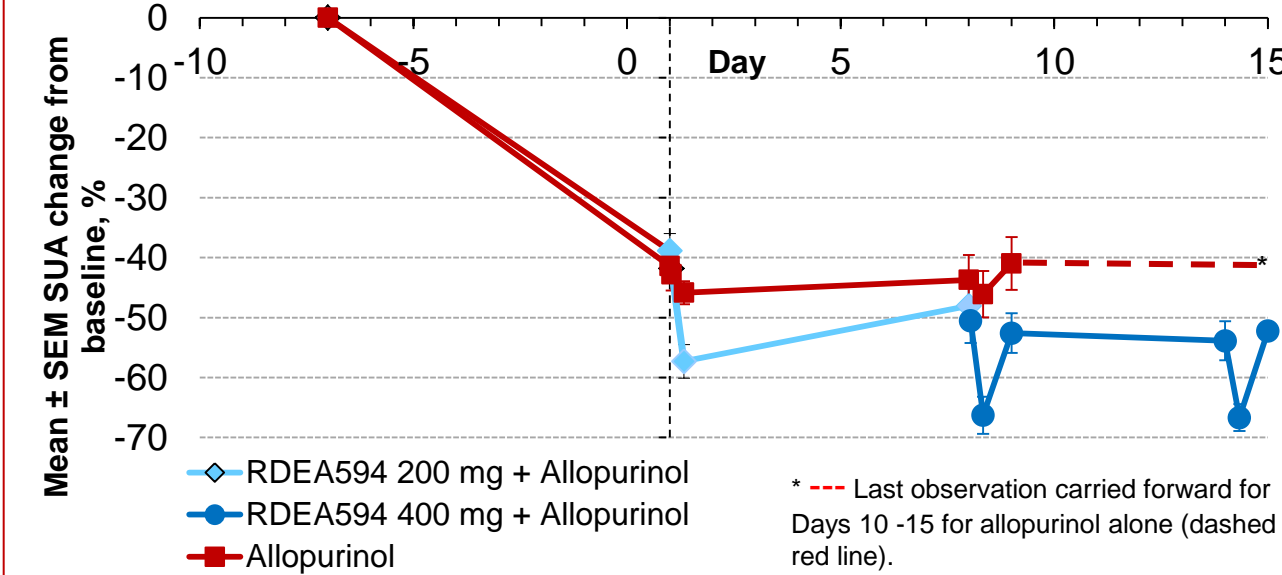
201 - Combination Dose Titration Study

This pilot, dose titration study included two cohorts. In Cohort 1, 21 patients were randomized to blinded RDEA594, placebo or to open-label allopurinol in a 2:1:1 ratio. In Cohort 2, 7 patients received allopurinol 300 mg QD for one week followed by RDEA594 or placebo in a 6:1 ratio. For analysis of the RDEA594-allopurinol combination versus allopurinol alone, the 5 patients from Arm 3 of Cohort 1 and 1 patient from Allopurinol + Placebo patients from Cohort 2 are combined.



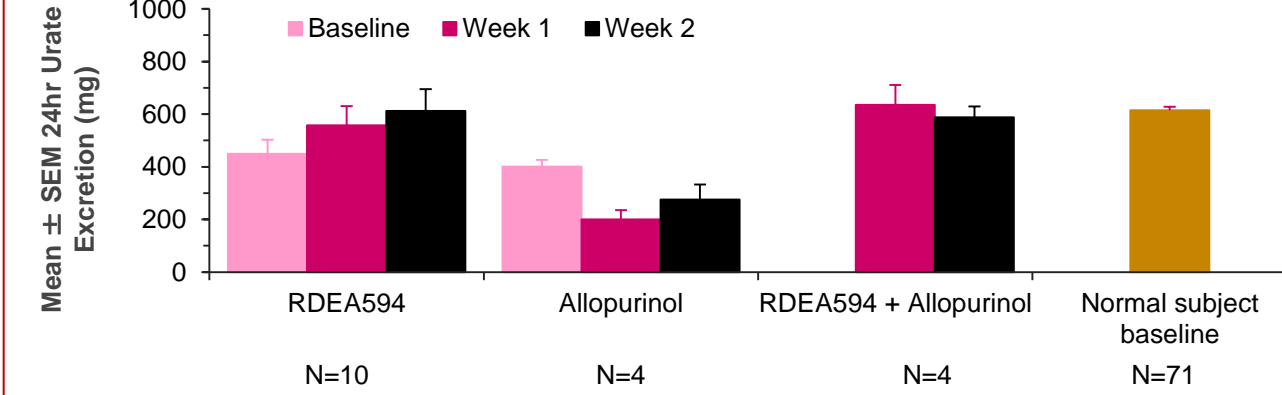
RDEA594 in combination with allopurinol produced substantially greater reductions in sUA than allopurinol alone (Figure 2). Response to treatment was defined as achieving an sUA < 6 mg/dL. **The combination of RDEA594 400 mg and allopurinol produced a 100% response, with 80% of patients also achieving an sUA < 5 mg/dL.**

Figure 2. Study 201 Demonstrates that the Combination of RDEA594 and Allopurinol Reduces sUA Greater than Allopurinol Alone



As shown in Figure 3, RDEA594 normalizes uric acid excretion in gout patients with inadequate excretion. Allopurinol reduces uric acid excretion even further in under-excretors, with already low excretion. Adding RDEA594 to allopurinol increases excretion back to normal levels, while reducing production, which results in substantial reductions in sUA. Keeping renal excretion of uric acid in the normal range should minimize risk of renal stones.

Figures 3. Combination of RDEA594 and Allopurinol Reduces Production and Increases Excretion of Urate to Normal Levels



110 - Combination Dose-Ranging DDI Study

Study 110 is an ongoing dose-ranging study that has enrolled 11 of the planned 20 gout patients. Both panels received allopurinol for two weeks; alone for one week, then combined with RDEA594 400 mg in Panel 1 and RDEA594 600 mg in Panel 2. Patients continued to receive RDEA594 alone in the third week. Full PK profiles were obtained on Day 7 after one week of allopurinol alone, on Day 14 after one week on the combination, and on Day 21 after one week on RDEA594 alone. sUA levels and safety labs are obtained weekly. Week 3 is currently being analyzed, as are allopurinol and oxypurinol plasma levels for Weeks 1-3.

110 - Combination Dose-Ranging Study (Cont.)

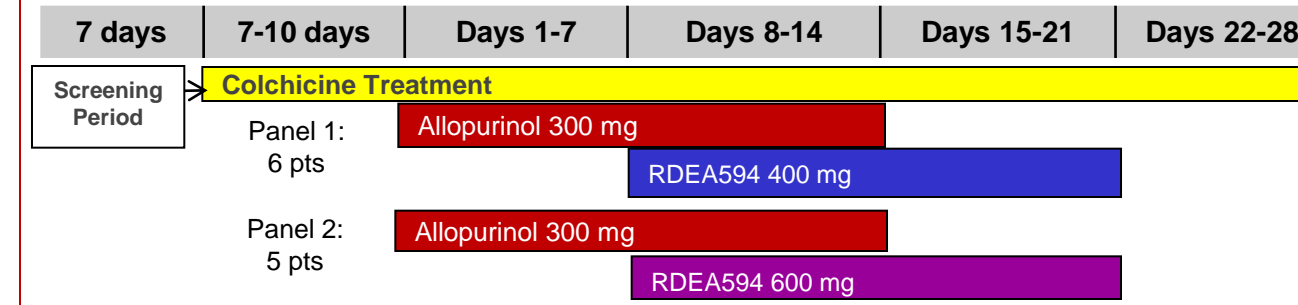


Figure 4. Study 110 Confirms Previous Results that Combination of RDEA594 and Allopurinol Reduces sUA Significantly More than Allopurinol Alone, with 60-70% Mean Reduction in sUA Observed in the 600 mg RDEA594 Group

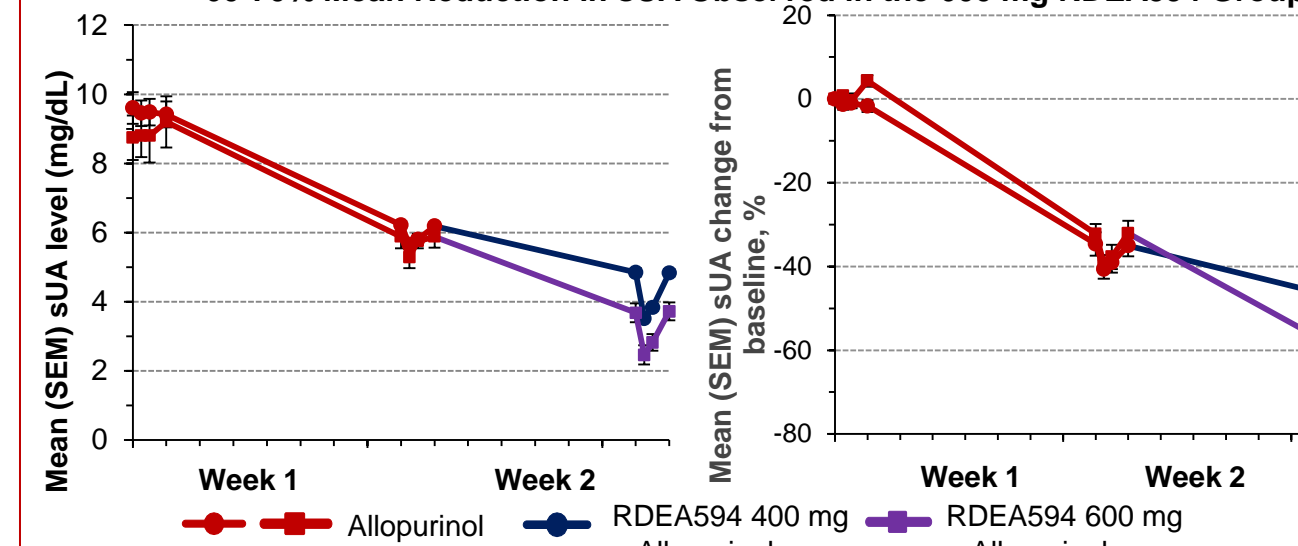


Figure 5. RDEA594 plus Allopurinol Produces 100% Response Rate

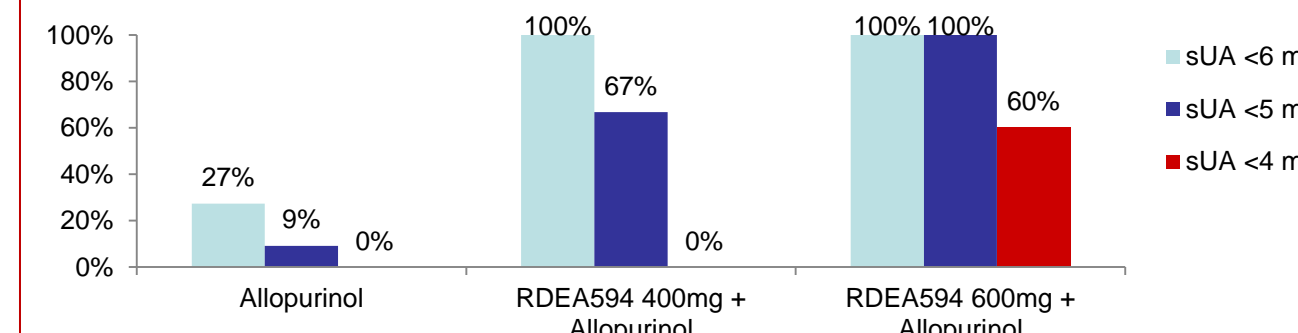


Figure 6. Allopurinol Does Not Alter RDEA594 Pharmacokinetics

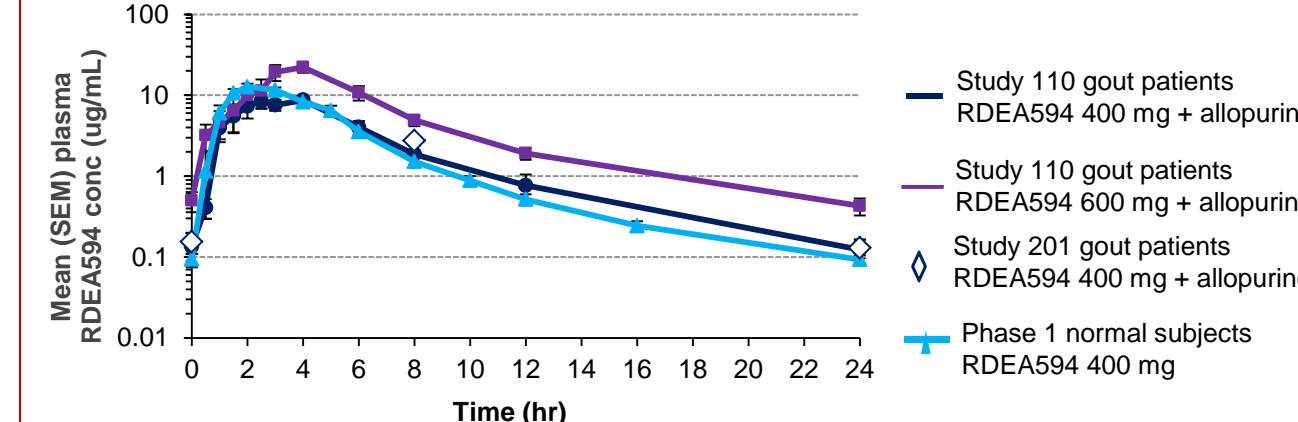
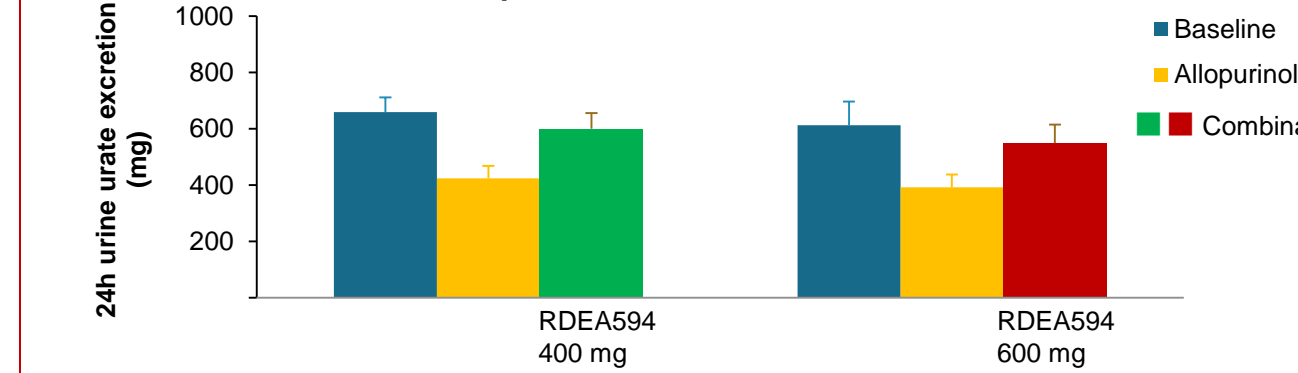


Figure 7. RDEA594 Returns Urinary Excretion of Uric Acid to Normal Range After Reduction with Allopurinol



Urinary excretion of oxypurinol increased modestly by 15-20% with the addition of RDEA594 400 mg and 600 mg.

Table 2. Mean(SD) 24h Undissociated Urine Urate (UUUA in mg/dL) is Well Below 20 mg/dL; the Combination Does Not Put Patients at Risk for Renal Stones³

Group	Baseline	Allopurinol Alone	Combination
RDEA594 400 mg	3.0 (1.4)	3.8 (1.4)	4.2 (2.4)
RDEA594 600 mg	11.2 (11.9)	6.0 (5.2)	5.8 (4.8)

204 - Add-on Study in Renally Impaired

Study 204 is an allopurinol add-on study in gout patients with moderate renal impairment that has enrolled and dosed 4 patients. Patients receiving a stable dose of allopurinol alone at entry had RDEA594 200 mg added for 5 days. Full PK profiles were obtained prior to adding RDEA594 and on the last day of RDEA594 dosing. sUA and serum creatinine levels are obtained daily and safety labs before and after RDEA594.

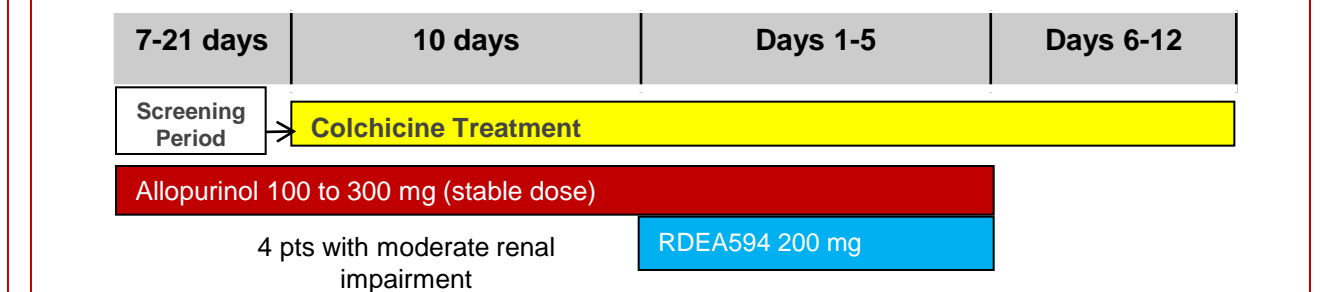
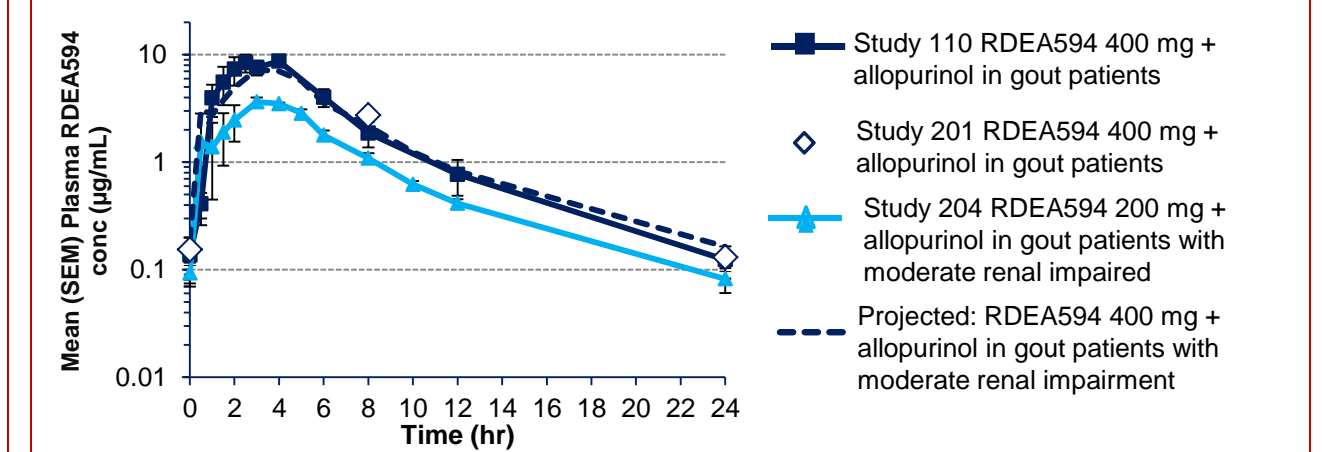


Figure 8. Study 204 Demonstrates that Moderate Renal Impairment Does not Affect RDEA594 Pharmacokinetics in Gout Patients



Serum Urate Lowering Activity: Mean sUA reductions observed in these patients with moderate renal impairment were similar to reductions observed with the 200 mg dose in Study 201 and consistent with results from the larger Phase 2b monotherapy study.¹

Safety - General

RDEA594 in combination with allopurinol:

- Well tolerated across the 3 studies.
- All adverse events (AEs) were either mild or moderate in severity, none were serious and none led to discontinuation.
- No subjects had a gout flare on RDEA594 in combination with allopurinol.
- There were no clinically significant changes in ECG parameters or in vital signs and no clinically significant changes in laboratory parameters, except for the desired decreases in sUA.
- No patients had a Grade 1 increase in serum creatinine.

Allopurinol alone:

- 2 patients reported gout flares and 2 patients discontinued early due to an AE, including one patient with a serious AE of severe acute coronary syndrome and one patient with a moderate gout flare.

Conclusions

- Combining RDEA594 with allopurinol produces robust reductions in sUA.
 - 100% of patients reaching target levels below 6 mg/dL at the RDEA594 400 mg or 600 mg dose levels.
 - 100% below 5 mg/dL at RDEA594 600 mg dose level, with reductions of 60-70%.
- In patients with inadequate urate excretion, allopurinol further reduces urinary excretion and the combination with RDEA594 returns excretion to normal levels.
 - UUUA was maintained well below the threshold for increased risk of renal stones with combination therapy.
 - Only a modest increase in oxypurinol excretion was observed.
- Pharmacokinetics of RDEA594 200 mg and sUA lowering was not affected by moderate renal impairment in gout patients.
- RDEA594 was well tolerated in combination with allopurinol in all 3 studies.
 - No SAEs or discontinuations due to adverse events
 - No clinically significant changes in serum creatinine or other laboratory parameters.

References: 1. Ardea Biosciences Inc. EULAR 2010, poster #SAT0375.
2. Becker MA, et al. 2009 ACR Annual Meeting, Abstract No. L11.
3. Perez-Ruiz F, et al. 2009 ACR Annual Meeting, Abstract No. 1499