

# RDEA594, A NOVEL URICOSURIC AGENT, SHOWS IMPRESSIVE REDUCTIONS IN SERUM URATE LEVELS AS MONOTHERAPY AND SUBSTANTIAL ADDITIVE ACTIVITY IN COMBINATION WITH FEBUXOSTAT IN NORMAL HEALTHY VOLUNTEERS

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## Abstract

**Background:** RDEA594, a uricosuric agent that acts through inhibition of the urate transporter (URAT1) in the proximal tubule of the kidney, is in development for the management of hyperuricemia in gout patients. In clinical trials, RDEA594 has been well tolerated with dose-dependent reductions in serum urate (sUA) in both healthy volunteers (n=304) and gout patients (n=140).

**Objectives:** To evaluate the sUA lowering effects of two doses of RDEA594 as monotherapy or in combination with xanthine oxidase inhibitor febuxostat, the pharmacokinetic (PK) drug-drug interaction potential, safety and tolerability.

**Methods:** This was a randomized, 2-panel (RDEA594 200 and 400 mg), placebo-controlled study in normal healthy volunteers with sUA levels generally above 6 mg/dL. In each panel, 18 subjects were randomly assigned to receive either RDEA594 or matching placebo randomized in a 2:1 ratio or 40 mg of febuxostat once-daily (QD) during the first week as single agents, the combination of the two agents in the second week and finally, the alternate single agent in the third week. sUA was evaluated daily with urine urate excretion and full PK profiles obtained at the end of each week. Safety was assessed by adverse events, clinical laboratory test results, vital signs, ECGs and physical examinations.

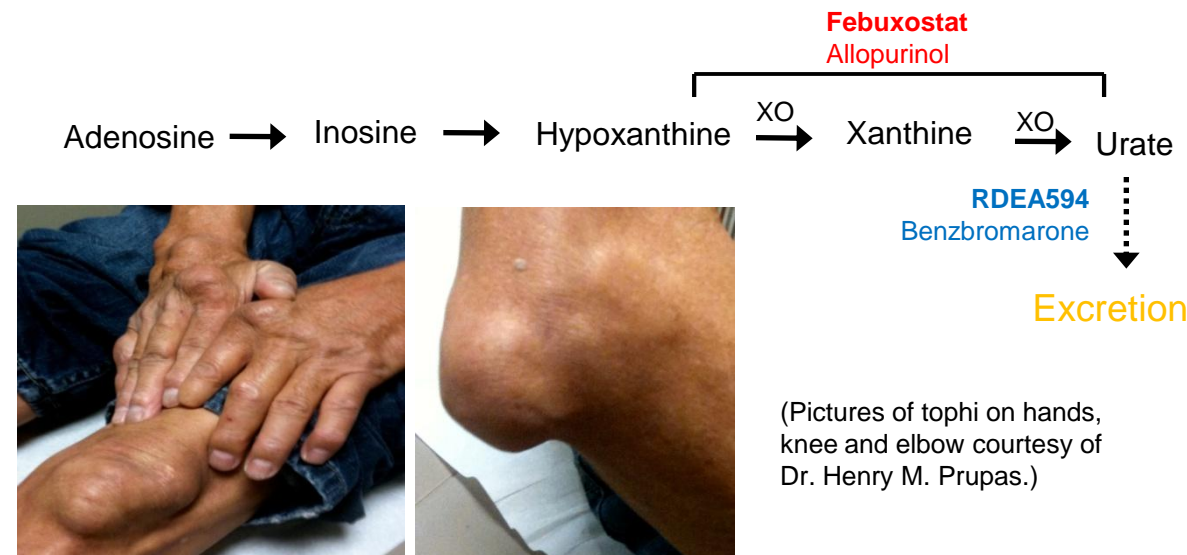
**Results:** When administered as a single agent in the first week, RDEA594 reduced sUA ~40% (200 mg) and ~50% (400 mg) from baseline compared to ~45% reduction from febuxostat (40 mg). The combination of febuxostat and RDEA594 reduced sUA by ~60% (200 mg QD RDEA594) and ~70% (400 mg QD RDEA594) at trough, with ~80% intraday sUA lowering. There were no clinically relevant PK drug interactions observed with either dose of RDEA594 and 40 mg febuxostat. RDEA594 was well tolerated with adverse events that were generally mild and transient, and no clinically significant laboratory abnormalities. Febuxostat was occasionally associated with elevated liver enzymes.

**Conclusion:** The combination of low doses of RDEA594 and febuxostat reduced sUA levels beyond what can be achieved with febuxostat alone at approved doses. Combining these two oral agents with complementary mechanisms may accelerate improvement in gout symptoms, including in patients with tophi.

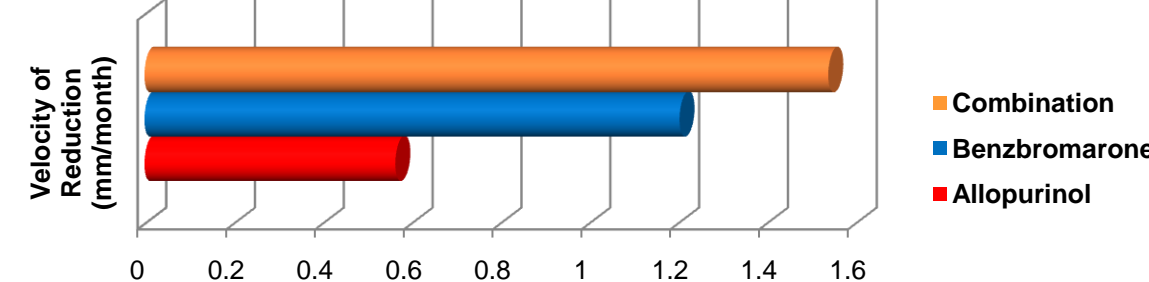
## Introduction

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 both healthy volunteers (n=304) and gout patients (n=140). Febuxostat (Adenuric®, Uloric®) is a xanthine oxidase (XO) inhibitor recently approved in the EU (80 mg -120 mg qd) and the US (40 mg - 80 mg qd). This study was designed as the initial trial to evaluate the combination of these two mechanisms for sUA lowering as illustrated in Figure 1. This dual mechanism approach with RDEA594 is expected to produce rapid and substantial reductions in sUA in gout patients and may ideally be suited to patients with high baseline sUAs and tophaceous gout.

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



**Figure 2. Increased Speed of Tophi Resolution with XO and URAT1 Inhibitors Given in Combination!**



## Methods

RDEA594-105 was a multiple-dose, placebo-controlled study in healthy volunteers designed to evaluate the sUA lowering effects, PK drug-drug interaction potential, safety and tolerability of RDEA594 in combination with febuxostat. The study included 36 subjects in 2 panels. Panel 1 received RDEA594 200 mg and Panel 2 received RDEA594 400 mg, both alone and in combination with febuxostat 40 mg.

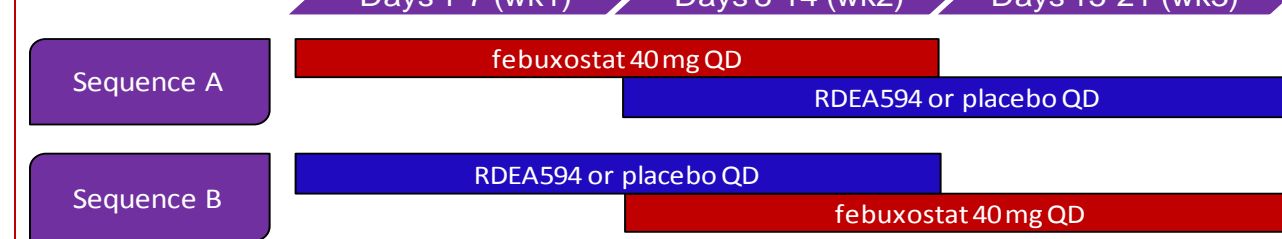
**Key Inclusion Criteria:**

- Healthy adult male or post-menopausal/surgically sterile females ≥ 18 and ≤ 65 years of age
- Body mass index of ≥18 and ≤ 34 kg/m<sup>2</sup>
- 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 ≥ 6 mg/dL (357 μmol/L)

**Assessments:**

- Adverse events (AEs), clinical laboratory test results, vital signs, 12-lead electrocardiograms (ECGs), and physical examination (PE) for safety.
- PK of RDEA594 and of febuxostat in plasma
- Pharmacodynamics (PD) including sUA lowering and urine urate excretion

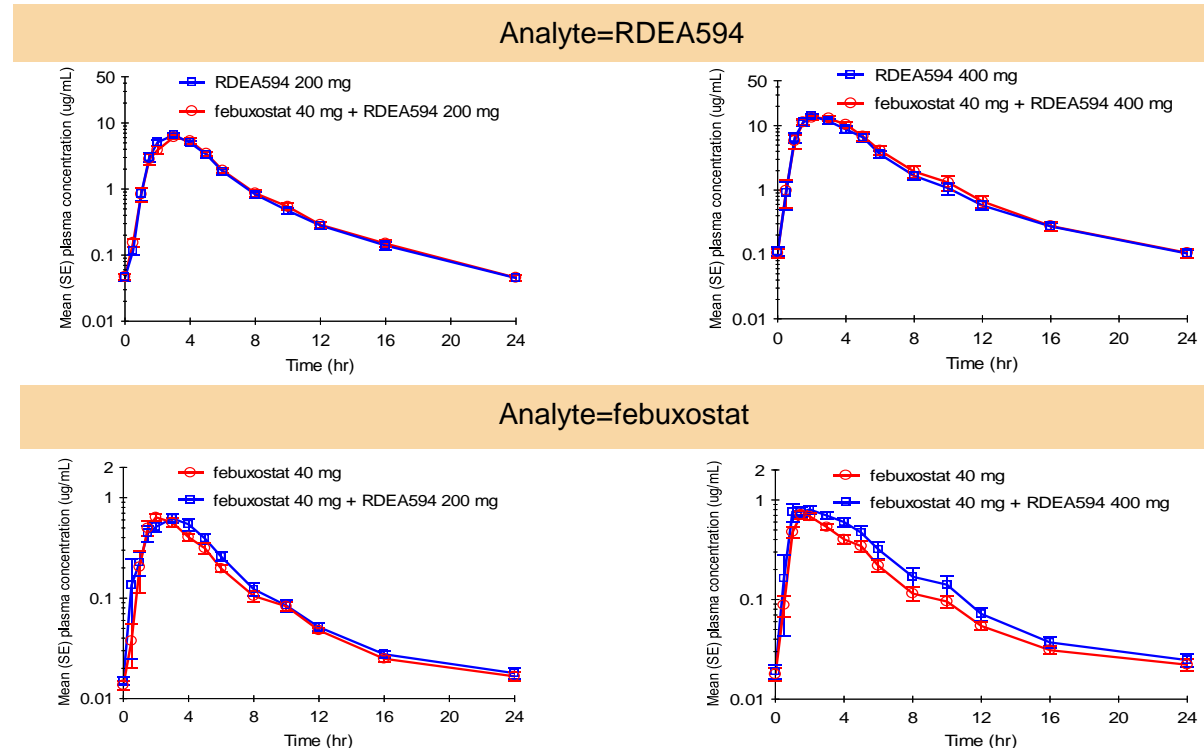
In each panel, the 18 subjects were randomly assigned to receive either RDEA594 or matching placebo in a 2:1 ratio and to be dosed according to Sequence A or Sequence B as follows:



## Results

Thirty-six subjects were enrolled and 35 completed the study. Of the 36 enrolled, the mean age was 43 years (range: 20-63), BMI was 26.6 (± 2.48) and baseline sUA of 6.2 ± 0.89 mg/dL (369 ± 53 μmol/L). The majority of subjects were male (34/36) and white (34/36) race. The baseline sUAs were similar across 2 sequences within same panel.

**Figure 3. No Clinically Relevant Pharmacokinetic Drug-drug Interactions between RDEA594 and Febuxostat**



**Table 1. Mean (CV%) Pharmacokinetic Parameters of RDEA594 and Febuxostat as Single Agents or in Combination**

| Parameter                       | Analyte = RDEA594 |             |                |             | Analyte = febuxostat |             |                |             |
|---------------------------------|-------------------|-------------|----------------|-------------|----------------------|-------------|----------------|-------------|
|                                 | RDEA594 200 mg    |             | RDEA594 400 mg |             | RDEA594 200 mg       |             | RDEA594 400 mg |             |
|                                 | Single            | Combo       | Single         | Combo       | Single               | Combo       | Single         | Combo       |
| T <sub>max</sub> - hr           | 3.42 (15.1)       | 3.00 (20.1) | 2.50 (42.6)    | 2.59 (28.4) | 2.29 (35.4)          | 2.54 (44.7) | 1.77 (44.4)    | 2.14 (63.7) |
| C <sub>max</sub> - μg/mL        | 6.69 (21.8)       | 6.92 (15.3) | 14.7 (22.4)    | 15.5 (17.9) | 0.74 (26.8)          | 0.79 (26.6) | 0.79 (26.7)    | 1.03 (29.5) |
| AUC <sub>0-24h</sub> - hr·μg/mL | 27.3 (18.6)       | 28.1 (20.0) | 61.0 (28.0)    | 65.0 (26.1) | 3.19 (18.9)          | 3.53 (19.2) | 3.62 (24.8)    | 4.85 (32.7) |

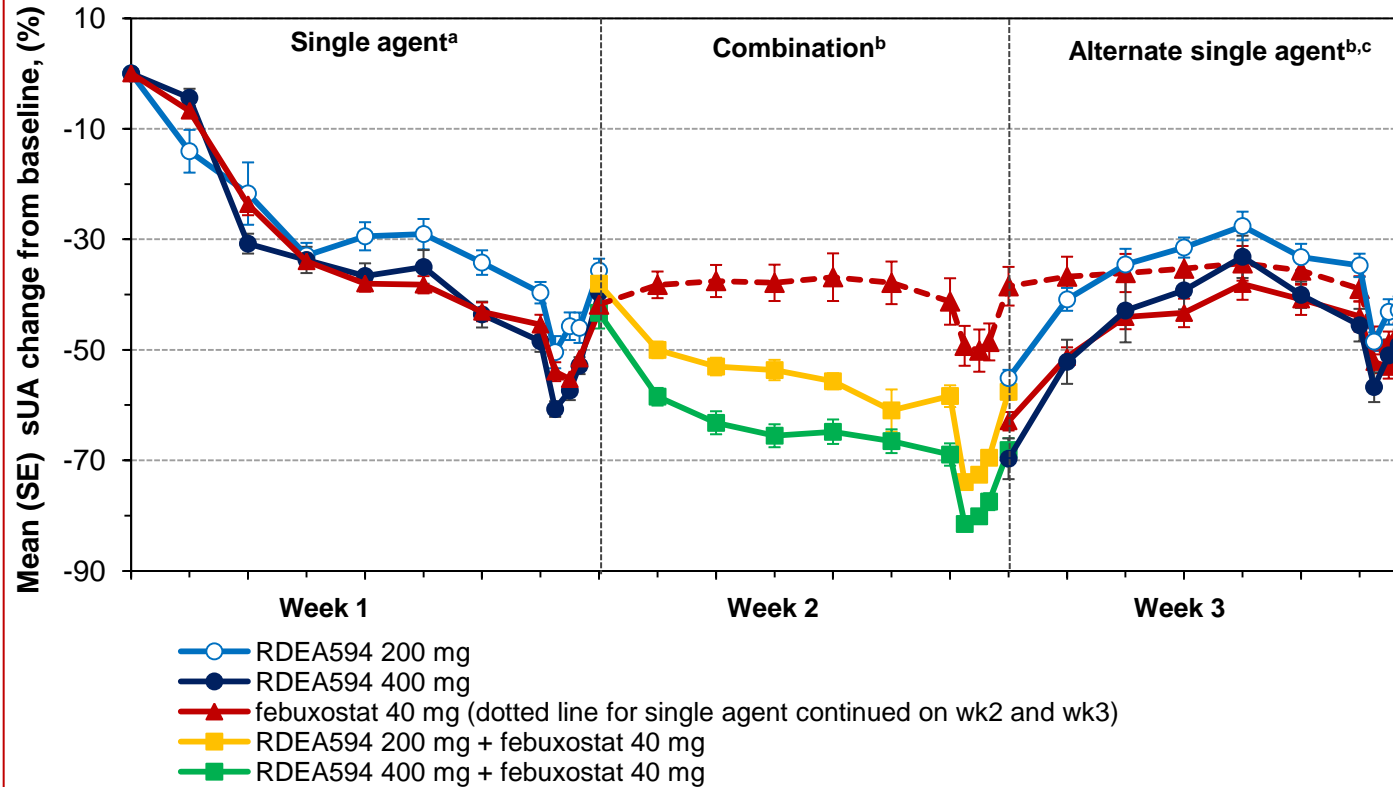
## Results

**Table 2. Combination of RDEA594 and Febuxostat was Well Tolerated**

| Adverse Event*       | Dose Received at Time of Event Onset     |                       |  |                       |                                   |                | Overall (N=36) |
|----------------------|--|-----------------------|--|-----------------------|-----------------------------------|----------------|----------------|
|                      | RDEA594 200 mg + Febuxostat 40 mg (N=12) | RDEA594 200 mg (N=12) | RDEA594 400 mg + Febuxostat 40 mg (N=12) | RDEA594 400 mg (N=12) | Placebo + Febuxostat 40 mg (N=12) | Placebo (N=12) |                |
| Constipation         |  |                       | 2  | 1                     |                                   |                | 5              |
| Fatigue              |  |                       | 1  | 1                     | 1                                 |                | 4              |
| Abdominal distension |  |                       |  |                       | 1                                 |                | 2              |
| ALT increased        |  |                       |  |                       | 1                                 |                | 2              |
| Back pain            |  | 1                     |  |                       |                                   |                | 2              |
| Ocular Hyperaemia    |  |                       |  |                       | 1                                 |                | 2              |
| Pain in extremity    |  |                       |  | 1                     |                                   |                | 2              |
| <b>Total</b>         | <b>0</b>                                 | <b>1</b>              | <b>3</b>                                 | <b>3</b>              | <b>4</b>                          | <b>0</b>       | <b>19</b>      |

a - table includes adverse events that occurred in more than one subject in the study.

**Figure 4. Significant sUA Lowering Effects Observed after RDEA594 Dosing and Excellent Additive Effects in Combination with Febuxostat**



a - febuxostat single agent arm in week 1 combines all 18 subjects receiving febuxostat 40 mg alone from both panels.  
b - febuxostat dotted red line includes 6 subjects from both panels on RDEA594 placebo who received continuous febuxostat in weeks 2 and 3.  
c - febuxostat arm in week 3 combines all 11 subjects who previously received combination with RDEA594 at 200 or 400 mg in week 2.

**Table 3. Mean Percent sUA Change from Baseline Following Dosing of Single Agents or Combination of RDEA594 and Febuxostat in Healthy Subjects**

|                  | Single agent      |                          | Combination              |                          |
|------------------|-------------------|--------------------------|--------------------------|--------------------------|
|                  | Trough % ± SE (N) | Intraday peak % ± SE (N) | Trough % ± SE (N)        | Intraday peak % ± SE (N) |
| RDEA594 200 mg   | -40 ± 2 (6)       | -50 ± 3 (6)              | -58 ± 2 (12)             | -74 ± 1 (12)             |
| RDEA594 400 mg   | -49 ± 2 (6)       | -61 ± 1 (6)              | -69 ± 2 (12)             | -82 ± 1 (12)             |
| Febuxostat 40 mg | -45 ± 2 (18)      | -55 ± 2 (18)             | (see above with RDEA594) | (see above with RDEA594) |

**Table 4. Observed Median Trough sUA Lowering Following RDEA594 or Febuxostat QD in Healthy Subjects and Gout Patients**

|                        | RDEA594 <sup>2</sup> |        | Febuxostat <sup>3,4</sup> |
|------------------------|----------------------|--------|---------------------------|
|                        | 200 mg               | 400 mg | 40 mg                     |
| Healthy subjects       | -40%                 | -49%   | -44%                      |
| Gout patients          | -28%                 | -35%   | -33%                      |
| Difference in response | 12%                  | 14%    | 11%                       |

## Discussion

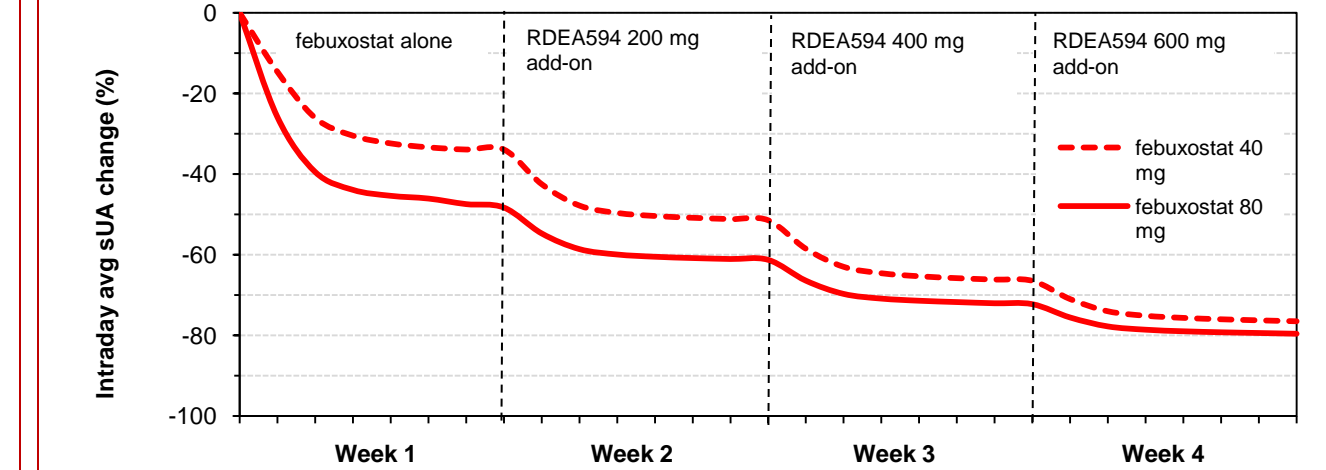
There was no change in RDEA594 drug exposure at the 200 mg or 400 mg dose levels in combination with febuxostat 40 mg (Figure 3, Table 1). Febuxostat plasma exposure increased by 7-10% with RDEA594 200 mg and ~25% with RDEA594 400 mg, but these minor changes were not considered clinically relevant.<sup>4</sup>

RDEA594 was well tolerated alone and in combination with febuxostat (Table 2) with all AEs mild or moderate in severity and no clinically significant changes in any ECG parameters, PE or in vital signs. One subject discontinued due to an AE of haemorrhoids after adding febuxostat to RDEA594, which led to hospitalization, but was not considered related to study medications. Three subjects had treatment-emergent Grade 2 ALT increases when receiving febuxostat alone or in combination with RDEA594, but not all were considered AEs.

The combination of RDEA594 with febuxostat resulted in approximately a 70% mean reduction in sUA levels compared to baseline, with intraday reductions over 80%, reaching mean sUA levels of 1.2 mg/dL (Figure 4, Table 3).

A 13% difference in sUA lowering effect was observed between healthy subjects and gout patients for RDEA594 and febuxostat (Table 4). To project the sUA lowering effect of febuxostat-RDEA594 combination treatment in gout patients, a 2-compartment PK/PD model was designed to simulate the sUA lowering effect for febuxostat alone or in combination with RDEA594 in healthy subjects utilizing data from this study. The simulation results were further corrected for the 13% difference in response between healthy subjects and gout patients based on the published data and shown in Figure 5. In gout patients, RDEA594 600 mg added on to febuxostat 40 mg would be expected to produce a substantial intraday average sUA reduction of up to 76%, compared to ~34% for febuxostat 40 mg alone.

**Figure 5. Projected Intraday Average sUA Lowering Effects in Gout Patients Receiving Combination Treatment with RDEA594 and Febuxostat**



## Conclusions

- RDEA594 alone or in combination with febuxostat was well tolerated.
- Pharmacokinetic drug-drug interaction between RDEA594 and febuxostat was minimal and not clinically relevant at tested doses.
- RDEA594 with a low dose of febuxostat produced substantial additive effects on serum urate in healthy volunteers, with reductions of ~70%.
- Combining these two oral agents with complementary mechanisms in the treatment of gout patients is expected to produce rapid and substantial reductions of serum urate that may accelerate resolution of tophi in patients with tophaceous gout.

### References

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