Evaluation of Drug-Drug Interaction Potential between RDEA594, Allopurinol and Febuxostat in Preclinical Species

Poster # 1102

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Abstract

Purpose: RDEA594 has demonstrated serum uric acid (sUA) lowering effects in humans following dosing of either of RDEA594 or its parent, RDEA806, in over 300 healthy volunteers and patients. The lowering of sUA is directly linked to increased urinary excretion of uric acid, which is believed to result from inhibition of the URAT1 transporter. Allopurinol, its active metabolite oxypurinol, and febuxostat, are xanthine oxidase inhibitors used in the treatment of gout. Because of a different mode of action, RDEA594 could be used in combination with allopurinol or febuxostat for uric acid lowering therapy. Assessment of the drug-drug interaction potential between RDEA594, allopurinol and febuxostat was conducted in monkeys and rats.

Method: In male Cynomolgus monkeys, a two period, one-way crossover study was conducted with oral administration followed by plasma and urine collection. In Period 1, a single dose of either RDEA594 at 25 mg/kg (group 1) or allopurinol at 12 mg/kg (group 2) was administered. After a 7-day wash out, in Period 2, RDEA594 was administered concomitantly with allopurinol (group 1), or allopurinol administered concomitantly with RDEA594 (group 2). In Sprague-Dawley rats, RDEA594 or febuxostat was dosed for 3 days before concomitant administration of the other compound on Day 4. The resulting pharmacokinetics of RDEA594 or febuxostat following co-administration was then compared to rats receiving single dose of either RDEA594 at 30 mg/kg or fexobustat at 10 mg/kg.

Result: RDEA594 had no effect on the plasma PK or urinary excretion of allopurinol and oxypurinol in monkeys. Comparing allopurinol plus RDEA594 versus allopurinol alone, the C_{max} and AUC for allopurinol were 0.55 µg/mL, 1.23 µg*hr/mL and 0.65 µg/mL, 1.61 µg*hr/mL, respectively, with $P > 0.05$, indicating an absence of interaction. The C_{max} and AUC for oxypurinol were 2.1 µg/mL, 15.1 µg*hr/mL and 2.0 µg/mL, 14.0 µg*hr/mL, respectively, with $P > 0.05$. The urinary excretion of allopurinol and oxypurinol were also found to be unaffected by concomitant RDEA594 administration. Similarly, allopurinol was found to have no effect on the plasma PK or the urinary excretion of RDEA594. Findings from *in vivo* rat study indicated that RDEA594 had no effect on the plasma PK of febuxostat, and vice versa.

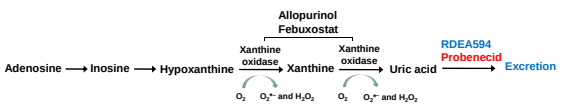
Conclusion: No drug-drug interactions were found between the xanthine oxidase inhibitors allopurinol, oxypurinol or febuxostat and RDEA594. RDEA594 coadministration did not alter plasma PK or urinary excretion of the xanthine oxidase inhibitors, and they did not affect the plasma PK and urinary excretion of RDEA594.

Introduction

RDEA594 has demonstrated serum uric acid (sUA) lowering effects in humans following dosing of either of RDEA594 or its parent, RDEA806, in over 350 healthy volunteers and patients. The lowering of sUA is directly linked to increased urinary excretion of uric acid, which results from inhibition of the URAT1 transporter. Unlike benzbromarone, a uricosuric agent, RDEA594 demonstrates no mitochondrial toxicity in *in vitro* assay. In preclinical evaluation, RDEA594 is negative in genotoxicity and safety pharmacology studies and indicates no cardiovascular risk for humans. In 6-month rat chronic toxicology study, 13-week interim data analyses including clinical chemistry and histopathology indicate no significant organ toxicity up to 300 mg/kg/day dosing. Following 6-month dosing, preliminary data analysis indicate similar outcome as 13-week results with pending histopathology evaluation. In 12-month monkey chronic toxicology study, there is no significant gross observation or clinical chemistry finding at doses up to 300 mg/kg/day in the 6-month interim necropsy. There is no kidney finding in histopathology evaluation in the 6-month interim necropsy.

Allopurinol, its active metabolite oxypurinol, and febuxostat, are xanthine oxidase inhibitors used in the treatment of gout. Because of a different mode of action and its potential ability to normalize renal clearance of urate in patients receiving a xanthine oxidase inhibitor, RDEA594 could be used in combination with allopurinol or febuxostat. Assessment of the drug-drug interaction potential between RDEA594, allopurinol and febuxostat was conducted in monkeys and rats. Probenecid, another uricurosic agent, and a classical competitive inhibitor of organic acid transport in the kidney, was also co-administered with allopurinol in monkeys to serve as a control.

Figure 1. Mechanism of uric acid reduction through reduction of uric acid production (xanthine oxidase inhibitor) or increase uric acid excretion (uricosuric agent)



Methods

- **Febuxostat and RDEA594 DDI study in rats**

  In Sprague-Dawley rats, RDEA594 or febuxostat alone was orally dosed for 3 days before beginning concomitant administration of the other compound on Day 4. The pharmacokinetics of febuxostat or RDEA594 following co-administration was then compared to rats receiving monotherapy of either febuxostat at 10 mg/kg or RDEA594 at 30 mg/kg.

- **Allopurinol and RDEA594 DDI study in monkeys**

  In male cynomolgus monkeys, a two-period, one way crossover study was conducted with oral administration followed by plasma and urine collection. In Period 1, a single dose of either RDEA594 at 25 mg/kg (group 1) or allopurinol at 12 mg/kg (group 2) was administered. After a 7-day wash out, in Period 2, RDEA594 was administered concomitantly with allopurinol (group 1), or allopurinol administered concomitantly with RDEA594 (group 2). After another 7-day wash out, in an add-on period 3, probenecid at 40 mg/kg was administered concomitantly with allopurinol.

Results

Figure 2. Similar pharmacokinetics were seen for febuxostat dosing alone or coadministered with RDEA594

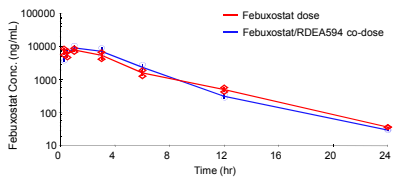


Table 1. RDEA594 has no impact on febuxostat pharmacokinetics following oral administration in rats

Dose (mg) RDEA594	Dose (mg) Febuxostat	Gender (N=3)		C_{max} µg/ml	AUC_{0-24} µg·hr/mL	T_{max} hr
Febuxostat 0	10	Male	Mean	8.63	39.9	0.75
			%CV	26.7	24.8	57.7
Febuxostat 30	10	Male	Mean	9.24	47.0	1.00
			%CV	32.9	33.9	0.00
Febuxostat 0	10	Female	Mean	10.5	33.1	0.25
			%CV	18.7	12.1	0.00
Febuxostat 30	10	Female	Mean	7.6	33.2	0.75
			%CV	23.8	8.7	47.1

- **There is no significant difference in exposure of either febuxostat or RDEA594 when these compounds are coadministered .**

Figure 2. Similar pharmacokinetics were seen for oxypurinol in monkey with allopurinol dosing alone or co-administered with RDEA594

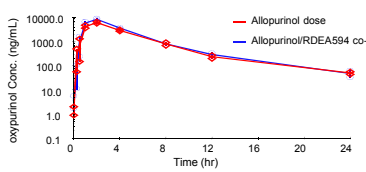


Table 2. RDEA594 has no impact on pharmacokinetics of allopurinol or its metabolite oxypurinol following oral administration in monkeys*

Dose (mg/kg) RDEA594	Dose (mg/kg) Allopurinol	Analyte		C_{max} (µg/mL)	AUC_{0-24hr} (µg·hr/mL)	$t_{1/2}$ (hr)
0	12	Allopurinol	Mean	1.2	1.6	0.9
			%CV	89	30	36
		Oxypurinol	Mean	6.1	26.7	8.3
			%CV	17	12	40
25	12	Allopurinol	Mean	0.55	1.3	0.76
			%CV	9.2	9.4	27
		Oxypurinol	Mean	8.4	34.0	5.6
			%CV	13	8.8	17

* Representative data set from multiple experiments

- **RDEA594 did not alter the plasma pharmacokinetics of allopurinol or oxypurinol ($p > 0.05$)**

Figure 3. Urinary excretion of RDEA594 and oxypurinol was not altered in monkeys when RDEA594 and allopurinol were co-administered

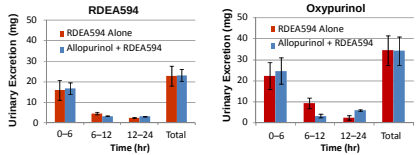


Figure 4. Probenecid dramatically affects the pharmacokinetics of oxypurinol following co-administration with allopurinol in monkeys

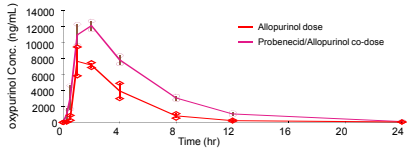


Table 3. Probenecid alters plasma pharmacokinetics of oxypurinol following oral coadministration with allopurinol in monkeys

Dose (mg/kg) Probenecid	Dose (mg/kg) allopurinol	Analyte		C_{max} (µg/mL)	AUC_{0-24hr} (µg·hr/mL)	$t_{1/2}$ (hr)
0	12	Oxypurinol	Mean	9.0	34	6.7
			%CV	18	21	18
40	12	Oxypurinol	Mean	12.5	73 *	8.0
			%CV	11	10	38

* p = 0.015

Animal Safety Update

Based on the mechanism of action of RDEA594 with the kidney being the primary pharmacological target, the kidney might also be a potential target for toxicity. As such, close attention has been given to this organ in animal safety studies.

- 6-month rat and 9-month monkey toxicology studies with RDEA806, in which high levels of RDEA594 were present (RDEA594 is the major metabolite of RDEA806), showed no evidence of drug induced renal toxicity.
- In the initial 28-day rat study with RDEA594, there was evidence of some minimal to mild renal tubular damage at the 14-day interim sacrifice at the top dose of 300 mg/kg; however, no such lesions were noted at Day 28, and by Day 28 the control arm had renal lesions.
  - The lack of drug related effects at Day 28 would indicate either an adaptive change in the animals or that the initial findings were not indicative of a true drug related observation. A true test article-related change is usually exacerbated with longer term dosing and can often be observed at lower doses with chronic dosing.
- 6-month chronic rat study with RDEA594, which included a 3-month interim sacrifice, has recently completed dosing.
  - At doses up to 300 mg/kg/day, same as the high dose in the 28-day study, there is no evidence of test article-related organ toxicity, including no evidence of kidney toxicity based on clinical chemistry, gross pathology and most importantly histopathology after 3 months of dosing with RDEA594. Drug exposures at this dose level are many fold above target human levels (Table 4).
  - Additionally clinical chemistry changes and gross observation through 6-months of dosing do not indicate any effects on renal function or toxicity; histopathology at 6-months is pending, but is expected to be clean.
  - Based on the longer term data, the renal observations seen after 14-days of dosing in the rats were not predictive of the potential for renal toxicity with RDEA594.
- A 6-month interim sacrifice was conducted in the chronic 12-month monkey study; no renal toxicity was noted in clinical chemistry, gross pathology or histopathology at doses up to 300 mg/kg/day.
- Based on the animal toxicology data generated to date, there is no long-term risk for renal toxicity with RDEA594.

Table 4. No significant organ toxicity seen up to 300 mg/kg/day in chronic toxicology studies

	Dose	HED	AUC* (µg·hr/mL)	C_{max}* (µg/mL)
Rat	300 mg/kg	3000 mg QD	1550	166
Monkey	300 mg/kg	6000 mg QD	308	43
Human	400 mg QD	400 mg QD	62	11

HED: human equivalent dose; * Average of male and female animals from 28-day study

Conclusions

- In male and female Sprague-Dawley rats, coadministration of RDEA594 and febuxostat did not alter the pharmacokinetics of each other.
- The pharmacokinetics and urinary excretion of allopurinol and oxypurinol were not affected by co-administration of RDEA594.
- The pharmacokinetics and urinary excretion of allopurinol and oxypurinol were significantly altered by co-administration of probenecid.
- Preclinical studies suggested RDEA594 has favorable safety properties, with minimal drug-drug interaction potential with xanthine oxidase inhibitors and no renal toxicity
- Because these favorable attributes and positive pharmacodynamic outcome from phase 2a study, RDEA594 is moving forward in development.

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