Poster # 28

RDEA594, a Potential Uric Acid Lowering Agent through Inhibition of Uric Acid Reuptake, Shows Better Pharmacokinetics than its Prodrug RDEA806.

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Abstract

Background: Significant reduction of serum uric acid was discovered in a multiple dose clinical study of RDEA806. The mode of action of has been determined to be associated with the inhibitory effect of RDEA594, a major metabolite of RDEA806, on uric acid re-absorption through the URAT1 renal transporter. *In vitro* and *in vivo* experiments have been conducted to evaluate the feasibility and dose range of administering RDEA594 in the clinical setting.

Method: RDEA594 was evaluated *in vivo* for metabolism profiling as well as *in vitro* P450 reaction phenotyping and drug-drug interaction potential. Exposure and urinary excretion of RDEA594 following RDEA594 dosing was compared to those obtained from RDEA806 dosing in the Sprague-Dawley rat and cynomolgus monkey following single dose. Safety evaluations were conducted following 14-day repeat dosing in monkeys and rats.

Results: RDEA594 was relatively stable following liver microsomal and hepatocytes incubation across species. Oxidation and reductive debromination metabolites were observed from *in vivo* metabolism studies in Sprague-Dawley rat and cynomolgus monkey. Drug-drug interaction potential of RDEA594 was predicted to be low as IC_{50} were all above 10 uM for five major P450 isoforms tested using HLM. RDEA594 was not extensively metabolized by any of the P450 isozyme tested. Following single dosing of RDEA594, exposure of RDEA594 was significantly higher than those obtained from RDEA806 dosing, > 5X at 20 mg/kg in rats and > 10X at 30 mg/kg in monkeys. In rat urine, significantly higher amount of RDEA594 (~6%) was excreted into urine following RDEA594 dosing compared to 0.7% following RDEA806 dosing. With no adverse effects noted in clinical conditions and macroscopic evaluation, RDEA594 was well tolerated in both rats and monkeys up to 100 mg/kg.

Conclusions: RDEA806, a prodrug of RDEA594, exhibited outstanding ability to reduce serum uric acid level at 300 and 500 mg BID (immediate release capsules) and 400 mg BID (modified release capsules) dosing regimens with 400 mg BID showing greatest uric acid reduction (47.9%). Pre-clinical studies show that RDEA594 was stable under *in vitro* evaluation and exhibited higher exposure following oral dosing in rats and monkeys than from dosing its prodrug RDEA806. In addition, approximately 10X of RDEA594 was recovered in urine following RDEA594 dosing in rat compared to RDEA806 dosing. These findings strongly suggest that a low dosage of RDEA594, can be anticipated in future clinical trials to produce similar uric acid reduction results. This dose level is significantly lower than the safety level established in the pre-clinical toxicology program

Introduction

Significant reduction of serum uric acid was discovered in a multiple dose clinical study of RDEA806. The mode of action has been determined to be associated with the inhibitory effect of RDEA594, a major metabolite of RDEA806, on uric acid re-absorption through the URAT1 renal transporter. *In vitro* and *in vivo* experiments have been conducted to evaluate the feasibility and dose range of administering RDEA594 in the clinical setting. Preliminary pharmacokinetics (PK) and pharmacodynamics (PD) data are available from ongoing phase I human single oral ascending dose to healthy volunteers.

Method

- *In vitro* metabolism stability evaluation and metabolism profiling using cryopreserved hepatocytes from multiple species
- Drug-drug interaction potential was evaluated in pooled human liver microsomes
- Pharmacokinetic and urinary excretion study following [^{14}C]RDEA594 oral and intravenous administration to Sprague-Dawley rats and cynomolgus monkeys
- Preliminary pharmacokinetics following single oral dose of RDEA594 to healthy volunteers
- Preliminary evaluation of pharmacodynamics (urinary uric acid excretion) following single oral dose of RDEA594to healthy volunteers

Results

Figure 1. Significant Serum Uric Acid Lowering Effect following Multiple Dosing of RDEA806

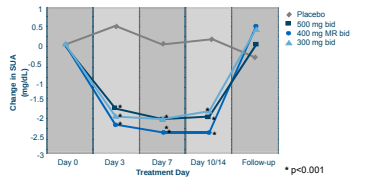
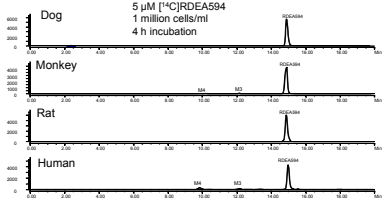


Figure 2. RDEA594 Exhibits Favorable Metabolic Stability *in vitro* (Cryopreserved Hepatocytes)



RDEA594 is stable in cryopreserved hepatocytes and only trace amounts of oxidation metabolites (M3, M4) were observed in monkey and human hepatocytes

Table 1. RDEA594 has low potential to cause P450 mediated drug-drug interactions at clinically relevant plasma concentrations in humans

Isozyme	CYP1A2	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4	
						Testosterone	Midazolam
IC_{50} (µM)	> 100	16.2 (4.15)	14.4 (2.07)	> 100	> 100	> 100	> 100

RDEA594 exhibits favorable P450 profile as multi-drug co-therapy is often used for gout patients.

Table 2. RDEA594 Exhibits Low Systemic Clearance in Animals following Intravenous Dosing

Species	Gender	Dose (mg/kg)	AUC_{last} (µg*hr/mL)	Vdss (L/kg)	CL	
					(L/hr/kg)	liver blood flow (%)
Rat	M	20	101	0.855	0.199	5.2
	F	20	115	0.502	0.178	4.6
Dog	M	10	78	0.360	0.130	7.0
Monkey	M	10	55	0.325	0.188	7.1

Table 3. RDEA594 Shows Good Absorption and Low Hepatic Extraction in Animals following Oral Dosing

Species	Gender	Dose (mg/kg)	AUC_{last} (µg*hr/mL)	AB (%)	F (%)	ER
Rat	M	20	74	80.8	73.1	0.095
	F	20	75	72.7	65.7	0.096
Dog	M	20	156	NA	100	0
Monkey	M	20	50	55.6	45.8	0.18

AB: absorption, F: bioavailability, ER: liver extraction ratio

Table 4. RDEA594 Exhibits Favorable Absorption and Low Clearance following Oral Dosing in Healthy Volunteers

Administrated		Pharmacokinetics of RDEA594 in Human					
			T_{max}	C_{max}	AUC_{last}	CL/F	$t_{1/2}$
Compound	mg		(hr)	(µg/mL)	(µg*hr/mL)	(L/h)	(hr)
RDEA806 (EC Tablet)	800	Mean	5.92	3.75	27.8	NA	10.7
		%CV	34.9	94.0	58.4	NA	35.5
RDEA594 (Liquid)	100	Mean	0.813	11.9	24.6	4.48	11.3
		%CV	102	43.6	30.4	60.2	40.8

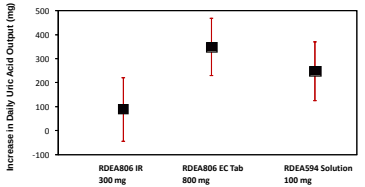
- RDEA594 exhibits low apparent clearance (CL/F) at approximately 5% of liver blood flow
- Exposure of RDEA594 after a single 100 mg dose approached the level observed with a single 800 mg dose of RDEA806
- Favorable $t_{1/2}$ indicates once a day dosing is likely
- A solid oral dosage formulation will be evaluated shortly with the goal of extending the T_{max}, and lowering the C_{max}, while maintaining the AUC

Table 5. Favorable Renal Excretion of RDEA594

Dose		Species	Gender	Route	Duration (hr)	Recovery of Dose (%)
Compound	(mg/kg)*					
RDEA594	20	Rat	M	PO	120	11.9 (64.5)
RDEA594	20	Rat	F	PO	120	36.3 (4.10)
RDEA594	20	Monkey	M	PO	120	33.0 (3.90)
RDEA594	**100**	**Human**	**M**	**PO**	**24**	**49.2 (25.3)**

* mg/subject dosing in human

Figure 3. Increase Urinary Uric Acid Excretion following Administration of 100 mg RDEA594 or RDEA806 to Healthy Volunteers



Conclusions

- RDEA806, a prodrug of RDEA594, exhibited outstanding ability to reduce serum uric acid level at 300 and 500 mg BID (immediate release capsules) and 400 mg BID (modified release capsules) dosing regimens with 400 mg BID showing greatest uric acid reduction (47.9%)
- Pre-clinical studies show that RDEA594 was metabolically stable *in vitro* and *in vivo* with low hepatic extraction, and a low potential for drug-drug interactions
- Preliminary pharmacokinetics of RDEA594 following a single 100 mg oral dose of a solution formulation in healthy volunteers shows rapid absorption, a low systemic clearance, and a long half-life
- The 100 mg dose of RDEA594 exhibited a pharmacological effect in the range of that produced by 300 mg to 800 mg single doses of RDEA806
- Higher single doses of RDEA594 are currently being explored, prior to moving into a 10-day multiple ascending dose study. A new solid oral dosage formulation will also be evaluated for future studies.
- The overall profile of RDEA594 looks very promising for the potential treatment of hyperuricemia and gout

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