

## Original article

## Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat in gout patients with hyperuricaemia

Roy Fleischmann<sup>1</sup>, Bradley Kerr<sup>2</sup>, Li-Tain Yeh<sup>3</sup>, Matt Suster<sup>4</sup>, Zancong Shen<sup>3</sup>, Elizabeth Polvent<sup>2</sup>, Vijay Hingorani<sup>2</sup>, Barry Quart<sup>4</sup>, Kimberly Manhard<sup>5</sup>, Jeffrey N. Miner<sup>6</sup> and Scott Baumgartner<sup>4</sup>, on behalf of the RDEA594-111 Study Group

## Abstract

**Objective.** The aim of this study was to evaluate the pharmacodynamics (PDs), pharmacokinetics (PKs) and safety of lesinurad (selective uric acid reabsorption inhibitor) in combination with febuxostat (xanthine oxidase inhibitor) in patients with gout.

**Methods.** This study was a phase IB, multicentre, open-label, multiple-dose study of gout patients with serum uric acid (sUA) >8 mg/dl following washout of urate-lowering therapy with colchicine flare prophylaxis. Febuxostat 40 or 80 mg/day was administered on days 1–21, lesinurad 400 mg/day was added on days 8–14 and then lesinurad was increased to 600 mg/day on days 15–21. sUA, urine uric acid and PK profiles were evaluated at the end of each week. Safety was assessed by adverse events, laboratory tests and physical examinations.

**Results.** Initial treatment with febuxostat 40 or 80 mg/day monotherapy resulted in 67% and 56% of subjects, respectively, achieving a sUA level <6 mg/dl. Febuxostat 40 or 80 mg/day plus lesinurad 400 or 600 mg/day resulted in 100% of subjects achieving sUA <6 mg/dl and up to 100% achieving sUA <5 mg/dl. No clinically relevant changes in the PKs of either drug were noted. The combination was well tolerated.

**Conclusion.** The clinically important targets of sUA <6 mg/dl and <5 mg/dl are achievable in 100% of patients when combining lesinurad and febuxostat.

**Key words:** lesinurad, febuxostat, drug–drug interaction, pharmacokinetic, pharmacodynamic, selective uric acid reabsorption inhibitor, xanthine oxidase inhibitor, gout.

## Introduction

Gout is an inflammatory arthritis that in most patients results from inefficient uric acid excretion. Hyperuricaemia

can lead to deposition of urate crystals in body tissues, including in and around joints, which can then lead to recurrent attacks of inflammatory arthritis and eventually chronic, progressive arthropathy and tophus formation [1]. Gout affects ~9 million people in Europe, 8.3 million in the USA and 3.25 million in Japan [2–5]. Chronic hyperuricaemia is also associated with metabolic syndrome and risk factors for cardiovascular disease [3, 6–9]. Non-pharmacological interventions rarely result in adequate urate lowering [10]. These interventions include weight reduction, reduction in alcohol consumption and dietary modifications.

Pharmacological management of gout includes treatment of the pain and inflammation associated with acute flares, prevention of acute gout flares and long-term

<sup>1</sup>Metroplex Clinical Research Center, Dallas, TX, <sup>2</sup>Ardea Biosciences and <sup>3</sup>Translational Sciences Department, <sup>4</sup>Clinical Department, <sup>5</sup>Regulatory Department and <sup>6</sup>Biology Department, Ardea Biosciences, San Diego, CA, USA.

Submitted 19 July 2013; revised version accepted 11 December 2013.

Correspondence to: Roy Fleischmann, Metroplex Clinical Research Center, 8144 Walnut Hill Lane, Suite 810, Dallas, TX 75231, USA. E-mail: rfleischmann@mcrcdallas.com

Roy Fleischmann, Bradley Kerr, Li-Tain Yeh, Matt Suster, Zancong Shen, Elizabeth Polvent, Vijay Hingorani, Barry Quart, Kimberly Manhard, Jeffrey N. Miner and Scott Baumgartner contributed equally to this study.

serum urate-lowering therapy (ULT) to lower serum uric acid (sUA) levels. Current guidelines for ULT in gout recommend target sUA levels  $<6$  mg/dl ( $360\text{ }\mu\text{mol/l}$ ) [4, 5] or  $<5$  mg/dl ( $300\text{ }\mu\text{mol/l}$ ) in some patients to improve signs and symptoms, including tophi [11–15].

Allopurinol, a xanthine oxidase inhibitor (XOI), is commonly used to lower sUA levels in the USA and the European Union. However, in multiple studies, some of which included up to 64% obese patients, ~60% of patients treated with the commonly used dose of allopurinol, 300 mg, failed to achieve sUA concentrations  $<6$  mg/dl [16–18]. Febuxostat, another XOI, is also approved for the treatment of gout. Approximately 21–53% of those receiving febuxostat therapy do not reach an sUA  $<6$  mg/dl [17, 18]. Clearly the medical need for additional treatment options for those patients who do not respond adequately to XOI monotherapy remains unmet [18, 19].

Since 90% of patients with hyperuricaemia inefficiently excrete uric acid, the addition of a uric acid reabsorption inhibitor to an XOI to increase renal excretion may facilitate better urate lowering in those patients not adequately treated with XOI therapy alone [20]. Probenecid and benzbromarone are uricosuric agents. Probenecid inhibits urate transporter 1 (URAT1), organic anion transporter 1 (OAT1), OAT3 and glucose transporter 9 (GLUT9), but has significant drug–drug interactions [21, 22]. Probenecid is administered two to four times per day and is contraindicated when the glomerular filtration rate (GFR) is less than  $\sim 50$  ml/min, a condition often present in patients with gout [23, 24]. Benzbromarone was withdrawn from many European markets in 2003 and has never been available in the USA because of the risk of fulminant hepatitis [25]. A clear unmet medical need exists for a new uric acid reabsorption inhibitor for the treatment of gout that can be used safely in combination with XOIs in patients not responding adequately to XOI therapy [26].

Lesinurad is a selective uric acid reabsorption inhibitor (SURI) that inhibits URAT1, thereby normalizing uric acid excretion and reducing sUA [22]. Lesinurad also inhibits OAT4, a URAT that is enhanced by diuretics (which are known to produce hyperuricaemia) [27]. In clinical studies, lesinurad did not inhibit OAT1 and OAT3, major renal transporters not specific to sUA [22]. Lesinurad is currently under clinical investigation as an add-on therapy to XOIs [22]. This study was designed to investigate the pharmacodynamics (PDs), pharmacokinetics (PKs) and safety of combining lesinurad, a SURI, with febuxostat, an XOI, in gout patients with hyperuricaemia.

## Methods

### Subjects

Prior to initiating the study, Mid\* Lands LLC Institutional Review Board and Independent Investigational Review Board Inc. reviewed and approved the study and consent form. Informed consent in accordance with the Declaration of Helsinki was obtained from participants. Eligible male or non-reproductive female subjects, who were otherwise relatively healthy, between the ages of

18 and 80 years, with a diagnosis of gout (per the American Rheumatism Association Criteria for the Classification of Acute Arthritis of Primary Gout) [28] and a screening sUA level of  $\geq 8$  mg/dl were screened to enrol in the study after signed informed consent was obtained. Eligible subjects had no clinically relevant abnormalities in blood pressure, heart rate, body temperature and respiratory rate. Exclusion criteria included consumption of  $>14$  U of alcohol/week, a history of drug abuse, kidney stones or malignancy within 5 years or a history or clinical manifestations of significant metabolic, haematological, pulmonary, cardiovascular (including a predisposition to a prolonged QT interval), gastrointestinal, neurological, hepatic, renal, infectious, HIV, inflammatory disease, urological or psychiatric disorders that were not well controlled. Additional exclusion criteria included peptic ulcer disease requiring active treatment, inadequate renal function (serum creatinine  $>1.5$  mg/dl or creatinine clearance  $<50$  ml/min), a history of xanthinuria or active liver disease, the use of other urate-lowering medication that they were unable to safely discontinue from 14 days prior to study start to 7 days after the last dose of study medication was administered, the use of naproxen that subjects were unable to discontinue from 7 days prior to study start to 7 days after the last dose of study medication was administered and the use of agents that could confound sUA analysis (e.g. long-term use of salicylates  $>100$  mg). Subjects who reported receiving a strong or moderate inhibitor of CYP3A4 or p-glycoprotein within 1 month prior to colchicine, had an acute gout flare during the screening period that had not resolved 1 week prior to the first dose of study medication, used an investigational drug within 30 days of the first dose of study medication or previously participated in a clinical study involving lesinurad or the prodrug of lesinurad were excluded. Also excluded were those with hypersensitivity or allergy to lesinurad, febuxostat or colchicine, those who had a BMI  $>40$  kg/m<sup>2</sup> or those who had any other medical or psychological condition that in the opinion of the investigator might have created undue risk to the subject or interfered with the subject's ability to comply with the protocol or complete the study.

### Experimental design

This phase 1B, open-label, multiple-dose study was designed to evaluate the PDs, PKs and safety of lesinurad in combination with febuxostat in patients with gout. The study was conducted at two study sites in the USA. Subjects were assigned sequentially to one of two groups: febuxostat 40 mg or 80 mg (Fig. 1). After 1 week of febuxostat alone, regardless of the sUA levels, lesinurad was added at a dose of 400 mg/day for 1 week and increased to a dose of 600 mg/day for another week.

Subjects were admitted to the clinical research unit on days  $-1$ , 7, 14 and 21 (or the afternoon/evening before) for serial PD and PK blood samples and 24-h urine collections and other scheduled assessments. Subjects returned to the clinical research unit each morning on days 2–6, 9–13 and 16–20 for study medication dosing.

Fig. 1 Study design

Day -21 to Day 0		Days 1-7		Days 8-14		Days 15-21		Days 22-28	
Colchicine Treatment 0.6 mg/day*									
Screening Period Day -21 to Day 0	Washout Period Day -14 to Day 0	Group 1	Febuxostat 40 mg/day X 7 days	Febuxostat 40 mg/day + Lesinurad 400 mg/day X 7 days		Febuxostat 40 mg/day + Lesinurad 600 mg/day X 7 days		Follow-Up Period	
		Group 2	Febuxostat 80 mg/day X 7 days	Febuxostat 80 mg/day + Lesinurad 400 mg/day X 7 days		Febuxostat 80 mg/day + Lesinurad 600 mg/day X 7 days			

\*Colchicine 0.6 mg/day was given as a prophylactic treatment for the prevention of gout flares from 14 days prior to the first dose of febuxostat [or 7 days prior to the first dose of febuxostat for subjects not washing out from urate-lowering therapy (ULT)] until 7 days after the last dose of febuxostat or the combination of febuxostat and lesinurad. Subjects who were intolerant of colchicine during the screening period were considered screen failures and were not enrolled.

Medication was administered each morning on days 1-21, ~30 min after finishing a standardized breakfast (~650 kcal and 35% fat). All subjects had a follow-up visit ~1 week after the last dose of study medication.

Serial PK plasma samples were collected at the following times on days -1, 7, 14 and 21: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h post-dose. Serial PD serum samples were collected at the following times on days -1, 7, 14 and 21: pre-dose, 6, 12 and 24 h post-dose. Urine (total catch) was collected over the intervals of 0-6, 6-12 and 12-24 h on days -1, 7, 14 and 21. Safety was assessed by adverse events, laboratory tests and physical examinations. During the study, subjects were questioned directly regarding the occurrence of any adverse medical event.

### Analytical methods

The analysis of lesinurad and febuxostat concentrations in plasma and lesinurad in urine was performed by Ardea Biosciences, San Diego, CA, USA. Plasma samples were prepared by protein precipitation and were quantified using HPLC with tandem mass spectrometric detection (LC-MS/MS). Urine samples were prepared by dilution and quantified using LC-MS/MS. The analysis of colchicine in plasma samples was performed by Anapharm, Quebec City, QC, Canada. Colchicine plasma samples underwent solid phase extraction and were quantified by LC-MS/MS.

### Data analysis

The PD parameters were determined by the Covance Clinical Research Unit (Madison, WI, USA) using SAS version 8.2 (SAS Institute, Cary, NC, USA). PD parameters for urate, xanthine and hypoxanthine in urine were determined. Percentage time-matched change from baseline (day -1) was assessed for sUA concentrations, urinary urate amounts and urate parameters. At each time point post-dose on each relevant day, the percentage change from baseline was calculated as follows: percentage change from baseline =  $[\text{urate}(\text{time } t) - \text{urate}(\text{time-matched day } -1)] / \text{urate}(\text{time-matched day } -1) \times 100$ . PD parameters estimated for urine urate included urate excretion, urate renal clearance, fractional excretion of urate (FEUA) and percentage changes in urine urate parameters from baseline (time-matched day -1). Urine urate concentrations obtained during the study were used to calculate undissociated 24-h urine uric acid (UUUA) concentrations at baseline, a measure that has been associated with increased risk of lithiasis [29]. The UUUA concentration was calculated as follows:  $\text{UUUA} = \text{TUUA} / [1 + 10^{(\text{pH} - \text{pKa})}]$  [30], where TUUA is the measured urine concentration of total urate, pH is the urine pH and pKa is defined as  $-\log_{10} K_a$ , where  $K_a$  is the acid dissociation constant of urate. For urate,  $\text{pKa} = 5.35$ . Both UUUA and TUUA are presented in milligrams per decilitre (mg/dl). PD parameters estimated for urine xanthine and hypoxanthine included the amounts recovered in urine.

Plasma PK parameters were derived using the validated program WinNonlin Professional, version 5.2 (Pharsight, Mountain View, CA, USA). The parameters from individual plasma concentration-time profiles of lesinurad, febuxostat and colchicine were determined using non-compartmental methods. Plasma PK parameters estimated for lesinurad, febuxostat and colchicine included the area under the plasma concentration time curve from time 0 to 24 h post-dose ( $\text{AUC}_{0-24}$ ) and the maximum observed plasma concentration ( $C_{\text{max}}$ ) after an oral dose on the steady-state day.

Plasma PK parameters were derived using the validated program WinNonlin Professional, version 5.2 (Pharsight, Mountain View, CA, USA). The parameters from individual plasma concentration-time profiles of lesinurad, febuxostat and colchicine were determined using non-compartmental methods. Plasma PK parameters estimated for lesinurad, febuxostat and colchicine included the area under the plasma concentration time curve from time 0 to 24 h post-dose ( $\text{AUC}_{0-24}$ ) and the maximum observed plasma concentration ( $C_{\text{max}}$ ) after an oral dose on the steady-state day.

## Results

### Study subjects

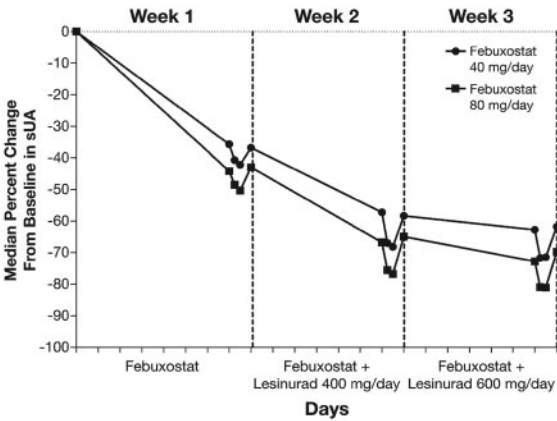
Twenty-one subjects were enrolled and 20 completed this study. One subject was withdrawn from the study following a positive drug screen for methamphetamine on day 14, after being assigned to group 1. The subject was not replaced. Table 1 summarizes the demographics and baseline characteristics of the subjects.

**TABLE 1** Subject demographics and baseline characteristics

Group	Sex, male/female, <i>n</i>	Age, mean (s.d.), years	Race, <sup>a</sup> <i>n</i>	BMI, mean (s.d.), kg/m <sup>2</sup>	Creatinine clearance, mean (s.d.), ml/min	sUA, median, mg/dl
1 ( <i>n</i> = 12) <sup>b</sup>	12/0	52 (14.3)	1/4/7	32.8 (5.8)	111.92 (29.11)	9.2
2 ( <i>n</i> = 9) <sup>c</sup>	9/0	43 (11.1)	0/3/6	32.1 (5.1)	126.22 (38.53)	10.4

<sup>a</sup>Number of Asian/black/white. <sup>b</sup>Group 1: febuxostat 40 mg/day × 7 days; febuxostat 40 mg/day + lesinurad 400 mg/day × 7 days; febuxostat 40 mg/day + lesinurad 600 mg/day. <sup>c</sup>Group 2: febuxostat 80 mg/day × 7 days; febuxostat 80 mg/day + lesinurad 400 mg/day × 7 days; febuxostat 80 mg/day + lesinurad 600 mg/day. sUA: serum uric acid.

**FIG. 2** Median percentage change in serum concentrations of urate



Colchicine 0.6 mg/day was given as a prophylactic treatment for the prevention of gout flares from 14 days prior to the first dose of febuxostat [or 7 days prior to the first dose of febuxostat for subjects not washing out from urate-lowering therapy (ULT)] until 7 days after the last dose of febuxostat or the combination of febuxostat and lesinurad.

Pharmacodynamics

Serum urate levels

The addition of lesinurad 400 or 600 mg/day to febuxostat in either group resulted in a greater decrease of the median and percentage change from baseline in serum concentrations of urate beyond that achieved with febuxostat 40 or 80 mg/day alone (Fig. 2 and Table 2). Statistical analysis determined the percentage change from baseline in sUA levels at the different post-dose time points in groups 1 and 2. The analysis confirmed that decreases in sUA levels were greater at all time points (at least *P* < 0.05) for both combination treatment groups compared with the single-agent febuxostat 40- and 80-mg/day treatment groups. Greater proportions of subjects receiving combination treatment achieved responses (sUA levels <6 mg/dl and <5 mg/dl) at 24 h post-dose compared with febuxostat alone, irrespective of dose (Table 3).

Urate clearance

Treatment with febuxostat 40 or 80 mg/day alone decreased FEUA in urine (over the 0- to 24-h interval) by ~21% and 26%, respectively. Combination treatment with lesinurad reversed this decrease. FEUA increased following 7 days of daily dosing with febuxostat 40 or 80 mg/day in combination with lesinurad 400 or 600 mg/day, with an 83–124% increase compared with baseline across all combination treatments. The increases in the FEUA were greater for the combination treatments (at both dose levels of lesinurad) compared with febuxostat alone (at both dose levels).

The 400- and 600-mg/day dose levels of lesinurad were equally effective at increasing the FEUA. The analysis showed no statistically significant differences in mean percentage change from baseline in the FEUA in urine when comparing the 400- and 600-mg/day dose levels of lesinurad in combination with either febuxostat 40 or 80 mg/day.

Mean urate renal clearance results were consistent with the FEUA results. Treatment with febuxostat 40 or 80 mg/day alone decreased urate renal clearance. Urate renal clearance (over the 0- to 24-h interval) increased following 7 days of daily dosing with febuxostat in combination with daily lesinurad 400 or 600 mg, with a 62–184% increase compared with baseline across all combination treatments. Greater increases in percentage changes of urate renal clearance were achieved with the combination treatments (at both dose levels of lesinurad) compared with febuxostat alone (at both dose levels). Measurements made at baseline, following febuxostat alone and following febuxostat in combination with lesinurad 400 and 600 mg/day showed that mean concentrations of UUUA did not rise above 10 mg/dl, below the threshold of concern for renal lithiasis (see supplementary Table S1, available at *Rheumatology* Online) [29].

Pharmacokinetics

Plasma PKs of lesinurad

When lesinurad at doses of 400 and 600 mg/day was co-administered with febuxostat 40 mg/day, the geometric mean lesinurad plasma *C*<sub>max</sub> values were 10.5 and 17.9 µg/ml (Fig. 3A) and the geometric mean lesinurad plasma AUC<sub>0–24</sub> values were 54.5 and 89.6 µg/h/ml, respectively. When lesinurad was co-administered with febuxostat 80 mg/day, the geometric mean lesinurad

TABLE 2 Serum urate levels

			Trough, median		12 h post-dose, median			
Group	sUA variable	Baseline	Febuxostat	Febuxostat + lesinurad 400 mg/day	Febuxostat + lesinurad 600 mg/day	Febuxostat	Febuxostat + lesinurad 400 mg/day	Febuxostat + lesinurad 600 mg/day
1 (n = 12) <sup>a</sup>								
		n = 12	n = 12	n = 12	n = 11	n = 12	n = 11	n = 11
	sUA levels, mg/dl	9.2	5.7	3.9	3.8	5.2	2.7	2.4
	Absolute reduction, mg/dl	—	−3.2	−5.4	−5.8	−3.9	−6.5	−6.8
	Percentage change	—	−35	−56	−61	−44	−68	−71
2 (n = 9) <sup>b</sup>								
		n = 9	n = 9	n = 9	n = 9	n = 9	n = 9	n = 9
	sUA levels, mg/dl	10.4	5.8	3.3	2.8	4.8	2.3	2.0
	Absolute reduction, mg/dl	—	−4.2	−6.7	−7.3	−5.1	−8.0	−8.4
	Percentage change	—	−47	−65	−73	−52	−78	−81

<sup>a</sup>Group 1: febuxostat 40 mg/day × 7 days; febuxostat 40 mg/day + lesinurad 400 mg/day × 7 days; febuxostat 40 mg/day + lesinurad 600 mg/day. <sup>b</sup>Group 2: febuxostat 80 mg/day × 7 days; febuxostat 80 mg/day + lesinurad 400 mg/day × 7 days; febuxostat 80 mg/day + lesinurad 600 mg/day. sUA: serum uric acid.

TABLE 3 Serum response rates

sUA	Time point	Group 1 <sup>a</sup> (n = 12)			Group 2 <sup>b</sup> (n = 9)		
		Febuxostat 40 mg/day			Febuxostat 80 mg/day		
		Febuxostat, %	Febuxostat + lesinurad 400 mg/day, %	Febuxostat + lesinurad 600 mg/day, %	Febuxostat, %	Febuxostat + lesinurad 400 mg/day, %	Febuxostat + lesinurad 600 mg/day, %
<6 mg/dl	Pre-dose	67	100	100	56	100	
	6 h	92	100	100	100	100	100
	24 h	67	100	100	56	100	100
<5 mg/dl	Pre-dose	17	75	100	22	100	
	6 h	42	100	100	33	100	100
	24 h	33	82	100	33	100	100

<sup>a</sup>Group 1: febuxostat 40 mg/day × 7 days; febuxostat 40 mg/day + lesinurad 400 mg/day × 7 days; febuxostat 40 mg/day + lesinurad 600 mg/day. <sup>b</sup>Group 2: febuxostat 80 mg/day × 7 days; febuxostat 80 mg/day + lesinurad 400 mg/day × 7 days; febuxostat 80 mg/day + lesinurad 600 mg/day. sUA: serum uric acid.

plasma  $C_{\max}$  values were 10.9 and 16.4 µg/ml (Fig. 3B) and the geometric mean lesinurad plasma  $AUC_{0-24}$  values were 55.1 and 78.2 µg/h/ml at lesinurad 400- and 600-mg/day dose levels, respectively.

As expected, the above results showed that lesinurad peak ( $C_{\max}$ ) and total ( $AUC_{0-24}$ ) plasma exposure measures increased dependently for the two evaluated lesinurad dose levels (400 and 600 mg/day). Lesinurad plasma exposure was not dependent on the dose of febuxostat.

#### Plasma PKs of febuxostat

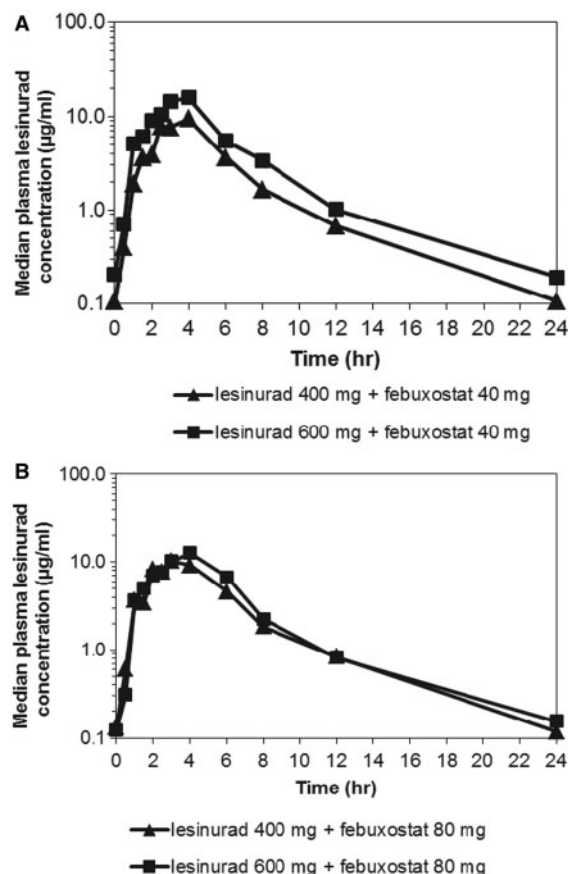
When febuxostat 40 mg/day was administered alone, the geometric mean febuxostat plasma  $C_{\max}$  was 0.65 µg/ml. When febuxostat 40 mg/day was given together with lesinurad 400 mg or 600 mg/day, the geometric mean of febuxostat plasma  $C_{\max}$  was 0.73 and 0.87 µg/ml, respectively [see supplementary Fig. S1(A), available at *Rheumatology* Online]. The geometric mean febuxostat plasma  $AUC_{0-24}$  values were 3.26 µg/h/ml for febuxostat

alone and 3.57 µg/h/ml for lesinurad 400 mg/day and 3.98 µg/h/ml for lesinurad 600 mg/day.

When febuxostat 80 mg/day was administered alone, the geometric mean febuxostat plasma  $C_{\max}$  was 1.68 µg/ml. When febuxostat 80 mg/day was given together with lesinurad 400 mg/day or with lesinurad 600 mg/day, the geometric means of febuxostat plasma  $C_{\max}$  were 1.90 µg/ml and 1.98 µg/ml, respectively [see supplementary Fig. S1(B), available at *Rheumatology* Online]. The geometric mean febuxostat plasma  $AUC_{0-24}$  values were 8.42 µg/h/ml for febuxostat alone, 10.0 µg/h/ml for lesinurad 400 mg/day and 10.2 µg/h/ml for lesinurad 600 mg/day.

As expected, the above results indicate that the febuxostat peak ( $C_{\max}$ ) and total ( $AUC_{0-24}$ ) plasma exposure measures increased dose dependently for the two evaluated febuxostat alone dose levels [40 mg/day (group 1) and 80 mg/day (group 2)]. The results also showed that co-administration of lesinurad (at either the 400- or 600-mg/day dose levels) with febuxostat (40 or 80 mg/day) did



**Fig. 3** Plasma pharmacokinetics of lesinurad

(A) Lesinurad 400 mg or 600 mg in combination with febuxostat 40 mg. (B) Lesinurad 400 mg or 600 mg in combination with febuxostat 80 mg.

not produce clinically meaningful increases in febuxostat plasma exposure measures.

#### Colchicine PKs

The colchicine peak ( $C_{max}$ ) and total ( $AUC_{0-24}$ ) plasma exposure measures were unaffected by febuxostat co-administration, but were modestly decreased by lesinurad co-administration (~20% and ~30–35% with lesinurad 400 and 600 mg/day, respectively). The decreased colchicine exposures are consistent with *in vitro* induction of CYP3A4 by lesinurad (data not shown).

#### Safety

A total of 12 treatment emergent adverse events (TEAEs) were reported in group 1 and 15 in group 2. The most frequently reported TEAEs were headache and gout flare (see supplementary Table S2, available at *Rheumatology* Online). Headache was reported in four subjects in each group. Gout flare occurred in three subjects in group 1 and five subjects in group 2. Dyspepsia was reported in one subject in group 1 and two subjects in group 2. No serious AEs occurred and no subjects discontinued secondary to an AE.

A total of 12 subjects (seven in group 1 and five in group 2) had at least one asymptomatic creatinine kinase (CK) elevation above the reference range (>195 IU/l), with a range of 197–686 IU/l. In eight subjects the elevations were present at screening and/or baseline prior to receiving febuxostat or lesinurad. The remaining four subjects (three in group 1 and one in group 2) experienced elevations during study treatment (one subject in group 1 had an elevation during febuxostat monotherapy and an elevation during combination therapy; three subjects had an elevation during combination treatment only). All subjects received colchicine for 1–2 weeks prior to febuxostat administration and throughout the trial.

No other treatment-related changes in clinical laboratory evaluations occurred, with the exception of decreases in sUA concentrations. No clinically significant findings and no treatment-related trends emerged in vital signs and physical examinations performed during the study.

## Discussion

In this study, once daily administration of lesinurad 400 and 600 mg in combination with either 40 or 80 mg/day doses of febuxostat achieved sUA-lowering effects that were significantly more pronounced than either dose of single-agent febuxostat in gout patients with high baseline sUA levels ( $\geq 8$  mg/dl). These data are consistent with other studies in which combination treatment with allopurinol and benzbromarone was more effective at lowering sUA levels than allopurinol alone [20, 31, 32].

The goal for long-term ULT is to keep sUA levels <6 mg/dl (360 µmol/l) [4] or <5 mg/dl (300 µmol/l) in patients to improve signs and symptoms, including tophi [11–15]. Febuxostat 40 or 80 mg/day in combination with lesinurad 400 or 600 mg/day resulted in up to 100% of subjects achieving sUA levels of 5 mg/dl, which was a higher response rate than with febuxostat monotherapy at either dose. These results are potentially clinically significant and could translate into improved outcomes for patients, especially those with tophaceous gout, in whom the lower the sUA levels achieved, the faster the reduction in tophaceous deposits [20].

Lesinurad significantly increased urate renal clearance and fractional excretion values when administered in combination with febuxostat. This increase is consistent with the mechanism of action of lesinurad (i.e. SUR1 increasing the excretion of urate). Surprisingly, modest decreases in FEUA and urate renal clearance were observed during treatment with febuxostat alone.

Only small, clinically insignificant increases in febuxostat plasma concentrations were noted in combination with lesinurad at either 400 or 600 mg/day, similar to the known and clinically unimportant effect of naproxen on febuxostat [33]. The small increase in febuxostat plasma exposure in the presence of lesinurad did not appear dependent on febuxostat dose, and increasing the febuxostat dose did not discernibly alter lesinurad plasma concentrations.

Colchicine plasma levels were unaffected by febuxostat, but were reduced by lesinurad treatment. The effect of lesinurad on colchicine exposure was dependent on the lesinurad dose level. Less change in colchicine exposure occurred at the lower 400-mg/day dose (colchicine AUC<sub>0-24</sub> decreased by ~20%) than at the higher 600-mg/day dose (colchicine AUC<sub>0-24</sub> decreased by ~30–35%). The effect of lesinurad on colchicine is consistent with weak CYP3A4 induction by lesinurad. The induction effect of lesinurad slightly decreases colchicine plasma concentrations and is therefore unlikely to exacerbate colchicine toxicity.

Multiple once-daily oral doses of lesinurad 400 or 600 mg were well tolerated when administered in combination with febuxostat 40 or 80 mg/day. No serious AEs occurred, no subjects were discontinued from the study due to AEs and there were no deaths. Asymptomatic CK elevations were seen in greater frequency at screening or baseline than during study treatment. All subjects were on colchicine and a few subjects were also on a statin; both drugs are known to increase CK levels. It is possible that the CK elevations were the result of use of these medications [34, 35]. In muscle toxicity studies conducted by Ardea Biosciences, lesinurad has not been shown to be toxic to myocytes, in contrast to statins and colchicine (data on file, Ardea Biosciences, San Diego, CA, USA).

Since 90% of patients with gout have inefficient renal excretion of uric acid, treating these patients with uric acid reabsorption inhibitors is consistent with a direct effect on the defect in these patients, thereby addressing an underlying cause of gout. The use of existing uricosuric agents (e.g. probenecid and benzbromarone) has been complicated by the limitation to subjects with a GFR of >50 ml/min and by an increased risk of kidney stones given the relative insolubility of uric acid in the acidic milieu of the urine. An analysis was conducted on urine urate concentrations obtained during the study to assess UUUA concentrations. Consistent with the mechanism of action of lesinurad, urate renal clearance and fractional excretion values were significantly increased by lesinurad administered in combination with febuxostat. These changes did not result in mean concentrations of UUUA >10 mg/dl level, suggesting little to no increased risk of urate stone formation with the combinations studied [29].

Both the 400- and 600-mg/day doses of lesinurad dosed with either febuxostat 40 or 80 mg/day demonstrated substantial reductions in sUA levels. In addition, both doses were generally well tolerated in this study. Since the 400-mg dose had similar sUA-lowering effects compared with the 600-mg dose, the 400-mg dose was selected as the highest dose for the phase 3 studies.

A limitation of the study was that neither the investigators nor the patients were blinded. However, as this study had laboratory-measured PD outcomes (e.g. sUA), this limitation should not have had an effect on the outcomes presented.

The results of this study suggest that lesinurad, a SUR1, combined with the XO1 febuxostat may be effective in treating patients with gout who have not responded to

XOIs alone and in treating those with tophaceous gout for whom sUA levels <5 mg/dl are recommended.

#### Rheumatology key messages

- Gout patients receiving xanthine oxidase inhibitor monotherapy do not consistently reach recommended serum uric acid (sUA) levels (<6 mg/dl or <5 mg/dl).
- All gout patients (100%) receiving lesinurad and febuxostat combination treatment achieved an sUA of <5 mg/dl.
- Combined administration of lesinurad and febuxostat did not result in any clinically meaningful pharmacokinetic effects in gout patients.

## Acknowledgements

The authors would like to thank the subjects and their families who participated in this study. The authors would also like to thank the investigator who participated in this study (Bradley Vince, DO, Vince and Associates Clinical Research, Overland Park, KS, USA). The authors would like to acknowledge the technical writing contributions of Starr L. Grundy, B.Sc.Pharm., of SD Scientific, and copyediting provided by Mary Ann McAdams of SCI Scientific Communications & Information, funded by Ardea Biosciences, USA, a wholly owned subsidiary of AstraZeneca.

**Funding:** This work was supported by Ardea Biosciences, San Diego, CA, USA, a wholly owned subsidiary of AstraZeneca.

**Disclosure statement:** J.N.M. is an employee of Ardea Biosciences. V.H. is a paid consultant of Ardea Biosciences. B.Q. was an employee of Ardea Biosciences at the time the manuscript was written. R.F. has received study grants from Ardea Biosciences. K.M. is an employee of Ardea Biosciences. L-T.Y. is an employee of Ardea Biosciences. Z.S. is an employee of Ardea Biosciences. E.P. is paid consultant of Ardea Biosciences. B.K. is a paid consultant of Ardea Biosciences. S.B. is an employee of Ardea Biosciences and holds AstraZeneca stock. M.S. is an employee of Ardea Biosciences.

## Supplementary data

Supplementary data are available at *Rheumatology Online*.

## References

- 1 Bieber JD, Terkeltaub RA. Gout: on the brink of novel therapeutic options for an ancient disease. *Arthritis Rheum* 2004;50:2400–14.
- 2 Gout: Novel biologics rev up a slow market. Burlington, MA: Decision Resources, 2010.

- 3 de Oliveira EP, Burini RC. High plasma uric acid concentration: causes and consequences. *Diabetol Metab Syndr* 2012;4:12.
- 4 Zhang W, Doherty M, Bardin T *et al.* EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006; 65:1312–24.
- 5 Zhang W, Doherty M, Pascual E *et al.* EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2006;65:1301–11.
- 6 Kim SY, Guevara JP, Kim KM *et al.* Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum* 2009;61:885–92.
- 7 Richette P, Bardin T. Gout. *Lancet* 2010;375:318–28.
- 8 Roddy E, Doherty M. Epidemiology of gout. *Arthritis Res Ther* 2010;12:223.
- 9 Ruggiero C, Cherubini A, Ble A *et al.* Uric acid and inflammatory markers. *Eur Heart J* 2006;27:1174–81.
- 10 Jordan KM, Cameron JS, Snaith M *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology* 2007;46:1372–4.
- 11 Emmerson BT. The management of gout. *N Engl J Med* 1996;334:445–51.
- 12 Perez-Ruiz F, Liote F. Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? *Arthritis Rheum* 2007;57:1324–8.
- 13 Edwards NL. Treatment-failure gout: a moving target. *Arthritis Rheum* 2008;58:2587–90.
- 14 Darmawan J, Rasker JJ, Nuralim H. The effect of control and self-medication of chronic gout in a developing country. Outcome after 10 years. *J Rheumatol* 2003;30: 2437–43.
- 15 Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. *Arthritis Rheum* 2004;51:321–5.
- 16 Pandya BJ, Riedel AA, Swindle JP *et al.* Relationship between physician specialty and allopurinol prescribing patterns: a study of patients with gout in managed care settings. *Curr Med Res Opin* 2011;27:737–44.
- 17 Becker MA, Schumacher HR Jr, Wortmann RL *et al.* Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005;353: 2450–61.
- 18 Becker MA, Schumacher HR, Espinoza LR *et al.* The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther* 2010;12:R63.
- 19 Uloric [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, 2013.
- 20 Perez-Ruiz F, Calabozo M, Pijoan JI *et al.* Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum* 2002;47:356–60.
- 21 Burns CM, Wortmann RL. Gout therapeutics: new drugs for an old disease. *Lancet* 2011;377:165–77.
- 22 Yeh L, Shen Z, Kerr B. RDEA594: a potent URAT1 inhibitor without affecting other important renal transporters, OAT1 and OAT 3 [abstract]. *Ann Rheum Dis* 2009;68:320.
- 23 Stamp LK, Jordan S. The challenges of gout management in the elderly. *Drugs Aging* 2011;28:591–603.
- 24 Sarawate CA, Brewer KK, Yang W *et al.* Gout medication treatment patterns and adherence to standards of care from a managed care perspective. *Mayo Clin Proc* 2006; 81:925–34.
- 25 Jansen TL, Reinders MK, van Roon EN *et al.* Benzbromarone withdrawn from the European market: another case of “absence of evidence is evidence of absence”? *Clin Exp Rheumatol* 2004;22:651.
- 26 Pandya BJ, Riedel AA, Becker LK *et al.* Renal impairment and poor outcomes of allopurinol therapy in US gout patients [abstract]. *Arthritis Rheum* 2009;60:702.
- 27 Tan PK, Hyndman D, Liu S *et al.* Lesinurad (RDEA594), a novel investigational uricosuric agent for hyperuricemia and gout, blocks transport of uric acid induced by hydrochlorothiazide [abstract]. *Ann Rheum Dis* 2011; 70:187.
- 28 Wallace SL, Robinson H, Masi AT *et al.* Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum* 1977;20:895–900.
- 29 Asplin JR. Uric acid stones. *Semin Nephrol* 1996;16: 412–24.
- 30 Hess B. Prophylaxis of uric acid and cystine stones. *Urol Res* 1990;18(Suppl 1):S41–4.
- 31 Mertz DP, Eichhorn R. Does benzbromarone in therapeutic doses raise renal excretion of oxipurinol? *Klin Wochenschr* 1984;62:1170–2.
- 32 Muller FO, Schall R, Groenewoud G *et al.* The effect of benzbromarone on allopurinol/oxypurinol kinetics in patients with gout. *Eur J Clin Pharmacol* 1993;44:69–72.
- 33 Khosravan R, Grabowski BA, Wu JT *et al.* Pharmacokinetics, pharmacodynamics and safety of febuxostat, a non-purine selective inhibitor of xanthine oxidase, in a dose escalation study in healthy subjects. *Clin Pharmacokinet* 2006;45:821–41.
- 34 Ly J, Gow P, Dalbeth N. Colchicine prescribing and safety monitoring in patients with gout. *N Z Med J* 2007;120: U2808.
- 35 Galtier F, Mura T, Raynaud de ME *et al.* Effect of a high dose of simvastatin on muscle mitochondrial metabolism and calcium signaling in healthy volunteers. *Toxicol Appl Pharmacol* 2012;263:281–6.