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Pharmacokinetics, Pharmacodynamics, and Tolerability of Concomitant Administration of Verinurad and Febuxostat in Healthy Male Volunteers

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Abstract

Verinurad (RDEA3170) is a selective uric acid reabsorption inhibitor in development for treatment of gout and asymptomatic hyperuricemia. This phase 1, single-blind, multiple-dose, drug-drug interaction study evaluated the pharmacokinetics (PK), pharmacodynamics, and safety/tolerability of verinurad in combination with febuxostat in healthy male volunteers. Twenty-three subjects were randomized and received once-daily doses of verinurad (or placebo) or febuxostat alone (days 1-7 and days 15-21), or verinurad + febuxostat on days 8-14. For combinations, subjects received verinurad 10 mg + febuxostat 40 mg or verinurad 2.5 mg + febuxostat 80 mg. Plasma/serum and urine samples were analyzed for verinurad, febuxostat, and uric acid. Safety was assessed by adverse events and laboratory tests. Febuxostat 40 mg had no effect on plasma exposure of verinurad 10 mg, whereas febuxostat 80 mg increased the maximum observed plasma concentration and the area under the plasma concentration-time curve of verinurad 2.5 mg by 25% and 33%, respectively. Verinurad had no effect on febuxostat PK. Maximal reduction in serum urate was 76% with verinurad 10 mg + febuxostat 40 mg versus verinurad 10 mg (56%) or febuxostat 40 mg (49%) alone and was 67% with verinurad 2.5 mg + febuxostat 80 mg versus verinurad 2.5 mg (38%) or febuxostat 80 mg (57%) alone. Verinurad increased, whereas febuxostat decreased, 24-hour fractional excretion and renal clearance of uric acid. There was no clinically significant drug-drug interaction between verinurad and febuxostat PK. The combination resulted in greater reductions of serum urate than either drug alone and was well tolerated at the studied doses.

Keywords

pharmacokinetics, pharmacodynamics, gout, verinurad, febuxostat

Gout is a common, chronic, progressive inflammatory arthritis characterized by the deposition of monosodium urate crystals in musculoskeletal structures (eg, joints), kidneys, and connective tissues, resulting from high concentrations of serum urate (sUA).[1] The condition, and its inadequate management, is associated with poor quality of life, increased burden on health-care systems, and increased risk of all-cause death and cardiovascular mortality.[2–6]

For long-term management of gout, maintenance of sUA levels below 6.0 mg/dL (or below 5.0 mg/dL for more severe disease) with urate-lowering therapy (ULT) is recommended.[7] The recommended first line of therapy to lower sUA is a xanthine oxidase inhibitor (XOI), allopurinol or febuxostat, which reduces the production of urate.[7–9] A considerable proportion of patients fail to attain target sUA levels or they report side effects with XOI therapy that can lead to treatment discontinuation or low treatment compliance.[10–13]

If desired sUA levels cannot be reached or maintained with an XOI at a medically approved dose,

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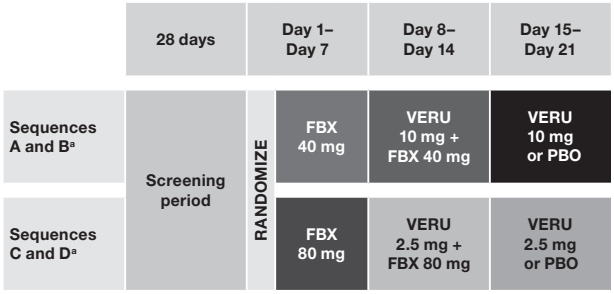

Figure 1. Study design. FBX, febuxostat; PBO, placebo; VERU, verinurad.
[a]Sequence B is the reverse of sequence A and sequence D is the reverse of sequence C.

treatment guidelines recommend combination therapy with an XOI and a uric acid reabsorption inhibitor.[7–9] The uricosurics probenecid, benzbromarone, sulfinpyrazone, and lesinurad increase renal excretion of uric acid by inhibiting its reabsorption.[14] Lesinurad, a selective uric acid reabsorption inhibitor, was recently approved in the United States and Europe in combination with an XOI for the treatment of hyperuricemia associated with gout in patients who fail to achieve target sUA levels on an XOI alone. Lesinurad inhibits the uric acid transporter URAT1, which is responsible for most of the reabsorption of urate from the renal tubule.[15,16] In the lesinurad phase 3 clinical development program, treatment with lesinurad 200 mg and 400 mg in combination with febuxostat 80 mg in tophaceous gout resulted in more patients achieving target sUA levels and experiencing reduction in overall tophus area compared with febuxostat 80 mg alone.[17] However, this treatment combination showed only a trend toward reduction in gout flares at the 400-mg dose, a dosage level with more renal side effects compared with lesinurad 200 mg + febuxostat and with febuxostat alone, and was neither submitted to nor approved by US or European regulatory agencies.

Verinurad, a selective URAT1 inhibitor in clinical development as combination therapy with an XOI, demonstrated high potency in inhibiting URAT1.[18] It has also shown significant sUA lowering at doses as low as 2.5 mg in humans.[19] The aim of this phase 1 study was to evaluate the potential pharmacokinetic (PK) and pharmacodynamic (PD) interactions between verinurad and febuxostat in healthy adult male subjects.

The human metabolism of verinurad involves 2 pathways mediated by uridine diphosphate glucuronosyltransferase (UGT) and cytochrome P450 3A4 (CYP3A4). Several UGTs (1A3, 2B4, 2B7, and 2B17) glucuronidate verinurad to form acyl glucuronide M1, while CYP3A4 is involved in the formation of an N-oxide. Two acyl glucuronide metabolites, M1 and an acyl N-oxide M8, circulate equimolar to verinurad in blood but are devoid of URAT1 activity. The formation of M8 occurs via sequential glucuronidation of M4 to M8 or by oxidation of M1 to M8 via CYP2C8.[20] The drug-drug interaction (DDI) potential of verinurad is low, as it does not inhibit the major CYPs (Ardea Biosciences, Inc., data on file). The DDI potential of verinurad as a victim is also low, as its disposition involves several metabolic enzymes.

Febuxostat is extensively metabolized by UGTs (1A1, 1A3, 1A9, and 2B7), CYPs (1A2, 2C8, and 2C9), and non-P450 enzymes.[21,22] As a consequence, the DDI potential of febuxostat as a victim is also low. However, CYP2C8 inhibition by febuxostat was demonstrated in an in vitro human liver microsomal study with inhibition constant (Ki) = 20 mM, and the potential for a clinical DDI with CYP2C8 is likely given a calculated [I]/Ki ratio of 0.47.[23] While the disposition of the verinurad metabolite M1 to M8 involves CYP2C8, febuxostat is not expected to alter the disposition of verinurad, as this CYP isoform is not involved in the primary branch of febuxostat metabolism.

Methods

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and with institutional review board (Welwyn Clinical Pharmacology Ethics Committee, Hatfield, UK) approval. Written informed consent was obtained from all subjects before starting the study.

Subjects

Prior to initiation of the trial, the Institutional Review Board (IntegReview IRB, Austin, Texas) reviewed and approved the study design and consent form. Informed consent in accordance with the Declaration of Helsinki was obtained from all participants. Healthy male subjects, aged ≥18 and ≤65 years, with a body weight ≥50 kg, a body mass index ≥18 and ≤40 kg/m^2, and sUA level ≥4.5 mg/dL, were screened for enrollment. Eligible subjects had no clinically relevant abnormalities in blood pressure, heart rate, body temperature, or respiratory rate. Exclusion criteria included a history or suspicion of kidney stones and an estimated creatinine clearance <90 mL/min calculated by the Cockcroft-Gault formula using ideal body weight.

Study Design

This was a phase 1, single-blind, multiple-dose, DDI study (RDEA3170-105; NCT01883167) conducted at the Jasper Clinic (Kalamazoo, Michigan). Subjects were admitted to the study site on day −2 and remained a resident until completion of PK/PD sample collection 24 hours after the last dose of study medication on day 22. Subjects returned for follow-up assessments on day 28 ± 1 day. Subjects were enrolled in 1 of 2 panels and

were randomly assigned to 1 of 2 treatment sequences in each panel (sequence A or B or sequence C or D) in a 1:1 ratio (Figure 1). Participants received once-daily doses of verinurad (or placebo) or febuxostat alone (days 1-7 and days 15-21), or verinurad + febuxostat on days 8-14. For combinations, subjects received verinurad 10 mg + febuxostat 40 mg (panel 1) or verinurad 2.5 mg + febuxostat 80 mg (panel 2). Within each treatment sequence, 6 subjects were randomized to receive either verinurad (n = 5) or placebo (n = 1). Study medication was administered orally with approximately 240 mL of water, 30-35 minutes after the initiation of a standardized moderate fat (approximately 30%-40% of calories) and calorie (approximately 642-800 calories) breakfast. Additional food was not allowed for 4 hours following treatment; water was allowed as desired, except for 1 hour before and after treatment.

Serial plasma PK samples were collected 30 minutes predose and up to 24 hours postdose on days 7, 14, and 21. Serial serum PD samples were collected on day −1, and on days 1, 7, 14, and 21 at predose and up to 24 hours postdose. Urine samples (total catch) for PK/PD were collected at the study site prior to dosing on day −1 from −24 to −18, −18 to −12, and −12 to 0 hours and postdose on days 7, 14, and 21 from 0 to 6, 6 to 12, and 12 to 24 hours. Safety/tolerability (adverse events [AEs], clinical laboratory tests, vital signs, electrocardiograms, and physical examinations) was assessed throughout the study.

Analytical Methods

The analysis of verinurad and febuxostat was performed by Ardea Biosciences, Inc. (San Diego, California). The quantitative determination of verinurad has been reported previously (24). Briefly, human plasma samples were extracted by protein precipitation with acetonitrile containing [$^2H_6$]RDEA3170 as internal standard. The supernatant was diluted with water and analyzed by high-performance liquid chromatography with tandem mass spectrometry (LC/MS/MS). Analytes were chromatographically separated by gradient high performance liquid chromatography at a flow rate of 0.9 mL/min using a Zorbax-SB-C18 4.6 × 50 mm, 3.5-μm pore column (Agilent Technologies, Santa Clara, California) and introduced into an API 5000 (plasma samples) or API 4000 (urine samples) triple quadrupole mass spectrometer (Sciex, Framingham, Massachusetts) where the mobile phase A was 0.1% formic acid in water and mobile phase B was 0.1% formic acid in acetonitrile. The chromatographic effluent was positively ionized using the positive TurboIonSpray (Sciex) mode to monitor the precursor → product ion transitions of m/z 349 → 263 and m/z 355 → 264 for verinurad and [$^2H_6$]RDEA3170, respectively. The calibration curves were linear over the concentration range between 0.100 ng/mL and 40.0 ng/mL with a lower limit of quantitation (LLOQ) of 0.100 ng/mL. A similar method was used to quantify human urine verinurad. The calibration curves were linear over the concentration range between 2.00 ng/mL and 1000 ng/mL with an LLOQ of 2.00 ng/mL.

The same method was used for quantitative determination of febuxostat. Human plasma samples were extracted by protein precipitation with acetonitrile containing [$^2H_7$]febuxostat as internal standard. The supernatant was diluted with injection solvent and analyzed by LC/MS/MS. An API 4000 triple quadrupole mass spectrometer, operated in positive TurboIonSpray mode, was used to monitor the precursor → product ion transitions of m/z 317 → 261 and m/z 324 → 262 for febuxostat and [$^2H_7$]febuxostat, respectively. The calibration curves were linear over the concentration range between 2.00 ng/mL and 1000 ng/mL with an LLOQ of 2.00 ng/mL.

Serum samples were analyzed for sUA and creatinine and urine samples for uric acid and creatinine by Covance Central Laboratory Services (Indianapolis, Indiana).

PK/PD Analyses

Pharmacokinetic parameters were calculated using Phoenix WinNonlin, Version 6.3 (Pharsight Corporation, Mountain View, California). Plasma PK parameters included time to maximum plasma concentration (T_{max}), maximum observed plasma concentration (C_{max}), and area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24}$). Urine PK parameters included the cumulative amount of drug excreted unchanged ($Ae_{0\text{-}24}$), the fraction of drug excreted unchanged ($fe_{0\text{-}24}$), and renal clearance ($CL_{R0\text{-}24}$) from time 0 to 24 hours postdose. PD parameters included percentage change from baseline sUA, fractional excretion of uric acid (FEUA), amount of uric acid recovered in urine (Ae_{UR}), and renal clearance of uric acid (CL_{UR}). Baseline sUA was calculated as the average of all sUA values obtained on day −1. Both baseline sUA and the maximum observed percentage change from baseline in sUA were determined for each subject in each treatment group and the mean values calculated for all subjects in each treatment group. Ae_{UR} was calculated as the urine concentration of uric acid multiplied by the urine volume. CL_{UR} was obtained from Ae_{UR} divided by serum urate AUC over the same time interval, while CL_{UR} divided by creatinine clearance (CrCl) × 100 yielded FEUA. CrCl was obtained from the amount of creatinine recovered in urine divided by the serum creatinine AUC over the same time interval.

A mixed-effects model with fixed effect for treatment and subject as random effect was used to

Table 1. Demographic Characteristics of Subjects

	Panel 1 Total (n = 11)	Panel 2 Total (n = 12)	Total (n = 23)
Mean age, y (SD)	36.0 (9.0)	31.0 (7.9)	33.0 (8.6)
Mean body weight, kg (SD)	87.8 (14.4)	87.8 (14.4)	87.8 (14.3)
Mean BMI, kg/m^2 (SD)	28.4 (5.1)	28.0 (4.7)	28.2 (4.8)
Race, n (%)			
American Indian or Alaska Native	0	1 (8.3)	1 (4.3)
Black	3 (27.3)	4 (33.3)	7 (30.4)
White	8 (72.7)	7 (58.3)	15 (65.2)
Ethnicity, n (%)			
Hispanic or Latino	1 (9.1)	2 (16.7)	3 (13.0)
Not Hispanic or Latino	10 (90.9)	10 (83.3)	20 (87.0)

BMI, body mass index; SD, standard deviation.

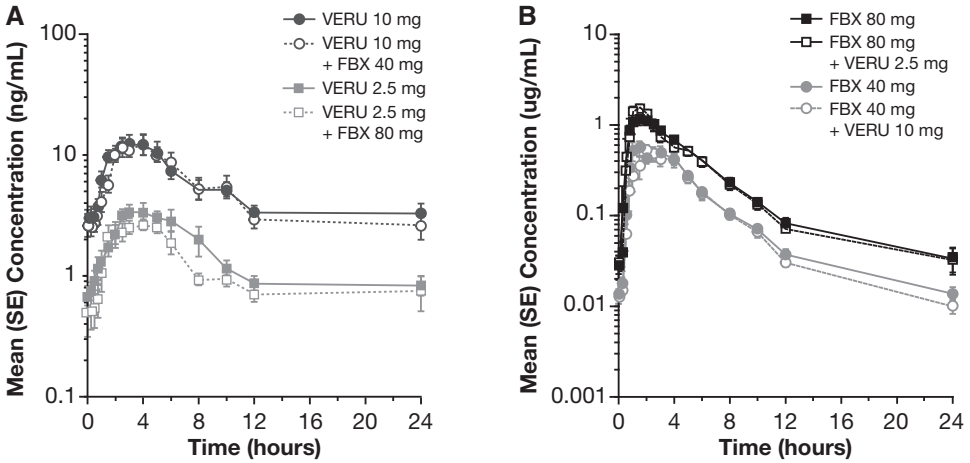

Figure 2. Arithmetic mean (SE) verinurad ([A] VERU, 10 mg or 2.5 mg); febuxostat ([B] FBX, 40 mg or 80 mg;) plasma concentration-time profiles following once-daily oral administration alone or in combination.

assess the potential DDIs between verinurad and febuxostat. The natural log-transformed PK parameters C_{max}, $AUC_{0\text{-}24}$, $Ae_{0\text{-}24}$ (verinurad only), and $CL_{R0\text{-}24}$ of verinurad were calculated for subjects receiving single-drug treatment (day 7 or day 21) versus in combination with the other drug (day 14). Estimations of the geometric mean ratios (GMR) of the above parameters with the corresponding 90% confidence interval (CI) were generated.

A mixed-effects model was used for the analyses of PD parameter sUA level percentage change from baseline. The model included treatment as a fixed effect, baseline value as a covariate, and subject as random effect. Statistical analyses for the PDs and safety data were performed by Covance Clinical Research Unit (Madison, Wisconsin) using SAS version 8.2 or later (SAS Institute, Cary, North Carolina).

Sample size was not based on formal power calculations, as this study was designed only to provide an assessment of the potential PK and PD interactions between verinurad and febuxostat.

Results

Study Subjects

Twenty-three subjects were randomized and entered the study: 11 subjects in panel 1 (5 for sequence A and 6 for sequence B) and 12 subjects in panel 2 (6 for each of sequences A and B). Of these, 20 subjects (10 in panel 1 and 10 in panel 2) completed the study. One subject in panel 1 (prior to dosing on day 9) and 2 subjects in panel 2 (1 after dosing on day 2 and 1 prior to dosing on day 7) were withdrawn from the study for noncompliance due to family emergencies. All subjects were included in the PK, PD, and safety populations. Table 1 summarizes the demographic characteristics of subjects.

Pharmacokinetics

Verinurad. Mean plasma concentration-time profiles and a summary of geometric mean (95%CI) plasma PK parameters for verinurad in the absence or presence of febuxostat are presented in Figure 2A and Table 2, respectively. PK parameters of verinurad 10

Table 2. Summary of PK Parameters for Verinurad (VERU) and Febuxostat (FBX) Alone or in Combination (Mean [SD] and Geometric Mean [95%CI])

Treatment	n		T_{max}[a] (hours)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	Ae_{0-24} (μg)	f_{e0-24} (%)	CL_{R0-24} (mL/min)
Verinurad								
VERU 10 mg	10	Mean (SD)		15.6 (5.82)	128 (56.3)	97.2 (49.7)	0.972 (0.497)	13.6 (5.04)
		Geomean	2.75	14.6	116	86.8	0.868	12.4
		(95%CI)	(1.50–5.00)	(11.0–19.3)	(82.8–164)	(60.8–124)	(0.608–1.24)	(8.7–17.7)
VERU 10 mg + FBX 40 mg	9	Mean (SD)		15.3 (6.03)	120 (55.1)	106 (44.2)	1.06 (0.442)	16.2 (5.43)
		Geomean	4.00	14.1	107	97.6	0.976	15.2
		(95%CI)	(2.00–5.00)	(10.2–19.6)	(72.3–159)	(69.2–138)	(0.692–1.38)	(11.1–20.8)
VERU 2.5 mg	9	Mean (SD)		3.84 (0.734)	27.4 (9.68)	23.3 (10.1)	0.932 (0.405)	15.1 (7.29)
		Geomean	4.00	3.82	26.1	21.2	0.849	13.6
		(95%CI)	(2.00–6.00)	(3.30–4.42)	(20.2–33.7)	(14.8–30.5)	(0.591–1.22)	(9.2–20.1)
VERU 2.5 mg + FBX 80 mg	9	Mean (SD)		4.94 (1.29)	35.6 (9.06)	32.3 (12.2)	1.29 (0.490)	15.4 (5.97)
		Geomean	3.00	4.78	34.6	30.0	1.20	14.4
		(95%CI)	(2.00–6.00)	(3.88–5.89)	(28.4–42.1)	(21.6–41.6)	(0.865–1.66)	(10.8–19.3)
Febuxostat								
FBX 40 mg	10	Mean (SD)			0.798 (0.283)	2.99 (0.933)		
		Geomean	1.50		0.736	2.83	–	– –
		(95%CI)	(1.00–3.00)		(0.529–1.02)	(2.16–3.70)		
VERU 10 mg + FBX 40 mg	9	Mean (SD)			0.664 (0.239)	2.66 (0.838)		
		Geomean	2.00		0.619	2.53	–	– –
		(95%CI)	(1.00–4.00)		(0.450–0.853)	(1.92–3.33)		
FBX 80 mg	10	Mean (SD)			1.76 (0.637)	6.21 (1.82)		
		Geomean	1.50		1.66	5.97	–	– –
		(95%CI)	(0.5–4.0)		(1.26–2.17)	(4.83–7.38)		
VERU 2.5 mg + FBX 80 mg	9	Mean (SD)			1.75 (0.373)	6.25 (1.39)		
		Geomean	1.50		1.72	6.11	–	– –
		(95%CI)	(0.750–2.00)		(1.46–2.02)	(5.17–7.23)		

Ae_{0-24}, cumulative amount of drug excreted unchanged in urine from time 0 to 24 hours postdose; AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 hours postdose; CI, confidence interval; CL_{R0-24}, renal clearance from time 0 to 24 hours postdose; C_{max}, maximum observed plasma concentration; f_{e0-24}, fraction of drug excreted in urine unchanged from time 0 to 24 hours postdose; n, number of subjects with data; T_{max}, time to maximum plasma concentration; geomean: geometric mean.

[a] T_{max} values represented by median (range).

mg were unaffected by the addition of febuxostat 40 mg, with GMRs (90%CI) for C_{max} and AUC_{0-24} of 96.2% (79.4-117) and 93.7% (84.0-105), respectively. A modest increase in verinurad 2.5 mg C_{max} and AUC_{0-24} was observed in the presence of febuxostat 80 mg (GMRs [90%CI], 125% [102-153] and 133% [102-172], respectively), whereas T_{max} remained unchanged.

Urinary excretion (Ae_{0-24}) and clearance (CL_{R0-24}) of verinurad 10 mg was not influenced by the addition of febuxostat 40 mg, with GMRs (90%CI) of 108% (94.3-124) and 115% (102-130), respectively. The Ae_{0-24} of verinurad 2.5 mg increased 41% in the presence of febuxostat 80 mg (GMR [90%CI] 141% [104-193]). However, the amount (geometric mean [95%CI]) of verinurad excreted was small in the absence (21.2 [14.8-30.5] μg) or presence (30.0 [21.6-41.6] μg) of febuxostat. CL_{R0-24} of verinurad 2.5 mg was unchanged in the presence of febuxostat 80 mg (GMR [90%CI], 106% [90.8-125]).

Febuxostat. Mean plasma concentration-time profiles and a summary of geometric mean (95%CI) plasma PK parameters for febuxostat in the absence or presence of verinurad are presented in Figure 2B and Table 2, respectively. PK parameters of febuxostat 40 mg were unaffected by the addition of verinurad 10 mg with GMRs (90%CI) for C_{max} and AUC_{0-24} of 87.9% (74.3-104) and 90. 3% (85.4-95.4). Similar results were obtained for febuxostat 80 mg + verinurad 2.5 mg, with C_{max} (GMR [90%CI] 96.7% [84.3-111]), AUC (GMR [90%CI] 96.2% [92.1-101]), while T_{max} remained unchanged.

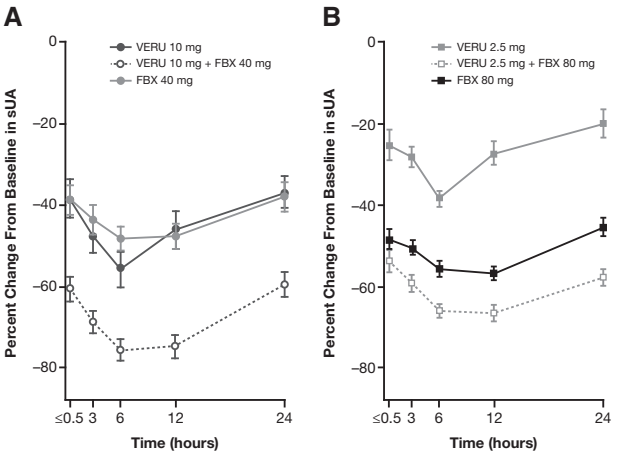

Figure 3. Arithmetic mean (SE) percentage change from baseline serum urate (sUA) at steady state following multiple doses of (A) verinurad (VERU) 10 mg alone or in combination with febuxostat (FBX) 40 mg or (B) VERU 2.5 mg alone or in combination with FBX (80 mg).

Pharmacodynamics

sUA Levels. Mean baseline sUA concentrations for each treatment group ranged from 6.3 to 6.9 mg/dL. The mean maximal change from baseline in sUA at steady state was greater with verinurad 10 mg + febuxostat 40 mg (−76.2%) than with verinurad 10 mg (−56.3%) or febuxostat 40 mg (−49.1%) alone (Figure 3A). The mean change in sUA was also greater with verinurad 2.5 mg + febuxostat 80 mg (−66.8%) than with verinurad 2.5 mg (−37.8%) or febuxostat 80 mg (−57.5%) alone (Figure 3B). The corresponding change in sUA at 24 hours was −59.6% for verinurad 10 mg + febuxostat 40 mg, and −38.0% and −36.9% for verinurad 10 mg and febuxostat 40 mg alone, respectively. With verinurad 2.5 mg + febuxostat 80 mg, the change in sUA at 24 hours was −57.9% compared with verinurad 2.5 mg (−19.9%) or febuxostat 80 mg (−45.4%) alone.

Urinary Uric Acid. A summary of the effects of each treatment alone and their combination on urinary uric acid parameters is shown in Table 3. Following multiple doses, the change from baseline in the amount of uric acid recovered in the urine (Ae_{UR}) was −64.1% and −72.4% with febuxostat 40 mg and 80 mg, respectively. By comparison, the change in Ae_{UR} with verinurad 10 mg and 2.5 mg was −17.0% and −21.0%, respectively. The change from baseline in Ae_{UR} with verinurad 10 mg + febuxostat 40 mg was −47.6% and was −69.4% with verinurad 2.5 mg + febuxostat 80 mg.

FEUA was increased by verinurad 10 mg (105%) compared with baseline; this increase was less prominent in the verinurad 10 mg + febuxostat 40 mg group (84.6%). FEUA increased slightly with verinurad 2.5 mg alone (17.2%) but decreased below baseline following the addition of febuxostat 80 mg (−17.3%). FEUA also fell below baseline following administration of febuxostat 40 mg or febuxostat 80 mg alone (−24.5% and −35.2%, respectively). Renal clearance of uric acid (CL_{UR}) followed a similar trend as FEUA.

Safety

Multiple once-daily oral doses of verinurad and febuxostat were generally well tolerated when administered alone or in combination. Of the 15 observed AEs , 13 were mild in severity, while 2 were of moderate severity. The only AE considered to be possibly related to verinurad was a mild headache (1 subject in the verinurad 10 mg–alone group), which resolved without treatment. Two subjects reported back pain on febuxostat 40 mg, but neither was considered to be possibly related to febuxostat. There were no deaths, serious AEs, or withdrawals due to AEs reported during the study.

No clinically meaningful changes in any laboratory values over time were observed, except for the expected treatment-related changes in sUA. Eight subjects (verinurad 10 mg, 2; febuxostat 40 mg, 1; verinurad 2.5 mg, 3; febuxostat 80 mg, 2) experienced an increase from baseline in serum creatinine (sCr) levels, but none had sCR ≥1.5 × baseline. The increase in sCr had resolved for 5 of the 8 subjects at follow-up. The 3 patients whose sCr elevation had not resolved had elevated sCr at screening. There were no clinically significant changes from baseline in vital signs, electrocardiograms, or upon physical examination.

Discussion

Results of this study show that once-daily dosing with verinurad 10 mg and 2.5 mg did not affect the systemic exposure of febuxostat. Similarly, the PK profile of verinurad 10 mg was not influenced by the addition of febuxostat 40 mg. Although a modest increase in C_{max} (25%) and $AUC_{0\text{-}24}$ (33%) were observed for verinurad 2.5 mg when combined with febuxostat 80 mg, these interactions were considered weak and therefore not clinically meaningful. The lack of any meaningful DDI between verinurad and febuxostat is consistent with the metabolism of both drugs. The PK properties of verinurad as well as its potency may enable it to be administered at a low dose, which could potentially lessen DDI in patients with gout, many of whom are also receiving treatment for comorbidities such as hypertension, cardiovascular disease, diabetes, and obesity.

Verinurad decreased sUA concentrations when administered alone at 2.5 mg or 10 mg, as did febuxostat 40 mg or 80 mg. As expected, the combinations of verinurad 10 mg + febuxostat 40 mg and verinurad 2.5 mg/kg + febuxostat 80 mg were more

Table 3. Summary of Urine PD Parameters at Baseline and Following Single or Combination Treatment With Verinurad (VERU) and Febuxostat (FBX) (Arithmetic Mean [95%CI])

Treatment	n	Baseline (Day −1) (−24 to 0 Hours)	Day 7 of Treatment (0 to 24 Hours)	% Change From baseline
		Ae_{UR}, mg		
VERU 10 mg	10	673 (552 to 795)	569 (421 to 717)	−17.0 (−33.2 to −0.739)
VERU 10 mg + FBX 40 mg	9	699 (578 to 821)	361 (302 to 420)	−47.6 (−54.5 to −40.6)
FBX 40 mg	10	695 (588 to 802)	246 (204 to 288)	−64.1 (−69.7 to −58.6)
VERU 2.5 mg	10	808 (696 to 920)	620 (485 to 755)	−21.0 (−34.1 to −7.93)
VERU 2.5 mg + FBX 80 mg	9	808 (680 to 936)	244 (197 to 292)	−69.4 (−74.7 to −64.0)
FBX 80 mg	10	818 (704 to 932)	221 (179 to 264)	−72.4 (−77.2 to −67.7)
		FEUA, %		
VERU 10 mg	10	5.98 (5.03 to 6.93)	12.8 (6.33 to 19.2)	105 (12.3, 197)
VERU 10 mg + FBX 40 mg	9	6.25 (5.43 to 7.08)	11.8 (8.07 to 15.5)	85.4 (37.9, 133)
FBX 40 mg	10	6.31 (5.58 to 7.05)	4.79 (3.78 to 5.79)	−24.5 (−35.9 to −13.1)
VERU 2.5 mg	10	6.49 (5.66 to 7.33)	7.55 (6.83 to 8.26)	17.2 (−3.67 to 38.0)
VERU 2.5 mg + FBX 80 mg	9	6.56 (5.62 to 7.50)	5.38 (4.39 to 6.37)	−17.3 (−30.2 to −4.42)
FBX 80 mg	10	6.54 (5.71 to 7.36)	4.18 (3.77 to 4.60)	−35.2 (−41.2 to −29.2)
		CL_{UR}, mL/min		
VERU 10 mg	10	7.34 (5.90 to 8.78)	12.3 (8.31 to 16.2)	65.8 (14.2, 117)
VERU 10 mg + FBX 40 mg	9	7.68 (6.29 to 9.07)	13.6 (10.5 to 16.7)	82.4 (40.7, 124)
FBX 40 mg	10	7.71 (6.49 to 8.94)	4.91 (4.26 to 5.57)	−34.4 (−45.3 to −23.5)
VERU 2.5 mg	10	8.32 (6.90 to 9.75)	9.00 (7.94 to 10.1)	10.7 (−7.92 to 29.3)
VERU 2.5 mg + FBX 80 mg	9	8.54 (7.03 to 10.1)	7.03 (5.40 to 8.67)	−16.5 (−34.5 to 1.40)
FBX 80 mg	10	8.73 (7.33 to 10.1)	4.96 (4.14 to 5.78)	−42.0 (−50.8 to −33.2)

Baseline was calculated for each treatment group based on the subjects who received the treatment.
Ae_{UR}, amount of drug excreted unchanged in urine; CL_{UR}, renal clearance of uric acid; FEUA, fractional excretion of uric acid.

effective in reducing sUA levels than each treatment alone, highlighting an advantage for such combination strategies to substantially reduce sUA levels. Achieving sUA levels below recommended targets may lead to improved outcomes such as lower gout flare incidence and/or more rapid tophus area reduction.[1,24–27] The current results are in line with those obtained with the combination of lesinurad and febuxostat in patients with gout,[28] where superior reductions in sUA were achieved when lesinurad 400 mg or 600 mg was administered with febuxostat 40 mg or 80 mg than when febuxostat 40 mg or 80 mg was given alone.

Consistent with its mechanism of action to reduce the production of urate, febuxostat reduced the urinary excretion of uric acid compared to baseline in the current study. In contrast, verinurad would be expected to increase urinary excretion of uric acid, given its mechanism of action to inhibit URAT 1. Ae_{UR} is increased following a single dose of verinurad.[19] However, Ae_{UR} was decreased from baseline at steady state following multiple dosing in the current study. Similar steady-state results have been reported previously for verinurad[19] as well as for lesinurad.[29] The lack of increase or the decrease in Ae_{UR} is due to the fact that the amount of uric acid in the serum was decreased during steady-state administration so there was less uric acid being filtered and less available to be blocked in reabsorption. The sUA was maintained at a low concentration by the continued inhibition of reabsorption.

Overall, multiple once-daily oral doses of verinurad and febuxostat were adequately tolerated by healthy adult male subjects when administered alone or in combination. No deaths, other serious AEs, withdrawals due to AEs, or other significant AEs of interest were reported during the study. Other than sUA, no clinically meaningful changes in laboratory values were observed. Likewise, there were no clinically significant findings for vital signs, 12-lead electrocardiograms, and physical examinations performed during the study.

Minimal increases in sCr were observed with similar frequency in subjects treated with verinurad or febuxostat alone or in combination. The mechanism of sCr elevation by selective reabsorption inhibitors is thought to be due to the increase in urinary uric acid excretion that could potentially induce microcrystallization of uric acid in the renal tubule. In contrast, febuxostat reduces urinary uric acid excretion by inhibiting urate

production.[30] The combination of verinurad and febuxostat did not increase urinary uric acid excretion above baseline. Therefore, the combination has the potential to reduce the incidence of renal uric acid crystallization and sCr elevation, while reducing sUA levels to a greater extent than either verinurad or febuxostat alone. Lower overall rates of sCr elevations and renal-related AEs were observed when lesinurad was added in combination with either febuxostat or allopurinol.[17,31,32]

In summary, the combination of verinurad 10 mg + febuxostat 40 mg or verinurad 2.5 mg + febuxostat 80 mg resulted in a greater reduction of sUA than when either verinurad or febuxostat were administered alone, while daily uric acid excretion remained below baseline. No PK DDI was found between verinurad 10 mg and febuxostat 40 mg, although the febuxostat 80-mg dose had minimal impact on the PK of verinurad 2.5 mg. The PK, PD, and safety data obtained in this study support the continued development of this approach for the treatment of gout and hyperuricemia.

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Declaration of Conflicting Interests

JH, XY, and ZS are former employees of Ardea Biosciences, Inc. MG is an employee of AstraZeneca.

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Author Contributions

Zancong Shen: conception or design of the work; acquisition, analysis, or interpretation of data for the work; review and revision of manuscript; and final approval of the version to be published.

Michael Gillen: conception or design of the work; acquisition, analysis, or interpretation of data for the work; review and revision of manuscript; and final approval of the version to be published.

Jesse Hall: design of the study, interpretation of the results, review and revision of manuscript, and final approval of the version to be published.

Xiaojuan Yang: analysis and interpretation of data, review and revision of manuscript, and final approval of the version to be published.

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