serious AEs, discontinuations due to AEs, or clinically significant laboratory or ECG abnormalities were noted.

Figure: Mean (SE) percent change from baseline in sUA at steady state following verinurad 10 mg or ALLO 300 mg or in combination

Conclusions: Although a modest drug-drug interaction was found between verinurad and ALLO, the combination was safe and well tolerated at the studied doses and resulted in greater reduction of sUA than either alone. These results support the evaluation of verinurad + ALLO as an alternative once-daily treatment option for hyperuricemia and gout.

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THU0433 PHARMACODYNAMIC AND PHARMACOKINETIC STUDY OF VERINURAD (RDEA3170) IN ADULT MALE SUBJECTS WITH MILD, MODERATE, AND SEVERE RENAL IMPAIRMENT: A PHASE 1, OPEN-LABEL STUDY

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Background: Verinurad (RDEA3170) is a high-affinity, selective URAT1 inhibitor in development for the treatment of gout and asymptomatic hyperuricemia.

Objectives: This Phase 1, single-dose, open-label study investigated the pharmacodynamics (PD), pharmacokinetics (PK), and safety of oral verinurad in adult subjects with mild, moderate, or severe renal impairment and matched controls with normal renal function (NCT02219516).

Methods: Adult males aged 18–85 years were enrolled with a screening serum uric acid (sUA) 4.5–10 mg/dL and creatinine clearance calculated by Cockcroft-Gault formula of 60 to <90 mL/min (mild renal impairment), 30 to <60 mL/min (moderate impairment), 15 to <30 mL/min (severe impairment), or ≥90 mL/min (matched controls). Oral verinurad 15 mg was administered once under fasted conditions. Serial blood and urine samples were taken 30 min before and up to 72 hours postdose. Safety assessments included laboratory, ECG, and vital sign parameters as well as adverse event (AEs) reporting.

Results: PD data were based on 7–8 subjects per group. Verinurad decreased sUA in all groups, with greatest changes in the normal function and mild renal impairment groups. Mean (SD) maximal % change in sUA from baseline (Emax) was -38.3 (14.8)%, -36.9 (13.6)%, -20.5 (6.64)%, and -12.6 (6.94)%, respectively, in the normal function and mild, moderate, and severe renal impairment groups. Increase in the amount of excretion of uric acid due to verinurad treatment decreased in subjects with moderate and severe renal impairment. Plasma Cmax and AUC of verinurad increased with decreasing renal function. Verinurad at the 15 mg dose was well tolerated, with no serious AEs, no subject withdrawals due to AEs, and no Renal Events Adjudication Committee (REAC)-adjudicated renal events during treatment. One patient in each renal impairment group had treatment-emergent AEs considered possibly related to verinurad, which were categorized as gastrointestinal in nature. There were no clinically meaningful changes noted in laboratory values or vital signs.

Conclusions: The sUA lowering effect of verinurad was observed across the spectrum of renal function. Consistent with the verinurad renal-dependent mechanism of action, decreasing sUA lowering was demonstrated with increasing renal impairment. Verinurad safety and tolerability were similar across all stages of renal impairment.

Disclosure of Interest: W. Smith Employee of: Volunteer Research Group, J. Hall Employee of: Ardea Biosciences, Inc., J. Berg Employee of: DaVita Clinical Research, M. Kazimir Employee of: DaVita Clinical Research, A. Yamamoto Employee of: Ardea Biosciences, Inc., S. Walker Employee of: AstraZeneca, C. Lee Employee of: Ardea Biosciences, Inc., T. Marbury Employee of: Orlando Clinical Research Center

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THU0434 PHARMACODYNAMIC EFFECTS AND SAFETY OF VERINURAD (RDEA3170) IN COMBINATION WITH FEBUXOSTAT VERSUS FEBUXOSTAT ALONE IN ADULTS WITH GOUT: A PHASE 2A, OPEN-LABEL STUDY

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Background: Verinurad (RDEA3170) is a high-affinity, selective URAT1 inhibitor in development for the treatment of gout and asymptomatic hyperuricemia.

Objectives: This Phase 2a, randomized, open-label, multicenter study investigated the multiple-dose pharmacodynamics (PD), pharmacokinetics (PK), and safety of oral verinurad in combination with febuxostat versus febuxostat alone in adults with gout (NCT02246673).

Methods: Patients aged ≥18 and ≤75 years with gout and serum uric acid (sUA) ≥8 mg/dL were randomized to 1 of 5 cohorts to receive febuxostat (40 mg and 80 mg) alone and in combination with verinurad (dose range 2.5 mg to 20 mg; 4 treatment periods per cohort, each treatment period 7 days). Medications were administered once daily ~30 min after breakfast. Colchicine 0.6 mg for gout flare prophylaxis was initiated at approximately Day -14 (start of urate-lowering therapy [ULT]) washout) or Day -7 if not on ULT. Serial blood and urine samples were measured at preset intervals on Days -1, 1, 7, 14, 21, and 28 for PD and PK endpoints. Safety assessments included adverse events (AEs) and laboratory, electrocardiograms, and vital sign parameters.

Results: Sixty-four patients were randomized (n=12–14 per cohort). Serum PD data pooled across cohorts demonstrated maximal % decrease in sUA from baseline (Emax) at 8–12 h after dosing. Addition of verinurad to febuxostat decreased sUA in dose-dependent manner (Figure 1). Greater sUA reductions were observed for dose combinations of verinurad ≥5 mg with febuxostat 40 mg versus febuxostat 80 mg alone. The rate of urinary uric acid excretion was reduced by febuxostat alone, but comparable to baseline levels with verinurad combined with febuxostat. Verinurad plasma exposures increased with verinurad dose and were comparable for febuxostat 40 mg and 80 mg doses. No drug-drug interaction on verinurad and febuxostat plasma PK parameters was observed. Verinurad at doses from 2.5 mg to 20 mg was well tolerated, with no serious AEs, withdrawals due to AEs, or renal-related events. The most frequent treatment-emergent AE possibly related to study medication was pain in extremity, in 2 patients receiving verinurad. Laboratory values and vital signs showed no clinically meaningful changes. There were no cases of serum creatinine elevation ≥1.5x baseline.

Figure 1. Maximum sUA percentage change

Conclusions: Verinurad coadministered with febuxostat dose-dependently decreased sUA while maintaining urine uric acid levels comparable to baseline. All dose combinations of verinurad and febuxostat in this study were generally well tolerated with no serious AEs or renal-related events during combination treatment.

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THU0435 PHARMACODYNAMICS, PHARMACOKINETICS, AND SAFETY OF VERINURAD (RDEA3170) IN COMBINATION WITH FEBUXOSTAT VERSUS FEBUXOSTAT ALONE AND VERINURAD ALONE IN JAPANESE ADULTS WITH GOUT OR ASYMPTOMATIC HYPERURICEMIA: A PHASE 2A, OPEN-LABEL STUDY

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Background: Verinurad (RDEA3170) is a high-affinity URAT1 inhibitor in development for the treatment of gout and asymptomatic hyperuricemia.

Objectives: This Phase 2a, randomized, open-label, single-site study investigated the multiple-dose pharmacodynamics (PD), pharmacokinetics (PK), and safety of oral verinurad in combination with febuxostat versus febuxostat alone and verinurad alone in Japanese male adults with gout or asymptomatic hyperuricemia (NCT02317861).

Methods: Japanese male patients aged ≥ 20 and ≤ 70 years with gout or asymptomatic hyperuricemia and serum uric acid (sUA) ≥ 8 mg/dL were randomized to 1 of 6 cohorts to receive febuxostat (10 mg, 20 mg, and 40 mg) alone, febuxostat in combination with verinurad (dose range 2.5 mg to 10 mg); verinurad (2.5 mg to 15 mg) alone; or benzbromarone (50 mg) alone (4 treatment periods per cohort, each treatment period 7 days). The study drugs were administered once daily in the morning after breakfast. Serial blood and urine samples were measured at preset intervals on Days -1, 1, 2, 7, 8, 14, 15, 21, 22, 28 and 29 for PD and PK endpoints. Safety assessments included adverse events (AEs) and laboratory, electrocardiograms, and vital sign parameters.

Results: Seventy-two patients with gout (n=37) or hyperuricemia (n=35) were randomized in this study. Addition of verinurad (2.5 mg to 10 mg) to febuxostat (10 mg, 20 mg, or 40 mg) decreased sUA in dose-dependent manner (Figure). Verinurad coadministered with febuxostat increased the amount of uric acid recovered in urine (Aeur), compared with baseline and the same dose of febuxostat administered alone, yet comparable with benzbromarone. Plasma Cmax and AUC exposures of verinurad and febuxostat exhibited dose proportional increases within the investigated dose range. No clear PK drug-drug interaction of verinurad and febuxostat with each other was observed. Verinurad at doses from 2.5 mg to 15 mg was well tolerated, with no serious AEs or withdrawals due to AEs. One treatment-emergent AE (diarrhea) was considered possibly related to both verinurad and febuxostat. Laboratory values and vital signs indicated no clinically meaningful changes.

Figure: Maximum percent change from baseline in sUA following varying verinurad doses in combination with FBX versus FBX 10, 20, or 40 mg alone

Conclusions: Verinurad coadministered with febuxostat dose-dependently decreased sUA while maintaining Aeur comparable to benzbromarone. All dose combinations of verinurad and febuxostat in this study were generally well tolerated.

Disclosure of Interest: M. Shiramoto Employee of: SOUSEIKAI PS Clinic, S. Liu Employee of: Ardea Biosciences, Inc., Z. Shen Employee of: Ardea Biosciences, Inc., J. Hall Employee of: Ardea Biosciences, Inc.

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THU0436 CLINICAL SIGNIFICANCE OF DELTA NEUTROPHIL INDEX IN THE DIFFERENTIAL DIAGNOSIS BETWEEN SEPTIC ARTHRITIS AND ACUTE GOUT ATTACK WITHIN 24 HOURS AFTER HOSPITALISATION

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Background: The most important differential diagnoses of acute monoarticular arthritis are septic arthritis and acute gout attack. Identifying infection is crucial in preventing the devastating outcome of septic arthritis.

Objectives: The delta neutrophil index (DNI) is a value that corresponds to the fraction of circulating immature granulocytes. As DNI reflects the burden of infection, we evaluated this index as a differentiating marker between septic arthritis and acute gout attack.

Methods: The medical records of 149 patients with septic arthritis and 194 patients with acute gout attack were reviewed. A specific cell analyser, ADVIA 2120, was used to measure DNI. Clinical and laboratory markers associated with predicting septic arthritis were assessed by using logistic regression.

Results: Patients with septic arthritis showed higher levels of DNI than those with acute gout attack (3.3 vs. 0.6%, $P < 0.001$). Similar results were observed in patients without monosodium urate (MSU) crystal confirmation or those with normouricemia (3.3 vs. 0.5 and 3.1 vs. 0.7%, respectively; $P < 0.001$ for both).

A DNI level of 1.9% was determined as the cut-off value for predicting septic arthritis. In the multivariate analysis, DNI was the most powerful independent value for predicting septic arthritis (odds ratio 14.003).

Table 1. Comparison of variables between patients with acute gout attack and those with septic arthritis

Variables	Patients with acute gout attack (n=194)	Patients with septic arthritis (n=149)	Total (n=343)	p-value
Age, years	65.0 $\pm$ 15.0	60.9 $\pm$ 16.4	63.2 $\pm$ 15.8	0.016
MSU crystals confirmed, n (%)	81 (41.8%)	N/A	81 (23.6%)	N/A
Positive culture, n (%)	N/A	98 (65.8%)	97 (28.3%)	N/A
WBC count, /mm ³	9600.0 $\pm$ 3000.0	11,200.0 $\pm$ 4700.0	10,300.0 $\pm$ 3900.0	<0.001
DNI, %	0.6 $\pm$ 0.9	3.3 $\pm$ 4.0	1.8 $\pm$ 3.0	<0.001
ESR, mm/h	61.7 $\pm$ 33.8	78.2 $\pm$ 32.5	69.3 $\pm$ 34.2	<0.001
CRP, mg/L	76.5 $\pm$ 68.7	126.6 $\pm$ 104.0	98.7 $\pm$ 89.6	<0.001
BUN, mg/dL	29.5 $\pm$ 21.9	22.7 $\pm$ 14.7	26.6 $\pm$ 19.4	0.001
Creatinine, mg/dL	1.9 $\pm$ 1.9	1.2 $\pm$ 1.7	1.6 $\pm$ 1.8	<0.001
Uric acid, mg/dL	7.6 $\pm$ 2.5	4.4 $\pm$ 1.6	6.3 $\pm$ 2.7	<0.001

Table 2. Multivariate analysis of the predictive values for septic arthritis in patients with acute gout attack and those with septic arthritis*

Variables	Odds ratio	95% Confidence interval	p-value
WBC count $\geq 14,000.0/\text{mm}^3$	1.888	0.563, 6.337	0.303
DNI $\geq 1.9\%$	14.003	5.683, 34.508	<0.001
ESR ≥ 70.0 mm/h	2.505	1.109, 5.657	0.027
CRP ≥ 106.0 mg/L	3.032	1.276, 7.209	0.012
Uric acid ≥ 7.0 mg/dL	0.031	0.011, 0.086	<0.001

Conclusions: This study showed the possibility of using DNI as a differentiating marker between septic arthritis and acute gout attack at the crucial early phase. DNI showed its relevance regardless of confirmation of MSU crystal deposition or serum level of uric acid.

Disclosure of Interest: None declared

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THU0437 IMPACT OF DIURETICS ON THE URATE LOWERING THERAPY IN PATIENTS WITH GOUT: ANALYSIS OF AN INCEPTION COHORT

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Background: Use of diuretics is a common bystander in patients with gout, and it has been reported to impair response to allopurinol [1,2] and likely lead to treatment failure and refractoriness. However, after the introduction of new urate-lowering therapies (ULT) and treat-to-target strategies, whether this inconvenient effect of diuretics persists has not received critical attention to date.

Objectives: To analyze the impact of the diuretic therapy on the response to ULT in patients with gout.

Methods: Retrospective analysis of an inception cohort in patients with crystal-proven gout (Jan2014-Nov2016). Patients were classified according to the use of diuretics (loop and/or thiazide) at baseline. The primary outcome variables were the reduction of serum uric acid (SUA) levels and the achievement of different objectives of SUA (6, 5, and 4 mg/dL); as secondary outcome variable the maximum dose of ULT was registered, as well as other clinical, analytical, and ULT-related data. A comparative analysis was performed according to the use of diuretics, using Student's t and chi-2 tests. Also, the analysis was stratified according to the ULT used.

Results: The inception cohort included 225 patients with an average age of 65 years (SD 14.1), being 86.2% of them men. The median duration of gout at inclusion was 4 years (p25-75 1-10) and 21.3% presented tophi. At baseline, the median (p25-75) SUA and estimated glomerular filtration rate were 8.2 mg/dL (7.2-9.2) and 75.9 mL/min (27.2-88.3), respectively. A total of 98 patients

Outcome variable	Diuretic therapy		p
	No	Yes	
Whole sample (N=209)	N=117	n=92	
- SUA reduction (mg/dL), mean (SD)	3.2 (2.1)	3.7 (2.5)	0.196
- SUA <6 (%)	80.0%	75.9%	0.458
- SUA <5 (%)	61.0%	50.6%	0.126
- SUA <4 (%)	31.4%	28.9%	0.575
Allopurinol (n=158)	N=92	N=66	
- SUA reduction (mg/dL), mean (SD)	3.1 (1.9)	3.2 (2.0)	0.813
- SUA <6 (%)	80.6%	74.2%	0.337
- SUA <5 (%)	60.2%	43.9%	0.043
- SUA <4 (%)	28.0%	21.2%	0.334
- Maximum dose (mg/day), mean (SD)	316.5 (126.9)	278.6 (121.8)	0.053
Febuxostat (n=33)	N=14	N=19	
- SUA reduction (mg/dL), mean (SD)	3.7 (3.4)	5.6 (3.1)	0.147
- SUA <6 (%)	70.0%	82.4%	0.456
- SUA <5 (%)	70.0%	76.5%	0.711
- SUA <4 (%)	60.0%	58.8%	0.952
- Maximum dose (mg/day), mean (SD)	80.0 (16.3)	80.0 (25.3)	0.348