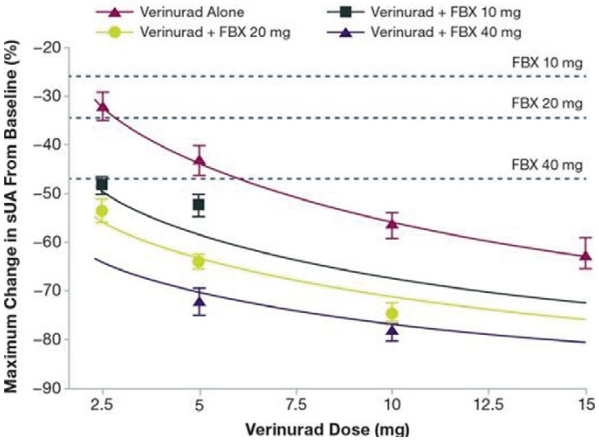
Objectives: This Phase 2a, randomized, open-label, single-site study investigated the multiple-dose pharmacodynamics (PD), pharmacokinetics (PK), and safety of oral verinurad in combination with febuxostat versus febuxostat alone and verinurad alone in Japanese male adults with gout or asymptomatic hyperuricemia (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±15.0	60.9±16.4	63.2±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±3000.0	11,200.0±4700.0	10,300.0±3900.0	<0.001
DNI, %	0.6±0.9	3.3±4.0	1.8±3.0	<0.001
ESR, mm/h	61.7±33.8	78.2±32.5	69.3±34.2	<0.001
CRP, mg/L	76.5±68.7	126.6±104.0	98.7±89.6	<0.001
BUN, mg/dL	29.5±21.9	22.7±14.7	26.6±19.4	0.001
Creatinine, mg/dL	1.9±1.9	1.2±1.7	1.6±1.8	<0.001
Uric acid, mg/dL	7.6±2.5	4.4±1.6	6.3±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 ≥14,000.0/mm^3	1.888	0.563, 6.337	0.303
DNI ≥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 4mg/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