THU0430 PHARMACOKINETICS, PHARMACODYNAMICS, AND TOLERABILITY OF CONCOMITANT MULTIPLE DOSE ADMINISTRATION OF VERINURAD (RDEA3170) AND FEBUXOSTAT IN HEALTHY ADULT MALE SUBJECTS

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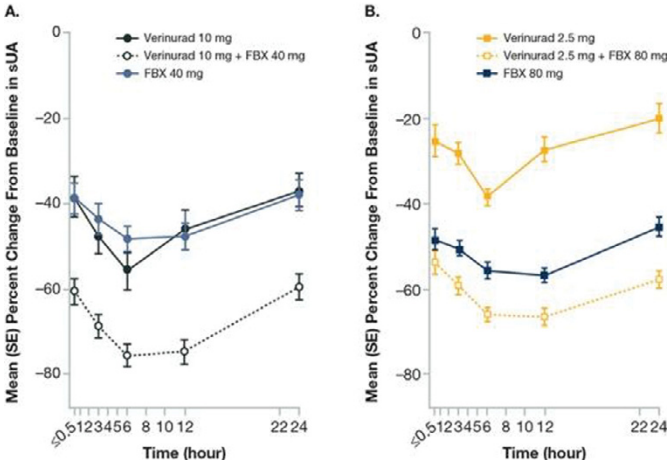
Background: Verinurad (RDEA3170) is a novel selective uric acid reabsorption inhibitor in clinical development for the treatment of gout and asymptomatic hyperuricemia.
Objectives: This Phase 1, single-blind, multiple dose, drug-drug interaction (DDI) study evaluated the pharmacokinetics (PK), pharmacodynamics, and tolerability of verinurad in combination with febuxostat (FBX) in healthy male volunteers.
Methods: Subjects were randomized to receive once-daily doses of FBX or verinurad or placebo alone for 7 days, FBX + verinurad or FBX + placebo on days 8–14, and the alternative single agent (FBX or verinurad or placebo) on days 15–21. Subjects received either the combination of verinurad 10 mg + FBX 40 mg or verinurad 2.5 mg + FBX 80 mg. Serial plasma/serum and urine samples were drawn at predetermined time points on Days 7, 14 and 21, and assayed for verinurad, FBX, and uric acid. Baseline samples were drawn on Day –1. Safety was assessed by adverse event (AE) reports, laboratory tests, vital signs, and electrocardiograms (ECGs).
Results: Of 23 randomized subjects, 20 completed the study. FBX 40 mg had no apparent effect on the plasma C_{max} and AUC for verinurad 10 mg, whereas FBX 80 mg increased the plasma C_{max} and AUC for verinurad 2.5 mg by 25% and 33%, respectively. Verinurad had no effect on FBX PK. Renal clearance of verinurad was unchanged by FBX.
The mean maximal reduction in serum uric acid (sUA) was 76% with verinurad 10 mg + FBX 40 mg compared with verinurad 10 mg (56%) or FBX 40 mg (49%) alone (Figure 1A) and was 67% with verinurad 2.5 mg + FBX 80 mg compared with verinurad 2.5 mg (38%) or FBX 80 mg (57%) alone (Figure 1B). Consistent with the mechanism of action (MOA) of verinurad, 24-hr fractional excretion of uric acid (FEUA) increased (2.5 mg: 7.6%; 10 mg: 12.8%) vs baseline (6.5% and 6.0%, respectively). Renal clearance of uric acid (CL_{UR}) increased similarly (2.5 mg: 9.0 mL/min; 10 mg: 12.3 mL/min) vs baseline (8.3 and 7.3 mL/min, respectively). The increases were maintained for 24 hours with verinurad 10 mg + FBX 40 mg (FEUA: 11.8%; CL_{UR}: 13.6mL/min). Consistent with its MOA, FBX 40 mg and 80 mg decreased the amount of uric acid excreted in urine (246 and 221 mg, respectively, vs baseline: 695 and 818 mg), FEUA (4.79 and 4.18%, respectively, vs baseline: 6.31 and 6.54%), and CL_{UR} (4.91 and 4.96 mL/min, respectively, vs baseline: 7.71 and 8.73 mL/min). No serious AEs, discontinuations due to AEs, or clinically significant laboratory or ECG abnormalities were noted during the study.

Figure 1: Mean (SE) percent change from baseline in sUA at steady state following verinurad 10 mg or FBX 40 mg or the combination (A) or verinurad 2.5 mg or FBX 80 mg or the combination (B)



Conclusions: No DDI was found with the verinurad 10 mg + FBX 40 mg combination and only a modest one with verinurad 2.5 mg + FBX 80 mg. Both combinations were safe and well tolerated and resulted in greater reduction of sUA than either verinurad or FBX alone. These results support the continued development of this novel approach for the treatment of gout and hyperuricemia.
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THU0431 COMPARATIVE EFFECTIVENESS OF ALLOPURINOL VERSUS FEBUXOSTAT FOR PREVENTING INCIDENT RENAL DISEASE IN OLDER ADULTS: AN ANALYSIS OF MEDICARE CLAIMS DATA

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Background: Large scale randomized studies are underway to assess whether compared to placebo, each XO-inhibitor, allopurinol or febuxostat, can prevent renal function loss. This evidence is needed and will confirm their nephroprotective potential. However, neither study will answer a key question: Does the renal protective effect of allopurinol differ from that of febuxostat?
Objectives: To assess the comparative effectiveness of allopurinol vs. febuxostat for preventing incident renal disease in elderly.
Methods: In a retrospective cohort study using Medicare claims data, we included patients newly treated with allopurinol or febuxostat (baseline period of 183 days without either medication). We used 1:5 propensity-matched Cox regression analyses to compare the hazard ratio (HR) of incident renal disease with allopurinol use and allopurinol dose vs. febuxostat (reference category). Sensitivity analyses included multivariable-adjusted regression models.
Results: There were 31,465 new allopurinol or febuxostat treatment episodes in 26,443 patients; 8,570 ended in incident renal disease. Crude rates of incident renal disease per 100,000 person-days were 53 with allopurinol vs. 93 with febuxostat. Crude rates of incident renal disease per 100,000 person-days were lower with higher daily dose: allopurinol $<$200, 200–299 and $\geq$300 mg/day with 65, 48 and 43; and febuxostat 40 mg and 80 mg/day with 93 and 89, respectively. In propensity-matched analyses, compared to febuxostat use, allopurinol use was associated with lower HR of incident renal disease, 0.61 (95% confidence interval (CI): 0.49, 0.77). Compared to febuxostat 40 mg/day, allopurinol doses $<$200, 200–299 and $\geq$300 mg/day were associated with lower HR of incident renal disease, 0.75 (95% CI: 0.65, 0.86), 0.61 (95% CI: 0.52, 0.73) and 0.48 (95% CI: 0.41, 0.55), respectively. Sensitivity analyses using multivariable-adjusted regression confirmed these findings.
Conclusions: Allopurinol was more effective than febuxostat in preventing incident renal disease in elderly patients. Future studies need to examine the mechanism of this renal benefit of allopurinol.
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THU0432 PHARMACOKINETICS, PHARMACODYNAMICS, AND TOLERABILITY OF CONCOMITANT MULTIPLE DOSE ADMINISTRATION OF VERINURAD (RDEA3170) AND ALLOPURINOL IN ADULT MALE SUBJECTS WITH GOUT

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Background: Verinurad (RDEA3170) is a novel selective uric acid reabsorption inhibitor in clinical development for the treatment of hyperuricemia and gout.
Objectives: This Phase 1, single-blind, multiple dose, drug-drug interaction study evaluated the pharmacokinetics (PK), pharmacodynamics, and tolerability of verinurad in combination with allopurinol (ALLO) in adult male subjects with gout.
Methods: Adult males with gout, aged 18–75 years, with serum uric acid (sUA) $\geq$8 mg/dL were randomized to receive once-daily oral doses of ALLO 300 mg or verinurad 10 mg alone for 7 days, ALLO 300 mg + verinurad 10 mg on Days 8–14, and the alternative single agent (verinurad 10 mg or ALLO 300 mg) on Days 15–21. Colchicine 0.6 mg was taken once daily from day –14. Serial plasma/serum and urine samples were drawn at predetermined time points on Days 7, 14 and 21 and assayed for verinurad, ALLO, oxypurinol (OXY), colchicine, and uric acid. Baseline samples were drawn on Day –1. Safety was assessed by adverse event (AE) reports, laboratory tests, vital signs, and electrocardiograms (ECGs).
Results: Subjects (N=12) were mostly white (58.3%) with mean (SD) age of 51 (10) years. Following multiple doses, ALLO had no effect on C_{max} and AUC of verinurad. ALLO C_{max} was increased 33% but AUC was unaltered by verinurad. The C_{max} and AUC for OXY, the active metabolite of ALLO, were reduced 32% and 38%, respectively, by verinurad. Colchicine plasma exposures were unaltered by verinurad. ALLO had no effect on urinary excretion of verinurad, whereas urinary excretion of OXY was increased 19% by verinurad.
The mean maximal decrease in sUA was 65% with verinurad + ALLO compared with verinurad (51%) or ALLO (43%) alone (Figure). Consistent with the mechanism of action (MOA) of verinurad, 24-h fractional excretion of uric acid (FEUA) and clearance of uric acid (CL_{UR}) were increased in the absence (9.2% and 11.5 mL/min, respectively) or presence of ALLO (7.9% and 11.8 mL/min) vs baseline (4.5% and 5.7 mL/min) or ALLO alone (3.7% and 5.0 mL/min). Consistent with its MOA, ALLO decreased the amount of uric acid excreted in 24-h urine (363 mg) compared with baseline (683 mg), verinurad alone (739 mg) or verinurad + ALLO (522 mg) but had no effect on FEUA or CL_{UR}. No