SUPPLEMENTAL MATERIALS

Supplemental Figure 1 Mean (SE) maximum percent change from baseline (Emax) in sUA (µmol/L) following varying verinurad doses in combination with febuxostat 40 mg or 80 mg versus febuxostat 40 mg or 80 mg alone (PD population, pooled across cohorts. Patient n in parentheses: *febuxostat 40 mg*: febuxostat alone (60), verinurad 2.5 mg (12), verinurad 5 mg (12), verinurad 10 mg (24), verinurad 15 mg (23), verinurad 20 mg (11); *febuxostat 80 mg:* febuxostat alone (48), verinurad 2.5 mg (12), verinurad 5 mg (12), verinurad 10 mg (11), verinurad 15 mg (12)).



Supplemental Figure 2Lowest mean (SE) sUA (mg/dL) following verinurad doses in combination with febuxostat 40 mg or 80 mg versus febuxostat 40 mg or 80 mg alone (PD population, pooled across cohorts. Patient n: see Supplemental Figure 1).



Supplemental Figure 3Mean (SE) plasma concentration profiles of verinurad (µg/mL) following verinurad 2.5, 5, 10, 15 or 20 mg in combination with (A) febuxostat 40 mg, and (B) febuxostat 80 mg; mean (SE) plasma concentration profiles of febuxostat (µg/mL) following (C) febuxostat 40 mg and (D) febuxostat 80 mg in combination with verinurad (2.5, 5, 10, 15 and 20 mg) (PK population. Patient n: see Table 2).



**Supplemental table 1** Lowest absolute sUA (mg/dL) following verinurad doses in combination with febuxostat 40 mg or 80 mg versus febuxostat 40 mg or 80 mg alone (PD population, data presented by cohort 1-4. Mixed effects model, with treatment as fixed effects, subject as random effects and baseline value as covariate for each cohort).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Cohort** | **Test (mg)** | **Comparator (mg)** | **Test least squares means** | **Comparator least squares means** | **Difference** | **P-value** |
| 1 | Verinurad 10 + febuxostat 40 | Febuxostat 40 | 2.3665 | 4.7127 | 2.3462 | <.0001 |
| 1 | Verinurad 10 + febuxostat 80 | Febuxostat 40 | 1.9301 | 4.7127 | 2.7825 | <.0001 |
| 1 | Verinurad 10 + febuxostat 40 | Febuxostat 80 | 2.3665 | 4.2483 | 1.8818 | <.0001 |
| 1 | Verinurad 10 + febuxostat 80 | Febuxostat 80 | 1.9301 | 4.2483 | 2.3182 | <.0001 |
| 2 | Verinurad 15 + febuxostat 40 | Febuxostat 40 | 2.2909 | 4.9455 | 2.6545 | <.0001 |
| 2 | Verinurad 15 + febuxostat 80 | Febuxostat 40 | 1.7000 | 4.9455 | 3.2455 | <.0001 |
| 2 | Verinurad 15 + febuxostat 40 | Febuxostat 80 | 2.2909 | 3.8545 | 1.5636 | <.0001 |
| 2 | Verinurad 15 + febuxostat 80 | Febuxostat 80 | 1.7000 | 3.8545 | 2.1545 | <.0001 |
| 3 | Verinurad 5 + febuxostat 40 | Febuxostat 40 | 3.6417 | 5.2750 | 1.6333 | <.0001 |
| 3 | Verinurad 5 + febuxostat 80 | Febuxostat 40 | 2.9917 | 5.2750 | 2.2833 | <.0001 |
| 3 | Verinurad 5 + febuxostat 40 | Febuxostat 80 | 3.6417 | 4.4250 | 0.7833 | 0.0003 |
| 3 | Verinurad 5 + febuxostat 80 | Febuxostat 80 | 2.9917 | 4.4250 | 1.4333 | <.0001 |
| 4 | Verinurad 2.5 + febuxostat 40 | Febuxostat 40 | 4.2405 | 5.1239 | 0.8833 | <.0001 |
| 4 | Verinurad 2.5 + febuxostat 80 | Febuxostat 40 | 3.3655 | 5.1239 | 1.7583 | <.0001 |

**Supplemental table 2** 24-Hour **f**ractional excretion of uric acid (FEUA) following administration of multiple doses of febuxostat 40 mg and 80 mg alone and in combination with varying doses of verinurad (PD population, cohort 1-5).

|  |  |  |
| --- | --- | --- |
| **Cohort** | **Baseline or treatment (mg)** | **FEUA (%)** |
| Cohort 4 | Baseline (n = 13) | 4.11 (3.51, 4.71)c |
|  | Febuxostat 40 (n = 12) | 3.30 (2.87, 3.73) |
|  | Febuxostat 80 (n = 13) | 3.15 (2.78, 3.52)a |
|  | Verinurad 2.5 + febuxostat 40 (n = 12) | 4.61 (3.89, 5.33) |
|  | Verinurad 2.5 + febuxostat 80 (n = 12) | 4.19 (3.48, 4.90) |
| Cohort 3 | Baseline (n = 12) | 3.80 (2.90, 4.70) |
|  | Febuxostat 40 (n = 12) | 3.51 (2.95, 4.08) |
|  | Febuxostat 80 (n = 12) | 3.08 (2.67, 3.50) |
|  | Verinurad 5 + febuxostat 40 (n = 12) | 5.60 (4.57, 6.63)b |
|  | Verinurad 5 + febuxostat 80 (n = 12) | 5.95 (4.55, 7.35) |
| Cohort 1 | Baseline (n = 11) | 4.36 (3.87, 4.85) |
|  | Febuxostat 40 (n = 13) | 3.25 (2.88, 3.61) |
|  | Febuxostat 80 (n = 11) | 3.32 (2.97, 3.66)c |
|  | Verinurad 10 + febuxostat 40 (n = 13) | 8.99 (6.67, 11.3) |
|  | Verinurad 10 + febuxostat 80 (n = 11) | 11.1 (8.30, 13.9)f |
| Cohort 2 | Baseline (n =12) | 4.08 (3.20, 4.96)c |
|  | Febuxostat 40 (n = 12) | 3.21 (2.67, 3.74) |
|  | Febuxostat 80 (N = 12) | 3.14 (2.44, 3.84)f |
|  | Verinurad 15 + febuxostat 40 (n = 12) | 9.83 (7.34, 12.3)f |
|  | Verinurad 15 + febuxostat 80 (n = 11) | 9.94 (7.47, 12.4) |
| Cohort 5 | Baseline (n = 12) | 3.98 (3.24, 4.71)b |
|  | Febuxostat 40 (n = 11) | 2.79 (2.35, 3.23)c |
|  | Verinurad 10 + febuxostat 40 (n = 11) | 7.00 (5.89, 8.11) |
|  | Verinurad 15 + febuxostat 40 (n = 11) | 8.43 (7.03, 9.82)c |
|  | Verinurad 20 + febuxostat 40 (n = 11) | 9.77 (7.98, 11.6)f |

a n = 12; b n = 11; c n = 10; d n = 7; f n = 9

**Supplemental table** 3 Incidence of TEAEs by treatment (safety population)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Adverse event category** | **Febuxostat****40 mg****(n=61)** | **Febuxostat****80 mg****(n=51)** | **Overall verinurad + febuxostat combination****(n=62)** | **Overall****(N=64)** |
| Subjects with TEAEs | 3 (4.9%) [3] | 8 (15.7%) [8] | 13 (21.0%) [19] | 20 (31.3%) [30] |
| Any serious AE | 0 | 0 | 0 | 0 |
| Any TEAE possibly related to verinurad | 1 (1.6%) [1] | 1 (2.0%) [1] | 3 (4.8%) [3] | 5 (7.8%) [5] |
| Any TEAE possibly related to febuxostat | 1 (1.6%) [1] | 5 (9.8%) [5] | 2 (3.2%) [2] | 7 (10.9%) [8] |
| **Individual TEAEs in >1 subject** |  |
|  Pain In extremity | 0 | 0 | 3 (4.8%) [3] | 3 (4.7%) [3] |
|  Dyspepsia | 1 (1.6%) [1] | 0 | 2 (3.2%) [2] | 2 (3.1%) [2] |
|  Headache | 0 | 1 (2.0%) [1] | 1 (1.6%) [1] | 2 (3.1%) [2] |
|  Musculoskeletal pain | 0 | 0 | 2 (3.2%) [2] | 2 (3.1%) [2] |

AE, adverse event; RCTC, Rheumatology Common Toxicity Criteria; TEAEs, treatment emergent AEs.

n=number of subjects studied; ( )=percent of subjects with AEs; [ ]=number of AEs.