Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplement Appendix Table of Contents

Supplement Appendix A: Study Acknowledgments

The following persons participated in the VA STOP Gout Study:

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RAIN Site Investigators and Coordinators – Mayo Clinic, MN: L. Peterson, J. Sletten; University of Nebraska Medical Center, NE: A. Cannella, B. Kramer, C. Marr, S. Edwards

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Data Monitoring Committee – L. Fraenkel (Chair), W. St. Clair, P. Shaw, H. Choi, A. Ozonoff

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VA Cooperative Studies Program Coordinating Center, VA Healthcare System, Boston, MA, - M. Brophy (Director), H. Wu, M. Androsenko, S. Cheekati, P. Macht, J. Haslam, S. Brown, T. Dinatale, G. Robben, C. Brown, A. Harvey, C. Donnelly, K. Howard, Y. Tayeh, T. Shaykevich

VA Office of Research and Development, Clinical Science R&D, Washington, DC - G. Huang (Deputy Chief R&D Officer – Enterprise Optimization, Director - Cooperative Studies Program)

Figure S1: Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Age ≥18 years
2. History of gout – crystal proven or historical as defined by ACR criteria[22]
3. Serum urate level ≥ 6.8 mg/dl

Exclusion Criteria:

1. Stage 4 or 5 Chronic Kidney Disease (CKD) – defined as eGFR of <30 ml/min/1.73 m2
2. Women younger than 50 years of age
3. Patients with a history of prior solid organ / hematopoietic transplantation
4. Previous allergy or intolerance to allopurinol
5. Patients who are not candidates for any of the recommended prophylactic medications (colchicine, naproxen, or glucocorticoids)
6. Patients who in the opinion of the investigator have a high genetic risk for allopurinol hypersensitivity syndrome (AHS*) unless they have been found to be negative for HLA B5801.
7. Previous history of failure to reach target uric acid levels despite therapy with allopurinol at dose > 300 mg/day
8. Prior febuxostat use
9. Patients with malignancies that are currently active with exception of non-melanoma skin cancer
10. Patients with serum uric acid levels >15 mg/dl
11. Patients with myelodysplasia and hemoglobin of < 8.5 g/dL
12. Patients with chronic liver disease with two or more of the following occurring within the past six months:
    a. INR ≥1.7, not on Warfarin therapy
    b. Bilirubin ≥2 mg/dL
    c. Serum albumin <3.5 g/dL
    d. Ascites
    e. Encephalopathy
13. Current use of azathioprine, mercaptopurine, didanosine, cyclophosphamide, probenecid** lesinurad or pegloticase***
14. Enrollment in another randomized interventional clinical trial****
15. Any severe medical condition that, in the enroller's opinion, is likely to compromise the participant's ability to complete the trial (e.g. unable to give informed consent).

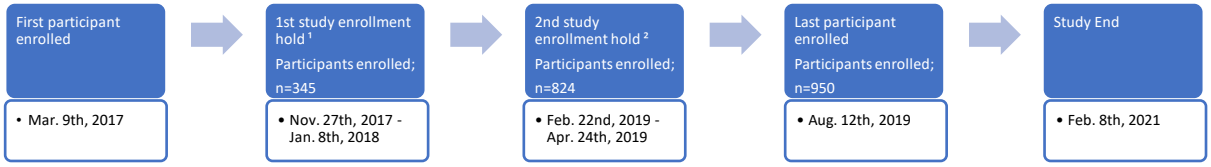
*Please see operational manual for further discussion on genetic risk for AHS.

** Participants on probenecid may be enrolled in the study provided they undergo a 14-day wash-out period before study entry.

*** Urate-lowering therapies approved after study kickoff are also excluded.

**** Unless the randomized interventional clinical trial is approved for dual enrollment by VACO

Figure S2: Study Timeline



[1] Enrollment hold due to CARES Trial preliminary findings/FDA public safety announcement. Executive Committee, Data Monitoring Committee, and VA Central IRB reviewed data and study resumed.

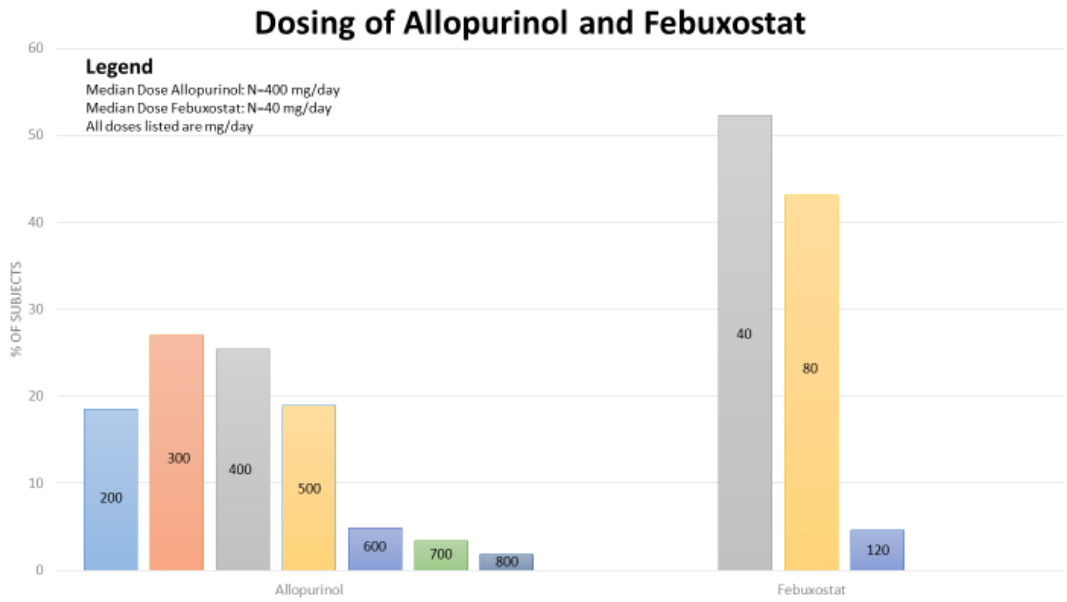
[2] Enrollment hold due to FDA boxed warning on febuxostat. Febuxostat maximum dose reduced from 120mg to 80mg per FDA guidance. CARES Trial findings discussed and reviewed with FDA, Executive Committee, Data Monitoring Committee and VA Central IRB; study resumed.

Figure S3: Pre-specified Secondary Outcomes to be Reported Elsewhere

Secondary Objectives:

- To determine if the number of gout flares in participants who achieve a sUA < 6.0 mg/dl by 48 weeks differ compared with those who do not, regardless of treatment assignment.
- To determine whether health-related quality of life measures differ between participants randomized to allopurinol compared to febuxostat and differ by achievement of sUA < 6.0 mg/dL, regardless of treatment assignment.
- To determine whether change in tophi area differ by location between participants randomized to allopurinol compared to febuxostat, and between participants who achieve or do not achieve sUA <6.0 mg/dL, regardless of treatment assignment.
- To explore the tolerability/toxicity of the two ULT dosing regimens, we will determine how adverse events, gout flares, CKD levels, and titration schedules influence the number of side effects during the study.
- To describe the effects of baseline covariates and time-dependent covariates on the primary results.

Figure S4: Dosing Distribution of Allopurinol and Febuxostat



***** Total participants reaching study visit week 48

Figure S5: Representativeness of Study Participants

Category	Explanation
Disease	Gout
Special considerations related to:	
Sex and gender	Gout affects men more than women (about 5.9% prevalence in men and 2.0% in women). Women who develop gout usually show signs and symptoms after menopause.
Age	In men, the majority of individuals first developing gout are between 30 – 50 years old. For women, it is any time after menopause.
Race or ethnic group	Gout affects Black, Asian, and Pacific Islander persons disproportionately to other races.
Geography	This study was conducted in the contiguous United States only. However, in general, areas with higher minority population/s (see races above) would be most at risk for developing gout.
Other considerations	Individuals most at risk for gout are those who: are overweight, have untreated high blood pressure, diabetes, metabolic syndrome, heart/kidney diseases, drink beer, eat purine rich foods (seafood and red meat), have a family history, have had an organ transplant and actively are taking anti-rejection drugs.
Overall representativeness of this trial	Participants in this trial were mainly from the Veterans Affairs Health Care System (19 of 21 sites) and therefore over-represent the male population (98.4% of our participants were male). The proportion of Black and Pacific Islander participants who underwent randomization overall was 21.9% and 2.0%, respectively, which is higher than the general population distribution in the United States.

Figure S6: Data Monitoring Committee Members and Schedule

Roster:
Liana Fraenkel, MD, MPH - Chair
Hyon K. Choi, MD, DrPH
Al Ozonoff, PhD, CPPS
Pamela Shaw, PhD
Eugene William (Bill) St. Clair, MD

Schedule:
2017-10-02 - Initial
2017-12-05 – FDA Alert
2017-12-12 – Routine
2017-06-14 – Routine
2017-11-29 – Routine
2019-07-25 – Routine
2020-02-20 – Routine
2020-08-27 – Routine
2021-06-17 – Final

Figure S7: Randomization Stratification Information

Randomization was stratified by site only. Four factors specified in SAP were continuously monitored during study enrollment. If an imbalanced had been discovered, a bended coin approach would have been implemented to fix the imbalance. Imbalance did not happen during the enrollment.

- CKD Stage 3;
- marked hyperuricemia defined as a sUA ≥ 9.0 mg/dl;
- presence of tophi;
- prior receipt of ULT.

Table S1: Study Dose Titration Protocol

Pre-FDA Febuxostat Box Warning (2017 – 2019)

	Baseline	3 wks.	6 wks.	9 wks.	12 wks.	15 wks.	18 wks.	21 wks.	24 wks.
Allopurinol[1,2](mg)	100	200	300	400	500	600	700	800	800
Febuxostat[1] (mg)	40	40	40	80	80	80	120[3]	120[3]	120[3]

[1] Blinded dose increases will occur until every third week sUA concentrations achieve a target level < 6.0 mg/dl, unless the tophi are present then the goal will be < 5.0 mg/dl, or an adverse event occurs mandating drug discontinuation or dose reduction.

[2] For pre-study allopurinol users, participants will continue with their current allopurinol dose or an equivalent dose of febuxostat until scheduled for dose escalation based on the above schedule. For example, a participant on allopurinol 300 mg daily would remain on 300/40 mg allopurinol/febuxostat until week 9 of the study, at which time they would be eligible for dose escalation. For a similar participant taking allopurinol 200 mg daily, the first possible titration will occur at week 6. We have opted for this approach to minimize the risks of gout flares that may occur because of sUA fluctuations and to ensure the same intensity of follow-up for all participants while maintaining the blind.

[3] Post-FDA box warning (2019), febuxostat 120mg was reduced to 80mg, max dose.

Table S2: Prophylactic Distribution

Total: 940	Allopurinol (468)	Percent	Febuxostat (472)	Percent	Total	Percent
Colchicine Only	417	89.10%	425	90.04%	842	89.57%
Naproxen Only	19	4.06%	24	5.08%	43	4.57%
Prednisone Only	15	3.21%	14	2.97%	29	3.09%
Colchicine + Naproxen or Prednisone	11	2.35%	4	0.85%	15	1.60%
Other	6	1.28%	5	1.06%	11	1.17%

Table S3: Baseline Characteristics of the Participants Who Completed the Study

	Allopurinol N=370	Febuxostat N=379	Total N=749
Demographics			
Age, years; mean (SD)	63.2 (11.5)	61.4 (12.8)	62.2 (12.2)
Male, %	98.4	98.2	98.3
Race, %			
White/Caucasian	69.5	69.7	69.6
Black/African American	20.8	19.8	20.3
Asian	2.7	3.2	2.9
Native Hawaiian/Pacific Islander/Maori	1.6	1.8	1.7
American Indian	0.8	0.5	0.7
Other	4.6	5.0	4.8
Comorbidity			
Chronic kidney disease, %			
GFR ≥ 90 mL/min	11.1	12.7	11.9
GFR = 60-89 mL/min	51.6	50.7	51.1
GFR = 30-59 mL/min	37.3	36.7	37.0
Serum creatinine, mg/dl; mean (SD)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Hypertension, %	78.6	74.7	76.6
Diabetes, %	34.9	31.4	33.1
Cardiovascular disease, %	27.3	24.3	25.8
Body mass index, kg/m2; (SD)	33.7 (6.8)	33.7 (6.7)	33.7 (6.7)
C-reactive protein, mg/L; mean (SD)	9.3 (17.9)	8.0 (15.1)	8.7 (16.5)
Gout Related Factors			
Serum urate, mg/dl; mean (SD)	8.6 (1.4)	8.5 (1.3)	8.5 (1.4)
Serum urate ≥ 9, %	33.8	32.7	33.2
Allopurinol use (300 mg/d or less), %	37.6	36.4	37.0
Gout duration, years; mean (SD)	9.7 (10.9)	9.7 (10.9)	9.7 (10.9)
Presence of tophi, %	16.5	14.8	15.6

Table S4: Other Outcomes

Labs Difference	Baseline mean	Wk. 48 mean	P value
Serum Urate (baseline – average in phase 2)	8.5	5.2	<0.001
C Reactive Protein (baseline – wk. 48)	8.9	6.8	<0.002
Serum Creatinine (baseline – wk. 48)	1.2	1.2	0.11

Table S5: Causes of Death in Study Participants

	Allopurinol	Febuxostat
Cardiac death*	1	
Cardiac failure	1	
COVID-19*		1
Failure to thrive*	1	
Hepatic cirrhosis	1	
Hypertensive cardiomyopathy		1
Malignant lung neoplasm*		1
Metastatic pancreatic carcinoma		1
Myocardial infarction		2
Pneumonia*	1	
Pulmonary hypertension	1	
Pulseless electrical activity		1
Squamous cell carcinoma	1	
Multiple drug overdose		1
Ventricular tachycardia	1	

*Died within 30 days following study exit

Table S6. Early Terminations, by Treatment

	Phase 1		Phase 2		Phase 3		Total	
	Treatment A N=468	Treatment B N=472	Treatment A N=411	Treatment B N=422	Treatment A N=389	Treatment B N=391	Treatment A N=468	Treatment B N=472
Total Participants with study termination	57 (12.2%)	50 (10.6%)	22 (5.4%)	31 (7.3%)	22 (5.7%)	18 (4.6%)	101 (21.6%)	99 (21.0%)
Reason for termination								
Death[1]	0 (0.0%)	0 (0.0%)	2 (0.5%)	4 (0.9%)	3 (0.8%)	2 (0.5%)	5 (1.1%)	6 (1.3%)
Side effects with study medications	10 (2.1%)	6 (1.3%)	3 (0.7%)	1 (0.2%)	0 (0.0%)	1 (0.3%)	13 (2.8%)	8 (1.7%)
Provider decision	2 (0.4%)	1 (0.2%)	4 (1.0%)	0 (0.0%)	0 (0.0%)	5 (1.3%)	6 (1.3%)	6 (1.3%)
Participant decision	32 (6.8%)	36 (7.6%)	9 (2.2%)	12 (2.8%)	6 (1.5%)	4 (1.0%)	47 (10.0%)	52 (11.0%)
Participant lost to follow-up	9 (1.9%)	4 (0.8%)	4 (1.0%)	9 (2.1%)	10 (2.6%)	5 (1.3%)	23 (4.9%)	18 (3.8%)
Study site closure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participant required to take exclusion medication on a regular basis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
Other	4 (0.9%)	3 (0.6%)	0 (0.0%)	5 (1.2%)	3 (0.8%)	0 (0.0%)	7 (1.5%)	8 (1.7%)

[1] Deaths not included: 5 participants died within 30 days of study completion or early termination.