CSP594 Comparative Effectiveness in Gout: Allopurinol vs. Febuxostat

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CSP #594

Comparative Effectiveness in Gout: Allopurinol vs. Febuxostat

VA Cooperative Studies Program (CSP)
A Department of Veterans Affairs Cooperative Study

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I. Executive Summary

Gout is the most common form of inflammatory arthritis affecting adults (1), with a disease prevalence that continues to increase relentlessly (2). Gout is associated with substantial morbidity and mortality, particularly in older men and in patients with chronic kidney disease (CKD) (3-6), demographics common to the Veterans Affairs (VA) Health System. Effective gout therapies are readily available and are centered primarily on the use of approved urate lowering therapy (ULT). Despite having excellent ULT options available to patients (7), gout is extremely poorly managed, especially in patients with CKD (8-10).

The two most widely used ULTs in clinical practice, allopurinol and febuxostat, have recently been endorsed by the American College of Rheumatology as the two acceptable treatment strategies in chronic gout (7). Although both agents appear to be efficacious, allopurinol and febuxostat have significantly different costs, safety profiles, and have never been compared to each other across their full dose ranges. In particular, randomized controlled trials completed to date comparing allopurinol with febuxostat in gout have used 'fixed' and, in many cases, insufficient doses of allopurinol (11-13), an approach that is contrary to current guideline recommendations (7). Furthermore, these studies have included only very small proportions of gout patients with CKD, even though CKD is present in approximately 1 of every 2 gout sufferers (14).

To test the hypothesis that allopurinol is non-inferior to febuxostat in the treatment of gout, we propose a randomized double-blind non-inferiority trial, which for the first time compares allopurinol with febuxostat using appropriately titrated doses and a "treat-to-target" approach. Further, we will assess the comparative effectiveness of these agents in a significant number of gout patients with co-morbid CKD.

We plan to enroll 950 participants with a diagnosis of gout, including participants with stage 3 CKD, who are hyperuricemic defined as a serum uric acid* concentration (sUA) above 6.8 mg/dl. Participants will be recruited from 20 Veteran Affairs and 5 Rheumatology and Arthritis Investigational Network (RAIN) sites. The total duration of the trial will be 4 years. Recruitment will occur over 24 months. Participants will be followed for 72 weeks. The trial will include a 24 week Dose Titration Phase (Phase 1), followed by a 24 week Maintenance and Optimization Phase (Phase 2) and then a 24 week Steady State Flare Observation Phase (Phase 3). We will use a "treat-to-target" approach with specified titration of ULT dosing to obtain goal sUA. Maximal daily drug doses will be the FDA approved doses of 800 mg/day for allopurinol or 80 mg/day for febuxostat.

The primary outcome will be the proportion of participants who have at least one gout flare in the allopurinol group compared to the febuxostat group during Phase 3. This primary outcome was endorsed by patient and VA provider groups whom we surveyed (see below). All participants will be followed during Phase 3 regardless of achievement of sUA goal. The primary hypothesis will test the non-inferiority of allopurinol with regards to proportions of flares. We anticipate that approximately 15 to 20% of patients will flare during Phase 3.

*For CSP 594 study purposes we will consider serum and plasma sUA levels interchangeable.

**Due to COVID-19, for CSP 594 study purposes we will consider any reference to "in person" or "clinic" visits as in person visits and/or telephone visits.

II. Abbreviations

ACR = American College of Rheumatology
AHS = allopurinol hypersensitivity syndrome
BRDP = Bio statistical and Research Data Processing
CKD = chronic kidney disease
CKD- EPI = Chronic Kidney Disease Epidemiology Collaboration
CRF = Case Report Forms
CSP = Cooperative Studies Program
CVA = Cerebrovascular Incident
DIR = Drug Information Report
ED = emergency department
EDC = Electronic Data Capture
eGFR = estimated glomerular filtration rate
EULAR = European League Against Rheumatism
GFR = glomerular filtration rate
MDRD= Modification of Diet in Renal Disease
NHANES = National Health and Nutrition Examination Survey
NSAID = non-steroidal anti-inflammatory drug
OMERACT = Outcome Measures in Rheumatology
RAIN = Rheumatology and Arthritis Investigational Network
RCT = Randomized Control Trial
sUA = serum uric acid
ULT = Urate Lowering Therapy
ULT = urate lowering therapy
US = United States
VA = Veterans Affairs

III. Background and Rationale

Gout and hyperuricemia are common in the general population and both have increased recently to near epidemic proportions. The reasons for the increased frequency of gout at a national level are multi-factorial and include an aging population, a significant increase in obesity prevalence and a marked increase in the incidence of chronic kidney disease (CKD), risk factors for hyperuricemia that are particularly common among U.S. veterans (15). The increase in gout frequency is most prominent among older men, the largest patient demographic encountered in the Veterans Affairs (VA) Health System. Over the last decade alone, gout prevalence in the U.S. has increased by more than 50% in men, 25% in women, and more than 100% among individuals over the age of 80 years (1). Gout is now estimated to affect 4% of the U.S. population, surpassing rheumatoid arthritis as the most common form of inflammatory arthritis. The impact of this growing epidemic in the VA is underscored by the robust associations of hyperuricemia and uncontrolled gout with cardiovascular disease (16-28), a leading cause of morbidity and mortality among U.S. veterans (15).

The treatment of chronic gout is based primarily on the use of urate lowering therapy (ULT). Available for more than 50 years, allopurinol is the most commonly prescribed ULT and represents one of the most frequent prescriptions dispensed in the VA. In 2009, a new drug to lower uric acid, febuxostat, was approved for the treatment of gout with drug costs that are 25 to 50-fold higher than allopurinol. Some of the recently published data leading to its approval attempted to make the case that febuxostat is more effective than the much older and much less expensive allopurinol(11-13). This is despite the fact that these studies compared febuxostat to inappropriately low doses of allopurinol. Although allopurinol is approved for the treatment of gout in doses as high as 800 mg daily in the United States and 900 in Europe, there have been no studies to date that have compared febuxostat to allopurinol in daily doses exceeding 300 mg. Importantly, despite a paucity of supporting data (29) and contrary to recently published management guidelines (7), older reports have recommended markedly reduced dosing of maintenance allopurinol in patients with renal impairment (30), a recommendation that is still frequently followed by clinicians. When this recommendation for renal dosing is strictly followed, the majority of patients with gout and CKD experience inadequate control of their hyperuricemia and continue to suffer from severe gouty arthritis (31). While the morbidity and expense of painful gout flares is substantial, the morbidity and costs associated with attempts to treat rather than prevent flares may be even greater. Moreover, the purported superior efficacy is perhaps not without risks, as the use of febuxostat was associated with a small but significant increase in risk of cardiovascular death and all-cause mortality compared to allopurinol. As of February 2019, the FDA-approved indication of febuxostat is limited to those patient's who have failed or cannot tolerate maximally titrated allopurinol doses (108).

The economic impact of gout and hyperuricemia are considerable both to the U.S. and the VA. Not only is gout extremely common among veterans but it is a common cause of clinic visits in addition to admissions to both the emergency department (ED) and inpatient setting. In preliminary analyses using the Nationwide Emergency Department Sample from 2008, gout was the primary diagnosis for more than 170,000 ED visits in the U.S. with corresponding total estimated charges of more than $160 million annually (32). Among younger gout populations, gout is independently associated with work absenteeism and losses in work productivity (33). Compared to employees without the diagnosis, employees with gout take nearly twice as much sick leave and twice as much short-term disability leave, translating into an estimated total loss of more than 3 million days annually across the U.S. civilian workforce (33). Consistent with these data, gout is also associated with substantially higher overall healthcare costs (34, 35) and accounts for 6% of all healthcare costs among elderly patients with gout (36).

For patients with gout, serum urate (sUA) levels serve as an independent predictor of both gout flare risk and total gout-related healthcare costs (37), suggesting that effective ULT can mitigate gout-related morbidity and expense. Indeed, allopurinol treatment among veterans with hyperuricemia has been associated with a significant reduction in all-cause mortality (38). The costs of recurrent, and therefore potentially preventable, gout flares make up the vast majority of the economic burden posed by gout. The cost of colchicine, among the most common agents used to treat acute gout flares, has recently increased from just cents per pill to approximately $5 per pill (39). Most gout experts believe that recurrent gout flares are almost entirely preventable if gout and hyperuricemia are appropriately managed. Unfortunately, gout is one of the most mismanaged conditions in "modern" medicine. Part of the problem with gout mismanagement occurs because ULT agents are not titrated (40) in concordance with recent gout

management guidelines (7). In addition, the adverse impacts of inadequately treated chronic gout may not be appreciated by many clinicians.

As part of recent efforts characterizing gout treatment in a large U.S. health care organization, it was shown that among more than 13,000 gout patients initiated on allopurinol only 10% ever received dose escalation over an average follow-up period of three years (Rashid & Mikuls, unpublished data). Furthermore, of those initiated on allopurinol only 3% ever received a dose of more than 300 mg/day over the same observation period. The vast majority of prescriptions for management of gout are for allopurinol doses of 300 mg or less, and the majority of patients remain on their initial dose prescribed (40-43). Fewer than 50% and 25% of participants receiving these doses of allopurinol achieved sUA <6mg/dL after 6 and 12 months, respectively (11, 12). This practice directly contradicts best practices in gout management that involve the use of maintenance doses of allopurinol gradually titrated upward in order to achieve a target sUA threshold (7). As a partial result of low adherence to these recommendations, a majority of gouty patients never reach sUA target levels below 6.0 mg/dl. Achieving and maintaining sUA levels below 6.0 mg/dl are critical goals in gout care and are strongly associated with decreased disease burden (including decreased total body urate stores, resolution of tophi, and decreased acute disease flares). Excellent observational data demonstrate that standard allopurinol dosing schemes lead to target sUA concentrations in only a small subset of gout patients (44). Further, the 2012 ACR guidelines for the management of gout recommend this as the treatment target.(7) Therefore, as part of this protocol, we will use a protocolized ULT dosing algorithm based on sUA levels and a treat-to-target approach geared to mimic current best-practice strategies in gout management (7).

While the management of gout in patients with normal renal function can be challenging, hurdles posed in gout management may be even greater in patients with CKD. The prevalence of gout increases with progressive degrees of severity of CKD (45). In an analysis of data from the most recent National Health and Nutrition Examination Surveys, the crude prevalence of gout was 2 to 3% among individuals without CKD, as compared to 11 to 13% among individuals with stage 3 CKD (eGFR 30-59 mL/min/1.73 m^2) and over 30% in individuals with stage 4 CKD (eGFR 15-29 mL/min/1.73 m^2), an approximate five-fold higher prevalence in individuals with stage 3 CKD and a more than 10-fold higher prevalence in patients with stage 4 CKD as compared to individuals with normal kidney function (45). Less than 0.5% of individuals with an eGFR >90 mL/min/1.73 m^2 were taking allopurinol as compared to ~5% of individuals with stage 3 CKD. Despite the high prevalence of ULT use, the mean sUA concentration in patients with stage 3 CKD was 6.5 mg/dL with 46% of individuals manifesting hyperuricemia (45). Notably, the prevalence of CKD in the US population has been increasing over time with an increase in patients with stage 3 CKD from approximately 5.4% of the US population during the period from 1988 to 1994 to approximately 7.6% during the interval from 1999 to 2010 (46). The burden of CKD in the VA population is even higher than in the general US population with 10.3% of VA populations having stage 3 CKD in 2011 (46). Thus, there is a strong rationale for inclusion of patients with CKD in our study, given the markedly increased prevalence of hyperuricemia and gout in this population.

It is important to note that despite common misconceptions, allopurinol administration in approved doses has never been associated with deterioration in renal function in patients with gout and renal impairment (29). Results from small studies have shown that the pharmacodynamics and

pharmacokinetics of febuxostat are unaltered in the context of CKD, suggesting that this agent does not require renal dose adjustments and ultimately leading many to favor use of this agent over allopurinol in patients with renal impairment (47, 48). Contrary to reports suggesting that allopurinol may lead directly to 'renal toxicity', small studies have shown that allopurinol (as well as febuxostat) may retard the progression of CKD (49-52).

In addition to unfounded concerns over potential deleterious effects on kidney function, results from a single case series of 78 patients reported by Hande et al suggested that 'higher dose' allopurinol may increase the risk of allopurinol hypersensitivity syndrome (AHS) (30), an uncommon (up to1%) but serious drug related adverse event that appeared in this study to be heightened in the context of CKD. These results led directly to the generation and widespread promulgation of non-evidence based dosing guidelines that were founded on the relationship of renal function with observed oxypurinol concentrations (an allopurinol metabolite) (30). It is important to note that the 'effectiveness' of these guidelines in preventing AHS has never been demonstrated (29). Indeed, many patients with CKD have developed AHS even with 'appropriately' dosed allopurinol (53, 54). In a recent review of 120 gout patients receiving allopurinol, more than half (57%) of patients required daily doses above the 'renal threshold' recommended by Hande to achieve target urate goals. In this study, only 1 patient developed AHS, a patient with normal renal function receiving 300 mg per day (55). In a more recent study of 90 gout patients, Stamp and colleagues found that increasing the dose of allopurinol above the thresholds proposed by Hande (30) led to significant reductions in sUA without increased toxicity (31). In a cohort of more than 1,200 gout patients treated with allopurinol, investigators observed no association of allopurinol dose with the occurrence of adverse drug reactions (56). Indeed, the risk of adverse drug reactions was related to the rate of the allopurinol dose increment and not the final dose in participants with CKD. Recent regulatory studies comparing allopurinol with febuxostat in gout have demonstrated low frequencies of rash leading to treatment withdrawal, rates that have generally well below 5% and similar across treatment groups (12).

Independent guidelines from the European League Against Rheumatism (EULAR) (57), the British Society for Rheumatology (58), and now the American College of Rheumatology (ACR) (7) have all recommended that allopurinol dosing should be gradually increased to doses as high as 800 (US) or 900 (Europe) mg/day with a goal of achieving and maintaining sUA concentrations below 6.0 mg/dl, recognizing the need for initial dose adjustments in the context of renal insufficiency (59). Indeed the ACR guidelines specifically suggest that allopurinol doses may be raised above 300 mg daily, even with renal impairment, as long as it is accompanied by adequate patient education and monitoring of drug toxicity (7). Thus, current day-to-day practice that adheres strictly to the Hande dosing guidelines (30) contrasts starkly with evidence-based recommendations of judicious dose escalation accompanied by appropriate surveillance to achieve a target sUA goal of < 6.0 mg/dl (29).

To optimally inform our revised application and address feedback from CSSEC, the planning committee sent out two surveys: a questionnaire to 179 VA providers from across the US responsible for gout management and a survey to 40 gout patients enrolled in the National Data Bank. A majority (71%) of the provider respondents were primary care physicians, highly relevant because the vast majority of gout care occurs in the primary care setting. Forty respondents (22%) were VA rheumatologists. Both provider groups and patients prioritized a reduction in acute gout flare rate as the most important outcome to investigate in a comparative effectiveness study of ULT with tolerability and sUA reduction prioritized as second and third priorities, respectively. When presented an established gout patient with comorbid CKD (stage III), there was substantially divided opinion among primary care respondents about the comparative efficacy, tolerance and likelihood of adverse events for allopurinol and febuxostat even though little data exists to support such a difference. Given the same patient, a vast majority of primary care providers invoked a maximum daily dose of allopurinol of 300 mg, despite available evidence suggesting that judicious titration above this threshold is both safe and tolerated even in patients with CKD. Together, these results support our primary and secondary endpoints and identify potential gaps in care that will be addressed and overcome with our rigorous study design.

As part of this VA Cooperative Studies Program (CSP) trial, we will for the first time compare allopurinol with febuxostat in the treatment of gout using appropriately titrated doses and a "treat-to-target" approach. Gout patients and VA providers were surveyed and both groups endorsed a reduction in gout flares as the most meaningful outcome (see below). Therefore, our primary outcome will be the percentage of patients who flare during maintenance phase (weeks 49-72) after ULT has been appropriately titrated (weeks 0-48). This large simple randomized study will include not only US veterans with gout, but also gout patients recruited from the Rheumatology and Arthritis Investigational Network (RAIN) including sites across the Midwest and Western US. RAIN has been led by the PI since 1989 and recently participated in CSP #551 (60), successfully enrolling 141% of its original target goal. In addition to capitalizing on the substantial track record of RAIN in patient recruitment, the inclusion of these select non-VA sites will be central in extending the generalizability of findings from this precedent setting effort.

IV. Significance of Proposed Research to the VA

Gout is common and increasing, accounts for significant morbidity, mortality and work disability, and is frequently miss-managed resulting in preventable morbidity and expense. Compared to veterans without gout, US veterans with gout report significantly more bodily pain in addition to having higher rates of comorbidity, more annual primary care visits, and admissions to the hospital (6). In a recent study of US veterans, only 24% of gout patients initiated on ULT underwent repeat sUA testing within 6 months, suggesting that rates of appropriate ULT titration and the achievement of urate goals are exceedingly low in the VA (10). Since gout is much more common in men and increases with age, gout related issues are significantly magnified in US veterans. Approved for the treatment of gout in 2009, febuxostat is much more expensive than allopurinol with direct drug costs that are approximately 25 to 50-fold higher. While marketing materials suggest that febuxostat may be more effective than allopurinol these comparisons have been done at inappropriately low fixed-doses of allopurinol. The misconception regarding superior ULT efficacy of febuxostat over allopurinol is evident in a substantial proportion of VA healthcare providers. In an effort led by our team in preparation for this application, we conducted a national survey that included 179 VA providers with approximately 1 in 5 responders reporting that febuxostat demonstrated superior efficacy compared to allopurinol in gout treatment (unpublished). Of note, a similar proportion of VA providers suggested that febuxostat also demonstrated superior tolerability to allopurinol, a difference that has never been reported in any of the head-to-head trials completed to date. The VA's annual expenditures for febuxostat have increased significantly over the last few years. Allopurinol is inexpensive and effective if used at appropriate doses and we believe will provide similar results to febuxostat in both patients with and without CKD. If allopurinol is shown in this trial to be non-inferior to febuxostat the cost implications for the VA and US health care in general are substantial. Further, if gout and hyperuricemia can be appropriately managed in more than 80% of participants as we predict, this will conclusively demonstrate that the incidence and expense associated with gout flares and their consequences can be dramatically reduced.

V. Study Objectives

Primary Objective:

To compare the efficacy of appropriately titrated doses of two ULTs, allopurinol and febuxostat, in reducing gout flares (during Phase 3, weeks 49-72) in participants with gout who are hyperuricemic prior to study entry.

Secondary Objectives:

1) To compare the efficacy and tolerability of allopurinol and febuxostat in reducing gout flares among participants with gout who have stage 3 chronic kidney disease (CKD 3) and are hyperuricemic at baseline.
2) To compare the efficacy of the two ULT dosing regimens in achieving sUA <6 mg/dL between weeks 36 and 48 (i.e., during Phases 1 and 2: the dose titration phase, and the dose maintenance and optimization phase).
3) 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.

4) 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.
5) 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.
6) To determine whether the number of gout flares during each of the trial's 3 phases differ between participants randomized to allopurinol compared with febuxostat.
7) 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.
8) To describe the effects of baseline covariates and time-dependent covariates on the primary results.

Other Objectives:

Consent will be sought for continued access to participant electronic health records for ten years following completion of study participation in order to examine long-term outcomes. Important outcomes will include comorbidities associated with gout over the long-term, including CKD and marked excess cardiovascular mortality as outlined in the Background. Therefore, records will be specifically evaluated for the development of cardiovascular complications (MIs, coronary artery bypass graft surgery or stent placement, CVAs and hypertension), progression of CKD, and mortality. This will not require the sites to remain open for these ten years, this will also not require sites to create repositories of data, consent will be sought simply for access to participants electronic health records for up to 10 years following the last participant completing phase 3 of the study.

There will be a biobank Substudy for identification of genetic factors and biomarkers that may predict disease progression, development of comorbidities, treatment response and toxicity. Consent will be sought for collecting specimens for the serum bank. Participation in the substudy will be optional.

VI. Experimental Design

***COVID-19:**

Due to COVID-19, in-person visits may be conducted via telephone if an in-person visit is not feasible. Safety for all subjects, health care staff and others should be considered prior to every study visit. The Local Site Investigator has the discretion to determine what type of visit (in-person or telephone) is most appropriate. Sites are to adhere to the strictest safety policies and procedures in place. If local policies and procedures allow for in-person research visits to occur, this is the preferred method of sample and data collection. However, if an in-person visit is not feasible and a telephone visit is conducted instead this would not be considered a protocol deviation. Sites are to collect the protocol specified lab values for weeks 48, 60 and 72 even if the visit is conducted via telephone. Sites are permitted to utilize a CBOC for lab draws. If subjects are unable to have labs drawn due to COVID-19, lab values within the CPRS system that are drawn during the visit window can be used to supplement the study specified labs at a given visit. If no lab values are obtained for weeks 48, 60 and 72, this will be considered a protocol deviation.

Proposed Design:

Participants will be recruited from 20 Veteran Affairs and 5 RAIN sites. Individuals with a history of gout who continue to be hyperuricemic (sUA ≥ 6.8mg/dl) and fulfill entry criteria will be invited to participate. In this prospective double-blind non-inferiority trial, 950 participants will be randomized in a 1:1 ratio to receive either allopurinol or febuxostat. Recruitment will occur over 24 months. The total duration of the trial will be 4 years.

Participants will be followed for 72 weeks: a 24-week Dose Titration Phase (Phase 1) followed by a 24-week Maintenance and Optimization Phase (Phase 2) and then a 24-week Steady State Flare Observation Phase (Phase 3). Patients will undergo active surveillance during Phases 1 and 2 with scheduled in-person study visits, while Phase 3 observation will be conducted remotely using telephone encounters. There will be one study visit at week 60 to return bottles and diaries and pick up a new three-month supply of study medication. Specified titration of ULT dosing, adhering to the currently recommended initial dosing in gout patients with both normal renal function and CKD stage 3 (7) will be used in Phase 1 (see Table 4 for dose titration schedule). Specified dose titration will occur until: 1) achievement of sUA concentrations at target level < 6.0 mg/dl or < 5.0 mg/dl if tophi present; 2) an adverse event occurs mandating drug discontinuation or dose reduction; or 3) maximal daily drug dose has been achieved (800 mg/day for allopurinol or 80 mg/day for febuxostat). During the 24-week 'Maintenance and Optimization Phase' (Phase 2) ongoing dose titration will be allowed if sUA level remains above 6.0 mg/dl, as long as maximal daily drug doses have not been achieved. Dose escalation will not be allowed during the final three study visits of Phase 2 occurring at weeks 36, 42, and 48, to allow for steady-state assessment through week 72 (Phase 3). During Phase 3, participants will be actively followed by monthly phone interviews for flare reporting. In order to reduce the frequency of acute gout flares that may complicate ULT initiation and titration, anti-inflammatory prophylaxis that conforms to recently published guidelines in gout management (61) will be used.

The primary outcome will be the proportion of participants who have at least one gout flare in the Allopurinol group compared with the febuxostat group during Phase 3. Flare ascertainment during Phase 3 has been deliberately chosen (rather than during Phase 1 or 2) with the understanding that gout flares are a commonly experienced physiologic consequence of ULT during the first year of therapy, and usually indicate successful urate lowering rather than treatment failure. All participants will be followed during Phase 3 regardless of the achievement of sUA goal. The primary hypothesis will test the non-inferiority of allopurinol based upon the proportion experiencing ≥1 flare in each of the two treatment groups in Phase 3.

Randomization:

Balanced randomization will be used to ensure that equal proportions of participants with the following characteristics are in the two treatment arms: 1) CKD Stage 3 (individuals with CKD Stages 4 and 5 will be excluded); 2) marked hyperuricemia defined as a sUA ≥ 9.0 mg/dl; 3) presence of tophi (focused examination involving the hands, elbows, feet, and ears, which are the most common sites for tophaceous deposits); and 4) participants with prior receipt of ULT. All of these factors have been associated with a lower likelihood of achieving sUA goals in recent head-to-head trials of these two agents (12, 13). Further, to guarantee enrollment of a sufficient number of gout participants with CKD stage 3 (eGFR ≥30 but <60 ml/min) to address a key secondary objective (see above), we will randomize at least one participant with CKD Stage 3 for every two participants with preserved renal function (eGFR ≥ 60 ml/min).

VII. Outcome Measures

Primary Outcome:

The primary outcome will be the proportion of participants who have at least one gout flare in the Allopurinol group compared with the febuxostat group during Phase 3.

Gout flares:

Prior randomized trials have used varying definitions of gout flares. In this study, the occurrence of gout flares will be documented according to recently published criteria (63); this approach is consistent with the approach used in gout RCTs (64-72). Subjects will be asked to keep a diary of flares. Information about the occurrence of flares will be reviewed at all ULT clinic visits and telephone encounters occurring at monthly intervals in Phase 3 with the aid of these diaries to avoid recall bias that could affect this measurement if longer intervals were used. A gout flare questionnaire will be used during each visit (Phase 1 and 2) and each call (Phase 3) to capture information on: 1) the presence of a 'warm' joint; 2) the presence of a swollen joint; 3) a corresponding pain at rest score > 3 (0 to 10 scale); 4) patient-reported gout flare; and 5) medications used to treat flares, if any. Participants will be considered to have an acute gout flare if 3 of the first 4 criteria are satisfied. This method has been demonstrated to have a sensitivity of 91% and a specificity of 82% (63). In addition to examining the proportion of patients with at least one flare, we will also examine the number of one-month intervals during Phase 3 with gout flares requiring treatment. Treatment of gout flares will be done at the discretion of the site investigator with guidelines provided within the protocol (See *Section X. Treatment Regimens* below). Because gout patients may treat their attack at the first symptoms of attack onset, which can abort the full presentation of an attack, a secondary flare definition will be used of patient-reported flare of typical characteristics above plus use of

appropriate gout anti-inflammatory medication; this is a standard approach used in gout RCTs in which flares are an outcome of interest (64-72).

Importantly, our focus on the occurrence of acute gout flare as the primary outcome is highly consistent with priorities of both healthcare providers and gout patients. As mentioned above, in preparing for this application we conducted separate surveys targeting both gout patients participating in the National Data Bank for Rheumatic Diseases (NDB) (n = 40) and a national sample of VA healthcare providers actively involved in gout management (n = 179). Both groups identified a reduction in acute gout flare as the top priority and the preferred primary endpoint for any future trial examining the comparative effectiveness of ULT (unpublished).

Secondary End Points

Key secondary outcomes will include:

1) Efficacy (occurrence of gout flare in Phase 3) and tolerability in patients with CKD 3.

   We plan to enroll approximately 317 participants with Stage 3 CKD; these participants will be enrolled in equal proportions in both arms. To determine whether the efficacy of allopurinol and febuxostat differ among those with Stage 3 CKD, a planned secondary endpoint will be the occurrence of gout flares during Phase 3 (as defined above) in this patient subset. Tolerability of the two treatments will also be compared in this patient subset and will include comparisons of adverse events, serious adverse events, and related study withdrawal.

2) The proportion of patients achieving a sUA threshold < 6.0 mg/dl in Phase 2 across treatment groups.

   The proportion of patients achieving a sUA < 6.0 mg/dl during Phase 2 (mean level assessed at weeks 36, 42, and 48) will be examined as a secondary study outcome. A sUA threshold of < 6.0 mg/dl is based primarily on the understanding that hyperuricemia is a necessary, although not always sufficient, precursor in gout development and progression. Indeed, a sUA, 6.0 mg/dl is the recommended initial treatment target of the American College of Rheumatology. Hyperuricemia is most commonly defined as a sUA concentration exceeding 6.8 mg/dl, the level at which extracellular urate super-saturation occurs and promotes the precipitation of monosodium urate crystals in both joints and surrounding tissues.

   Lowering and maintaining sUA concentrations below the level of 'supersaturation' is absolutely essential in reducing the total body urate burden and achieving long-term benefits. Targeting a slightly lower threshold of < 6.0 mg/dl accounts for both the issues of day-to-day variability in sUA and assay imprecision (estimated in College of American Pathologists Proficiency Testing [CAP PT] to approach 4 to 5%). Although the predominance of literature suggests no significant diurnal variation in sUA (73, 74), others have suggested a small degree of such variability approaching 0.5 mg/dl (75). In particularly, this level of sUA is considered an evidence-based target for treatment, and necessary to achieve outcomes pertinent to patients, such as reduction of flare frequency (7, 76). Understanding its essential role in gout treatment, we have adopted the biochemical threshold of a sUA concentration below 6.0 mg/dL as a secondary end-point, and one which regulatory agencies require for approval (11, 13).

To facilitate point-of-care ULT dose titration, all sUA measurements will be performed by the clinical laboratory at the participating study site. Importantly, sUA measurement is internationally standardized and readily accessible across all participating clinical laboratories. The prevailing technique used for sUA measurement used in the U.S. (including VA centers and RAIN sites) uses the Trinder reaction with uricase, an assay that has been shown to be highly reliable with between-laboratory and between-method coefficients of variation routinely below 5% (77).

3) Determining if gout flares in Phase 3 differ in those who reach a target sUA of < 6.0 mg/dl compared with those who do not by 48 weeks.

As detailed above, achieving a sUA goal of <6.0 mg/dl is a universally recommended treatment goal for ULT in practice as well as regulatory trials. However, the true relationship of achieving this target with reducing gout flares has not been well documented in long-term clinical trials. The design of this trial will allow us to address this important question. Specifically, we will compare the gout flare rates in Phase 3 of those who did and did not achieve a sUA of < 6.0 mg/dl at the end of Phase 2.

4) The impact of study treatments and sUA levels on health-related quality of life.

Both the five-item EurQol (EQ-5D-3L) and Veterans RAND 12 (VR-12) will be collected from all participants at baseline, 24, and 48 weeks. The EQ-5D-3L is a widely used measure of generic health-related quality of life, which is relatively brief and provides a single index utility value (78). This measure has been shown to be valid and reliable in assessing health-related quality of life in a number of chronic health conditions and will enable future cost-effectiveness analysis. Results from the EQ-5D-3L will be supplemented with those from the VR-12, an alternative measure of health-related quality of life. Similar to the EQ-5D-3L, the VR-12 survey is relatively brief and demonstrates excellent validity and reliability. Of special note, the VR-12 allows for computation of both Physical and Mental Health Scale scores. Although gout-specific health-related quality of life measures have been proposed, these measures have not been consistently demonstrated to have sufficient levels of validity or reliability (79).

5) Changes in tophi area by location among those with tophaceous gout across treatment groups and sUA levels.

Based on data from a recent clinical trial in chronic gout, we anticipate that ~20% of study participants will have tophi at enrollment (12). Change in tophi area (see below for assessment procedure) will be examined as a secondary outcome among this informative subset of patients with tophaceous gout. Providing rationale for their consideration as a secondary outcome, tophi are pathognomonic of gout and are problematic for patients as they mediate joint damage, often result in troubling cosmetic issues, and frequently obstruct normal joint function.

For this study, a sentinel tophus will be measured at enrollment and the same tophus will then be measured in follow-up at weeks 24 and 48 using tape measurement as recently detailed by Dalbeth et al. (80). The sentinel tophus will be defined as the most prominent and/or most readily measured

tophus found at the time of the baseline evaluation on the hands, elbows, feet, or ears (i.e., the most common sites for tophi). In addition to having face validity, the tape measurement technique is inexpensive, requires minimal training, and a very short time for acquisition (estimated to be < 5 minutes). Moreover, this technique yields excellent inter- and intra-observer reliability with interclass correlation coefficients exceeding 0.9. In a 52-week study, patients with tophaceous gout achieving a final serum urate < 6.0 mg/dl demonstrated a 75% reduction in tophus size using this technique (11).

6) The impact of treatment on the flare rate over time (comparison of flare rates during each phase).

To determine whether the total number of gout flares differs between the two treatment groups the total flare numbers occurring during observation (week 0 to 72) will be compared. Recognizing that the duration of a gout flare typically extends from several days to 2-3 weeks, and that it may sometimes be difficult for patients to distinguish between two or more back-to-back flares and one persistent but fluctuating flare, a maximum of one gout flare will be counted for each one-month observation period. Thus, as an example during Phase 3 (24 weeks) patients could experience a number of gout flares ranging from 0 to 6 flares.

7) Exploring the tolerability/toxicity of the two ULT.

Toxicity data will be carefully collected throughout the 72 weeks of the trial (See Section XI, Baseline and Follow-up Assessment) and compared across treatment arms. Adverse events will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) terminology and reported by count and frequency (%) for participants reporting an event for each term. Toxicity data that will be systematically collected include rises in sUA levels, serum creatinine, CBC, liver function tests (LFTs), blood pressure and reports of skin rashes. The frequency of cardiovascular safety events of interest will also be collected and analyzed, with particular emphasis on cardiovascular and all-cause mortality. Investigators will report other treatment-related adverse events should they encounter them. All hospitalizations and other adverse events defined as serious per ICH guidelines will be collected and analyzed by treatment group.

Serious adverse events which are considered by site staff or the study sponsor to be potentially cardiovascular in nature will be reviewed to determine whether the event should be considered a major adverse cardiovascular event (MACE) as defined by the CARES trial (CARES appendix s2). Adjudication will be performed independently by at least two experienced cardiologists, with a third adjudicator used to break ties. Each potential cardiovascular SAE will be assigned to one of the following categories.

- Arrhythmias not associated with ischemia
- Cardiovascular Death
- Hospitalization for Heart Failure
- Non-fatal Myocardial Infarction
- Stroke
- Transient Ischemic Attack (TIA)

- Unstable Angina requiring urgent revascularization
- Other cardiac event
- Not a cardiac event

The decision as to whether participants who experience a cardiovascular event should be continued in the protocol is at the discretion of the local site investigator. The study chair should be consulted for any questions or concerns.

Patients reporting skin rash at any time during the study will be evaluated in-person by a study investigator, with structured data collection completed in order to precisely characterize the nature and severity of the rash. Data to be collected pertinent to rashes will include the individual components of the provisional classification criteria for the definition of allopurinol hypersensitivity syndrome (AHS) (81) (see criteria below). We will modify these criteria slightly to include the use of either allopurinol or febuxostat, recognizing that the frequency of rashes for the two drugs has been similar in head-to-head trials conducted to date and serious cutaneous reactions have been reported for febuxostat during post-marketing surveillance. Participants satisfying criteria for drug-related hypersensitivity will discontinue study medication and will be counted as a treatment failure but will continue to be followed. Participants presenting with rashes that do not satisfy these criteria may be continued in the protocol at the discretion of the site investigator and the study chairman. Such participants will have the option of continuing on protocol at stable or reduced doses of study medications at the discretion of the site investigator.

Participants will be considered to have drug-related hypersensitivity if they satisfy two of the following major classification criteria, or if one major plus at least 1 minor criterion is present in the absence of other exposures (e.g. alternative medications) that might explain the clinical picture:

Major Criteria:
Worsening renal function (drop in eGFR >50% from study baseline)
Acute hepatocellular injury (ALT >3 times upper limit of normal)
A rash including features of toxic epidermal necrolysis, erythema multiforme, or a diffuse maculopapular or exfoliative dermatitis

Minor Criteria:
Fever (T≥100.4°F concurrent with the rash)
Eosinophilia (absolute eosinophil count >2 times upper limit of normal)
Leukocytosis (WBC >2 times upper limit of normal)

8) To describe the effects of baseline covariates and time-dependent covariates on the primary results.

VIII. Bio statistical Considerations

Overview of the Study Design

The proposed study is a blinded, intent-to-treat, two-arm intervention trial testing whether allopurinol is non-inferior to febuxostat. The trial will test the primary hypothesis that appropriately titrated allopurinol is non-inferior to appropriately titrated febuxostat.

The trial has three phases: Phase 1 (weeks 0-24) titration, Phase 2 (weeks 25-48) maintenance, and Phase 3 (weeks 49-72) steady-state-evaluation.

The primary outcome measure is the proportion of study participants in each arm who have one or more gout flares during Phase 3, weeks 49-72 of the follow-up period. During Phase 1 of the study (first 24 weeks), participants will have gradual titration of their assigned urate-lowering medication in a protocolized fashion to achieve the sUA target of <6mg/dL. During Phase 2, participants will maintain the achieved dose of the assigned treatment during weeks 25-48, with dose titration allowed if the target sUA is not yet achieved and if maximal dose of ULT is not yet achieved. During Phase 3, participants will continue on their achieved dose without any titration. While we will be collecting information on gout flares during both Phase 1 and 2, our primary outcome is the proportion of study participants experiencing at least one gout flare during Phase 3 because flares during the first two phases are likely reflective of the known increased risk of flares during initiation and early maintenance of ULT, whereas participants should be in steady-state by Phase 3. Thus, during Phase 3 we will record the occurrence of gout flares for each participant (as will also have been done for the first two phases) and record the binary outcome of either no gout flares (event absent) or one or more gout flares (event present).

If the null hypothesis of inferiority is rejected, then the treatment allopurinol will be considered 'non-inferior' (see below for specific parameters). We wish to reject the one-sided null hypothesis that allopurinol is inferior to febuxostat. This has particular clinical and health economic relevance given the substantially higher cost of febuxostat.

A single analysis of the effect of the study medications will be conducted at the end of the trial. No interim analysis is planned.

The study will enroll and randomize a total of 950 study participants to receive either allopurinol or febuxostat. We expect to enroll, on average, approximately 40 study participants per month for 24 months. All participants will be followed for 72 weeks.

Estimated Incidence of the Primary Endpoint

The primary outcome is the occurrence of gout flares during Phase 3 (final 24 weeks). We have chosen as the expected rate of outcomes for febuxostat a 20% rate of one or more flares within Phase 3, midway between 15% and 25%. Uncertainty arose because relevant studies used different definitions of flare, different treatment dosages, and provided little detail about recurrent flares. Also, we cannot precisely project the proportion of participants who will have sUA < 6 mg/dl when Phase 2 ends. Hence, we believe that in Phase 3, 75%-85% of participants will be flare-free and 15-25% will have one or more flares.

This range is based on four studies of gout patients on maintenance doses of one of the study treatments (11, 82-84).

Becker et al (11) tested the non-inferiority of allopurinol to febuxostat using a bound of 10% for the binary endpoint of sUA <6 mg/dl and showed monthly rates of gout flares declining over time to approximately 10%. During the final month only 6% of those achieving sUA < 6 mg/dl required treatment for a flare compared to 14% of those with sUA ≥ 6 mg/dl. Shoji et al (83) conducted a retrospective study of the rate of gout flares with observation periods ranging from 1 to 3 years. In the medication group, starting one year after the first visit, 24% had at least one gout attack and the rate was about 5% per month. Rothenbacher et al (82) studied a cohort of over 20,000 gout patients and noted that almost 20% of patients had a first flare within the first year of follow-up. Wortman et al (84) reanalyzed data from three clinical trials that enrolled 4101 gout patients and showed that rates among treated participants with sUA < 6 mg/dl declined to 5% per month. In addition, in a community-based cohort of gout patients, of whom less than half were on urate-lowering therapy (45%), the risk of having at least one attack in a year was ~70-75% (85).

A strategy of dose titration for each treatment will be employed to bring as many participants as possible below the threshold of sUA < 6.0 mg/dl, established by guidelines and recommendations (7). The Phase 1 titration is intended to bring sUA < 6.0 mg/dl within 24 weeks. All participants will be analyzed during Phase 3 regardless of whether their sUA is < 6.0 or ≥ 6.0 mg/dl. We expect that roughly equal numbers of participants in each study arm will reach this threshold. We expect that 75% - 80% participants will have a mean sUA < 6.0 mg/dl across the last 3 study visits occurring during Phase 2 at 36, 42, and 48 weeks. For secondary analysis, we define the binary outcome, mean sUA < 6.0 mg/dl as a treatment success and mean sUA ≥6.0 mg/dl, as a treatment failure.

Choice of a Bound, B, for the Non-inferiority Test

Non-inferiority tests require expert choice of a bound, B, larger than the true difference, D, between the treatment proportions of participants with flare events (the proportion for febuxostat minus the proportion for allopurinol). The bound marks where clinicians might begin to doubt that the difference, D, is very small and close to zero. Seven rheumatologists on our Planning Committee, selected for their expertise in gouty arthritis and clinical trial design, chose B = 8%.

The null hypothesis will be rejected if U, the upper limit on the one-sided 95% confidence interval on the difference between the two flare-event rates (D), is less than B = 8%. (See Figure 1) If U exceeds B then this indicates that the true difference may be large and that allopurinol is inferior to febuxostat. (See Figure 2)

It is important to note that our choice of a bound is more conservative when compared to many other recent studies. Previous studies have chosen the true bound to be 10% and a true difference in the proportions to be 0% (11). For the non-inferiority test, this more conservative estimate requires CSP 594 to enroll a larger sample size.

Primary Data Analysis Plan

The primary hypothesis to be tested is that allopurinol is non-inferior to febuxostat. The primary outcome is the difference (D) in proportion of patients with one or more gout flares during Phase 3. The proposed test is a one-sided non-inferiority test of the null hypothesis that U > B, which the upper limit on the 95% confidence interval on the difference between two proportions exceeds 8%. We posit a true difference in proportions of 0%.

Formal statement of the primary hypothesis

H_0: Allopurinol is inferior to febuxostat. The Phase 3 proportion of one or more gout flare events among Allopurinol participants is more than the Phase 3 proportion of one or more gout flare events among Febuxostat participants by 8% or more (D ≥ 8%).

H_a: Allopurinol is non-inferior to febuxostat. The Phase 3 proportion of one or more gout flare events among Allopurinol participants is not more than the Phase 3 proportion of one or more gout flare events among Febuxostat participants by 8% or more (D < 8%).

The estimate of D, $\widehat{D}$, is the observed treatment difference. The difference is defined so that it is positive when febuxostat has the higher success rate. To test the null hypothesis we will compute the upper limit of a one-sided 95% confidence interval for D:

U = $\widehat{D}$ + 1.645*stderr($\widehat{D}$).

The graphic below displays the decision process. In **Figure 1** the upper limit (U) is less than B, and we accept the alternative hypothesis of non-inferiority; allopurinol is non-inferior to febuxostat. In **Figure 2**, U exceeds B indicating that the true difference may be larger than the posited value of D; we cannot reject the null hypothesis that allopurinol is inferior to febuxostat.

Figure 1: One-Sided 95% Confidence Interval for the Non-inferiority Test Depicting 'Rejection' of the Null Hypothesis

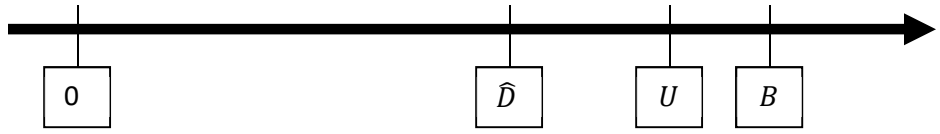


Figure 2: One-Sided 95% Confidence Interval for the Non-inferiority Test Depicting 'Acceptance' of the Null Hypothesis

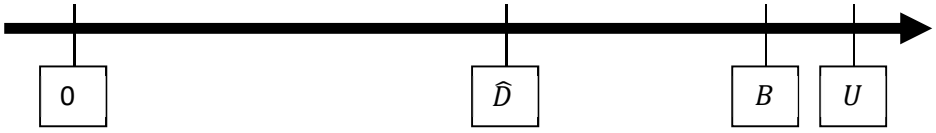


Figure 2 shows that the estimated difference, $\widehat{D}$, need not exceed B to retain the null hypothesis that allopurinol is inferior to febuxostat. For example, if the observed event rate of gout flares for allopurinol is

24% and for febuxostat is 20%, then the difference is 4%, but U = 8.4% which exceeds B = 8%. In other words an observed difference of $\widehat{D}$=4% or more will preserve the null hypothesis and only an observed difference, $\widehat{D}$ < 4% will establish non-inferiority. In effect, an observed difference in proportions of 4% or more undercuts the belief in equivalence. Metaphorically, if the bound B were an electric fence then, for safety, the observed difference, $\widehat{D}$, must be more than an arm's length from B.

Sample Size and Statistical Power Considerations for the Primary Hypothesis

The results for the primary hypothesis will be analyzed by means of a one-sided 95% confidence interval on the difference in proportion of participants with one or more gout flare events. The test of the difference between proportions will have one-sided type I error of 5%. Starting with a total of 950 participants, allowing 5% dropout, and retaining 900 participants, the test has 90% power to reject the null hypothesis of inferiority with a total of 900 participants, 450 participants per arm,

For large samples, regarding the difference between proportions as the difference between means, the use of the standard Student's t distribution closely approximates the non-central t-distribution and justifies use of the power formula 3.2.4 (in section 3.2.2) below (Chow, Shao, and Wang (86):

$$n = n_1 = n_2 = \frac{\left(Z_\alpha + Z_\beta\right)^2 2\sigma^2}{(D-B)^2}$$

Note: n = 450 is the number of participants in each of the two study arms, Z_α = 1.645 is the cut point for a one-sided test with a 5%, Type I error, Z_β = 1.28 provides 90% power, Bound = 8%, D=0% is the true difference between the treatment outcome measures, and σ^2 = 0.16 is the variance associated with the distribution of for a single Bernoulli observation.

As rates are uncertain, we note that if the Phase 3 rate of gout flares is either 15%, 20%, or 25% then the respective statistical powers are 96%, 91%, and 87%. With a rate of 20%, but a higher dropout rate of 10%, the power is 90%. Non-adherence to treatment, inability to attain sUA < 6 mg/dl, or failure to appear for clinic visits will not affect dropout, only the explicit decision of the patient to leave the study. Participants who experience toxicity that either reduced dosage or other medications reduce to a tolerable level can remain on study if they wish to do so.

The binomial test fails to account for dropout during phase 3. We suspect that only 1 or 2 of the cohort may drop out flare-free, survive, and refuse to allow us to passively follow them until the end of phase 3. Only a few will die before having a flare and they will be counted as treatment failures as if death were a flare. Others will drop out of follow-up protocols, but remain alive and on-study. With their permission we will passively follow them reviewing their charts to see if and when during phase 3 they report a gout flare to their physician. For them dropout entails discontinuing phone contact with study staff and declining to complete study forms during clinic visits. Reluctance to adhere to the titration regimens and treatment side effects should account for 3% of the annual 5% dropout during phases 1 and 2. This leaves 2% who drop out for other reasons. During phase 3 the adverse events will merely lead to adjustments in treatments but not dropout. Thus, during the half-year of phase 3, only about 1% = (1/2 of 2%) of participants will drop out.

The following speculative but conservative scenario suggests about 1 among the cohort of 900 will drop out before having a flare and have a truly censored outcome. Assuming that dropout is equally likely before or after a gout flare, we will have 4.5 = 0.005*900 expected dropouts. Rounding up to 5 participants, we suspect 2 will die without a flare (counted as failures) and 2 of the surviving 3 will agree to passive follow-up. The remaining survivor who declines passive follow-up will be counted as a failure.

A more rigorous survival analysis will be done to confirm the primary result. It can treat dropout as censored data. However, while we could elicit from physicians a bound B for the proportion of flares, we could easily elicit the bound B for the non-inferiority test in terms of beliefs about tolerable deviations from a hazard ratio.

The test of the primary hypothesis compares the treatments without adjustment for any covariates. The secondary analyses, particularly secondary analysis will confirm or not confirm the primary hypothesis by considering variations on the primary analysis including logistic regression models that adjust for covariates. We note that logistic regression analysis yields a treatment odds ratio rather than the difference between proportions. In this case, to carry out the non-inferiority test, we will estimate the difference between treatments by linking the odds ratio to the overall proportion of participants who have one or more gout flares.

In addition to testing the primary hypothesis, extensive descriptive analyses outlined in (BRDP) will compare treatments with respect to selected variables among the demographic, medical history, laboratory values, anthropomorphic, vital sign, quality-of-life, alternative outcome, and side effect variables. Simple unadjusted comparisons will apply Student's t-test to continuous variables, the Wilcoxon test to highly skewed continuous or ordinal variables and will apply the Chi-square test (or Fisher's exact test) to categorical variables.

Non-adherence

Of relevance to this study, observational studies have indicated relatively poor adherence in patients with gout (40, 87-90) However, Dalbeth et al. (91) found that higher doses of allopurinol were associated with sUA levels at target independent of adherence with treatment. Because all study participants will receive active therapies of proven efficacy for lowering sUA levels as well as prophylactic treatment of acute gout symptoms, compliance issues are expected to be minimal in this trial. Other studies in rheumatoid arthritis have shown that if patients are doing well, issues of poor treatment adherence are minimized (92).

Participant adherence to protocol-directed study treatment will be assessed via pill counts, prescription renewals, and participant interview. We will use the question and pill count data to determine if a participant took 80% or more of treatment medication. The per-protocol population will be defined as participants remaining on the same treatment throughout the entirety of the study with 80% adherence.

The primary analysis follows the ITT principle that adjusts for, at most, a few covariates and seldom directly accounts for non-adherence. We will compare the primary results with the analogous results for the per-protocol participants. Also, we will model the effects of non-adherence in the secondary analyses.

In this case adherence is a time-dependent covariate requiring that the treatment comparison be made using a GEE analysis to account for varying periods of follow-up between treatments.

Secondary Data Analysis

All secondary analyses are descriptive exploratory analyses and will be done with and without covariate adjustment (age, sex, disease severity, comorbidities, etc.). All secondary analyses deal with dropping out in the same way described in the primary analyses

We describe the proposed analysis for each of the eight secondary objectives:

1) To compare the efficacy and tolerability of allopurinol and febuxostat in hyperuricemic participants with gout and stage 3 chronic kidney disease (CKD 3) in reducing gout flares.

   Based on VISN 1 data, over half the participants should have stage 3 CKD. We will carry out exactly the same non-inferiority analysis proposed for the primary objective but restricted to participants with stage 3 CKD, using only gout flares observed during Phase 3. In addition we will carry out logistic regression analyses that adjust for covariates as described in the confirmatory analyses in objective 8. Also, using the full cohort we will compare gout flare rates of participants with stage 3 CKD to participants with an eGFR ≥60 mL/min/1.73m^2 within a logistic regression model. Tolerability of the two treatments will also be compared in this patient subset and will include comparisons of adverse events, serious adverse events, and related study withdrawal.

2) To explore the efficacy of the two ULT dosing regimens in achieving the goal of sUA <6.0 mg/dl evaluated at the end of phase 2. Besides treatment, the primary predictors include the series of sUA measures and dose titrations prior to 48 weeks. This longitudinal analysis will model deviations from the titration protocol.

   The primary analysis for these longitudinal data will be the mixed effects model with a variance-covariance structure that assumes auto correlated AR(1) sUA measurements over time. We will use PROC MIXED in SAS. At each clinical visit a binary factor will indicate if the titration protocol is or is not maintained. Besides baseline factors such as age, sex, and duration of disease, the model will incorporate time-dependent factors including side effects. Missing data methods will address potential censoring of events among patients who fail to attend clinic visits. We will run this same analysis using the biological threshold of sUA <6.8 mg/dl after 48 weeks.

3) To determine if gout flares in phase 3 in participants who achieve a sUA < 6.0 mg/dl by 48 weeks differ compared to those who do not, regardless of treatment assignment.

   This binary outcome for this logistic regression analysis will be the 48-week status of sUA; namely, sUA < 6 mg/dl vs sUA >= 6 mg/dl. The analysis will model the gout flares in phase 1 and phase 2 as time-dependent covariates as in the second secondary analysis above. Models with additional factors are described in objective 8.

4) 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.

EQ-5D-3L & VR-12 instruments will be administered at baseline, 24 and 48 weeks. At each time we will compare the mean scores by treatment groups, using both an unadjusted t-test and linear regression with adjustment for baseline covariates. Also, with outcome change from baseline to 24 weeks and change from baseline to 48 weeks, we will compare mean changes with and without covariates using linear regression. Finally, we will carry out a repeated measures analysis using all three time points. Missing data methods will address potential censoring of events among patients who fail to complete the instrument at a particular time. Analogous analyses will be carried out controlling for sUA levels.

5) To determine whether change in tophi area differ by location between participants randomized to allopurinol compared to febuxostat and differ by achievement of sUA < 6.0 mg/dL, regardless of treatment assignment.

Tophi area will be assessed at baseline, 24 and 48 weeks. At each time point we will compare the mean areas by location by treatment groups, using an unadjusted t-test and linear regression with adjustment for baseline covariates. Also, with area change from baseline to 24 weeks and area change from baseline to 48 weeks, we will compare mean changes by location with and without covariates using linear regression. Finally, we will carry out a repeated measures analysis using all three times. Missing data methods will address potential censoring of events among patients who fail to complete the instrument at a particular time. Analogous analyses will be carried out controlling for sUA levels.

6) To determine whether the number of gout flares during all three phases differ between participants randomized to allopurinol compared to febuxostat and then extend this analysis to the entire 72-week period.

We will model the number of gout flares, which can have substantial variation, as Poisson random variables. The analyses will compare treatments using a longitudinal repeated measures analysis with Poisson counts (PROC GLIMMAX and GENMOD in SAS). Missing data methods will address potential censoring of events among patients who appear to fail to report flares. Flare counts will be analyzed separately during Phases 1, 2, and 3 because dose titration during Phase 1 tends to increase the counts, and this effect may still persist in Phase 2, particularly for those still undergoing dose titration; participants are expected to be in steady-state by Phase 3. Also, Phase 2 analysis will consider prophylactic treatment after a gout flare and severe side effects of treatment as predictors of subsequent counts. During Phase 3 the same set of factors as well as Phase 2 counts will be used to predict gout flare counts. These time-dependent associations will require a mixed effects model using an auto correlated variance-covariance to model the series of events. For these analyses we may treat

the counts as continuous measures in order to introduce more subtle variance-covariance structure and a variety of random effects.

7) To determine the patterns of tolerability/toxicity for each treatment during Phase 3 and then overall from weeks 1-72.

Toxicity events include rises in sUA levels, adverse changes in serum creatinine, CBC, liver function tests (LFTs), blood pressure, and the incidence of skin rashes. The incidence of cardiovascular events of interest, with particular emphasis on cardiovascular and all-cause mortality, will also be included in this analysis. Within each Phase we will determine if the incidence of such events differs between treatments. In the Phase 3 analysis baseline covariates will include the summary of toxicity events during Phases 1 and 2 as well as the 48-week sUA level. As in the sixth secondary analysis the same statistical methods for Poisson counts will be used to express time-dependent events.

At each clinic visit we will assess the count of each type of major side effect episodes between visits. Deviations from the titration protocol will be modeled as a binary factor. We will model counts that have substantial variation as Poisson random variables. These outcome measures include each count and the aggregate count. These counts will be coarsened into binary outcomes of no events versus one or more events. The analyses will compare treatments using a longitudinal repeated measures analysis with Poisson count, negative binomial counts, and binary outcomes (PROC GLIMMAX and GENMOD in SAS). Missing data methods will address potential censoring of events among patients who fail to attend clinic visits. We will run this same analysis using the biological threshold of sUA <6.8 mg/dl after 48 weeks.

8) To describe the effects of baseline covariates and time-dependent covariates on the primary results.

Baseline data include demographic characteristics (e.g. age, sex), disease history including CKD level, presence of tophi at baseline, height, weight, laboratory values, medications, other comorbidities, and quality-of-life measures. Data obtained often after baseline include sUA values, titration levels, side effects, and gout flare counts. Many baseline measurements are repeated at 24 and 48 weeks. All data obtained before Phase 3 may be used as baseline factors for Phase 3 analyses such as the primary hypothesis and secondary object #1. Secondary analyses 2-7 can adjust for covariates obtained at baseline and at 24 weeks.

All major analyses will be repeated on the per-protocol population with adherence and non-adherence as defined above. The objective is to either confirm our results or detect that adherence to treatment alters the result.

Missing Data

Rate of attrition has been estimated as being up to 15% with up to 7.5% data loss, and sample size has been adjusted accordingly to maintain 90% statistical power for the primary analysis. Distribution of participants lost to follow-up and missing data on key variables across the treatment groups will be monitored throughout the study. Missing endpoint data will not be imputed. The intent-to-treat principle

will be used to analyze endpoint data. Missing covariate data will be imputed in selected circumstances as described in Little and Rubin (93). We will explore the possibility of non-random dropout on endpoint data (94).

IX. Study Population and Patient Recruitment

Patient Population:

Patients with a history of gout who are hyperuricemic defined as a sUA ≥ 6.8 mg/dl will be approached for participation in this trial. Gout will be defined based on satisfaction of American College of Rheumatology (ACR) and EULAR gout classification criteria (95) as defined below:

1) Entry Criterion. Criteria scoring will only be applied to subjects that meet this requirement: At least one episode of swelling, pain, or tenderness in a peripheral joint or bursa.
2) If the entry criterion is met, then the subject should be assessed for the Sufficient Criterion: Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus. If the sufficient criterion is met, then ***the subject is classified as having gout*** and no further scoring is required.
3) If the entry criterion is met but the subject does not meet the sufficient criterion, then the criteria score must be obtained by selecting the highest category within each of the domains in the table below.
4) If a score of ≥8 is achieved, the subject is classified as having gout.

Domains		Categories	Score	Total
CLINICAL	Pattern of joint/bursa involvement during symptomatic* episode(s) ever	Joint(s) or bursa(e) other than ankle, midfoot or 1st MTP (or their involvement only as part of a polyarticular presentation)	0	
		Ankle OR midfoot (as part of monoarticular or oligoarticular episode without MTP1 involvement)	1	
		MTP1 (as part of monoarticular or oligoarticular episode)	2	
	Characteristics of symptomatic episode(s) ever: i) Erythema overlying affected joint (patient-reported or physician-observed) ii) Can't bear touch or pressure to affected joint iii) Great difficulty with walking or inability to use affected joint	No characteristics	0	
		One characteristic	1	
		Two characteristics	2	
		Three characteristics	3	
	Time-course of episode(s) ever: Presence (ever) of ≥2, irrespective of anti-inflammatory treatment: i) Time to maximal pain <24 hours ii) Resolution of symptoms in ≤14 days	No typical episodes	0	
		One typical episode	1	
		Recurrent typical episodes	2	

	iii) Complete resolution (to baseline level) between symptomatic episodes			
	Clinical evidence of tophus: Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles).	Absent	0	
		Present	4	
LAB	**Serum urate:** Measured by uricase method. Ideally should be scored at a time when the patient was not taking urate-lowering treatment and patient was beyond 4 weeks of the start of an episode (i.e., during intercritical period); ***if*** practicable, retest under those conditions. The highest value irrespective of timing should be scored.	<4mg/dL [<0.24mM] †	-4	
		4-<6mg/dL [0.24-<0.36mM]	0	
		6-<8mg/dL [0.36-<0.48mM]	2	
		8-<10mg/dL [0.48-<0.60mM]	3	
		≥10mg/dL [≥0.60mM]	4	
	Synovial fluid analysis of a symptomatic (ever) joint or bursa:** Should be assessed by a trained observer.	Not done	0	
		MSU negative	-2	
IMAGING‡	**Imaging evidence of urate deposition in symptomatic (ever) joint or bursa:** Ultrasound evidence of double-contour sign¶ ***or*** DECT demonstrating urate deposition§.	Absent OR Not done	0	
		Present (either modality)	4	

	Imaging evidence of gout-related joint damage: Conventional radiography of the hands and/or feet demonstrate at least one erosion.‡‡	Absent OR Not done	0	
		Present	4	
Total Score				

* Symptomatic episodes are periods of symptoms that include any of swelling, pain, or tenderness in a peripheral joint or bursa.

† If serum urate <4mg/dL (0.24mmol/L), **take away 4 points**; if serum urate ≥4-<6mg/dL (≥0.24mmol/L - <0.36mmol/L), score this item as 0

If polarizing microscopy of synovial fluid from a symptomatic (ever) joint or bursa by a trained examiner fails to show MSU crystals, **take away 2 points. If synovial fluid was not assessed (not done), score this item as 0.

‡ If imaging not available, score these items 0.

¶ Hyperechoic irregular enhancement over the surface of the hyaline cartilage that is independent of the insonation angle of the ultrasound beam (note: false positive DCS (artifact) may appear at the cartilage surface that should disappear with a change in the insonation angle of the probe).[31,32]

§Presence of color-coded urate at articular or peri-articular sites. Images should be acquired using a dual energy computed tomography scanner, with data acquired at 80 and 140 kV and analyzed using gout-specific software with a two material decomposition algorithm which color-codes urate.[33] A positive scan is defined as the presence of color-coded urate at articular or peri-articular sites. Nailbed, submillimeter, skin, motion, beam hardening and vascular artefacts should not be interpreted as evidence of DECT urate deposition.[34]

‡‡Erosion is defined as a cortical break with sclerotic margin and overhanging edge; excluding DIP joints and gull wing appearance.

Participant ID _____

LSI/Sub I Name: _____ LSI/Sub-I Signature _____ Date: _____

The study will include gout patients not only receiving first-time ULT but will also allow for the inclusion of gout patients who remain hyperuricemic (serum urate ≥ 6.8 mg/dl) despite ongoing therapy with uricosurics (e.g. probenecid) or allopurinol at daily doses ≤ 300 mg. Uricosurics will require a 14-day wash-out prior to study enrollment. Because febuxostat is non-formulary in the VA and considered only for patients failing or intolerant to allopurinol, patients with prior use of this agent will be excluded from study participation.

Inclusion Criteria:

1. Age ≥18 years
2. History of gout – crystal proven or historical as defined by ACR criteria listed above
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 m^2
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 that 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

Defining Chronic Kidney Disease:

Chronic kidney disease (CKD) is defined on the basis of abnormalities of kidney structure or function that are present for >3 months and have implications for health (96). The severity of CKD is stratified based on the magnitude of reduction in glomerular filtration rate (GFR) into five categories (Table 3), with the presence of decreased GFR (<60 mL/min/1.73 m^2) for >3 months defining the presence of CKD independent of other markers of kidney damage, such as albuminuria, hematuria or structural abnormalities of the kidney. Inulin, iothalamate or iohexol clearance measurements are the "gold standards" for measurement of GFR but are highly cumbersome and are impractical in clinical practice. While creatinine clearance measurements based on 24-hour urine collections have been widely used for estimation of GFR, 24-hour urine collections are subject to numerous inaccuracies, including over- and under-collection of the urine sample. In addition, creatinine clearance systematically overestimates true GFR by 10% to 40% due to tubular secretion of creatinine. Thus, measured creatinine clearance does not improve the estimate of GFR over that provided by estimating equations (96-98). Multiple estimating equations using serum creatinine and demographic data have been developed and validated including the Cockroft-Gault equation (99), the Modification of Diet in Renal Disease (MDRD) equation (100, 101) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations utilizing creatinine, cystatin C or both (97, 102). In this study we will utilize the MDRD equation for estimation of GFR and assessment of kidney function. Although the CKD-EPI equation performs modestly better than the MDRD equation, particularly in patients with near normal serum creatinine values, this enhanced performance is relatively trivial in comparison to the overall precision of the equations (97, 102). More importantly, the VA utilizes standardized reporting of MDRD estimated GFR (eGFR) across all facilities.

Patients with stage 1 or 2 CKD, based on the presence of persistent albuminuria or known structural abnormalities of the kidney (e.g. polycystic kidney disease), but with preserved kidney function with an eGFR of ≥60 mL/min/1.73 m^2, will be included in the "normal" kidney function cohort for the purpose of this study. On the basis of GFR, these patients are indistinguishable from the large numbers of healthy elderly who have an eGFR between 60 and 90 mL/min/1.73m^2 on the basis of age. Furthermore, significant abnormalities in renal urate and drug handling are not seen in patients with eGFR ≥60 mL/min/1.73 $m^{2.}$

Table 3: Staging of Chronic Kidney Disease based on Glomerular Filtration Rate

GFR Stage	GFR (mL/min/1.73 m^2)
1	≥90
2	60-89
3	30-59
4	15-29
5	<15

Changes in Renal Function during the Protocol

With a 950 patient study and particular in this gouty population some patients will have renal function deterioration during the study. In most cases this will not require any changes in treatment regimens with regard to ULT (allopurinol or febuxostat). However, in the case where patients develop stage 3 CKD (eGFR 30 to <60 mL/min/1.73 m^2) investigators will be encouraged to stop naproxen if being used for prophylaxis and instead use colchicine 0.6 mg q day or prednisone. If patients progress to more severe stages of CKD (eGFR <30 mL/min/1.73 m^2) the colchicine dose should be decreased to 0.6 mg every-other day or 0.3 mg daily or prednisone should be substituted for the colchicine. Colchicine should be avoided in patients who develop advanced CKD (eGFR <30 mL/min/1.73 m^2) with concomitant hepatic dysfunction. At all times investigators will be encouraged to use their best clinical judgment.

Participant Recruitment/Enrollment:

Potential participants will be identified via a number of mechanisms including through primary care and rheumatology clinics, self-referrals, and medical record review (through use of HIPAA waiver to screen for gout diagnosis, medications used to treat gout, renal function, and uric acid level).

Several approaches will be used to identify potential participants for the study. The recruitment methods we plan on employing are as follows:

- Potential participants will also be identified via VA national electronic health record data through the VA Informatics and Computing Infrastructure (VINCI) program. We will ask VINCI to provide a list of potential participants, including name, address, phone number, upcoming clinic visits, primary care panel assignment, and history of clinic attendance who meet our inclusion and exclusion criteria. PIs and Study Staff will use this information to inform primary care providers (PCP) of potential eligible patients in their patient panel and provide them with contact information to refer interested patients, the primary care providers will refer their interested patients to the study team and the study team will follow up with the patient regarding participation in the study. If a member of the study team is in the clinic at the time the PCP is seeing an interested patient then the PCP will introduce the patient to that study team member. If there is no member of the study team in the clinic the PCP or delegate will use email encryption to contact the study team regarding the interested patient.

- Primary care providers or Rheumatologists will also be notified by Study staff about eligible patients with pending clinic appointments and will be requested to ask about patients' interest in participation in the study
- There will be a standardized letter sent to those patients who do not have appointments coming up in the near future. The letter may be sent by the local site investigator (LSI) and will reference their health care provider and make note that the provider is aware they are being contacted regarding this study. The letter will request for them to indicate if they do not want to be contacted in the future regarding their interest in participating in the study. If interested, or no response is received within 2 weeks the local site investigator or study staff will contact the patient on the phone to discuss their possible participation in the study.
- No written documentation will be kept of patient's interest; however a list of potentially eligible patients will be maintained at each site to allow study staff to contact primary care providers or Rheumatologists about upcoming patients.
- Nurses, primary care providers, or Rheumatologists will be regularly reminded about the study and those with eligible patients will be contacted and encouraged to speak with the study staff about possible enrollment
- Educational materials in the form of posters and brochures may be displayed and distributed around the clinics describing the study and giving contact information for those interested.
- If patient expresses interest in participation they will be screened by study personnel using the Eligibility and Randomization case report form that will be saved in IWRS to confirm eligibility criteria is met.

If participants are eligible after screening, they may be randomized and enrolled in the study. Feasibility of recruitment is discussed in Section XIII below.

RAIN Site Participation:

When patients are recruited at RAIN sites identical procedures as described above will be followed. All RAIN sites will operate under their own IRB guidance, and will be managed by their own investigators. This will require no additional VA personnel. Clinical data will be collected at CSP Coordinating Center and information will be sent to Albuquerque who will be providing study drug for patients and safety monitoring at RAIN sites. The VA will not be using RAIN databases. The RAIN site will be operating under their own IRB and their informed consent/HIPAA form will describe who will have access to PHI and PII and what information will be shared with the VA. Veteran PHI will not be disclosed to non-VA site investigators. Aggregate study data, such as DMC reports, will be provided to non-VA RAIN investigators as required for conduct of the study.

X. Treatment Regimens

Dosing of study medications:

Study medications will be titrated in participants as described below. Participants will be assigned to allopurinol active and febuxostat placebo or allopurinol placebo and febuxostat active. Titration of both allopurinol and febuxostat will occur simultaneously, as shown below in Table 4. ULT dosing adheres to the currently recommended initial dosing in gout patients with both normal renal function and CKD stage 3 and

mandates careful monitoring of patients as the dose is increased (7). Dose increases will occur until 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.

The 72-week study will be divided into 3 Phases: a 24-week Dose Titration Phase (Phase 1) followed by a 24-week Maintenance and Optimization Phase (Phase 2) and then a 24-week Steady State Flare Observation Phase (Phase 3). If sUA level is 6.0 mg/dl (5.0 mg/dl if tophi present) or above at week 30 (the first visit occurring during the second phase of the study), dose titration will be allowed as long as maximal daily drug doses have not been achieved (800 mg/day for allopurinol or 80 mg/day for febuxostat). Dose escalation will not be allowed during the final three study visits of Phase 2 occurring at weeks 36, 42, and 48 or during Phase 3. During Phase 3 participants will be actively followed by monthly phone interviews for flare reporting; no dose titration will be allowed during this phase to enable capture of flare data while participants are in steady-state.

Table 4*: Phase 1 Dose Titration for CSP 594; Weeks 0 to 24 (maximum ULT dose in mg/day by study week)

	Baseline	3 wks.	6 wks.	9 wks.	12 wks.	15 wks.	18 wks.	21 wks.	24 wks.
Allopurinol	100	200	300	400	500	600	700	800	800
Febuxostat	40	40	40	80	80	80	80	80	80
Prophylaxis	All participants required to be on prophylactic medication for a minimum of 6 months (see "Prophylaxis" section for details)								

For patients not at sUA goal prior to the week 36 visit, including patients who were previously at goal, up-titration is required up to the maximal daily dose, with exceptions permitted for patients experiencing adverse effects. For patients with an increase in sUA which is believed to be unrelated to medication dose (e.g., suspected analytic error or patient non-adherence), up-titration is generally encouraged but may be deferred based on clinical judgment until sUA can be retested.

Gout patients who remain hyperuricemic (sUA ≥ 6.8 mg/dl) despite ongoing allopurinol use in daily doses ≤ 300 mg will be allowed to enroll in the study. These patients will be randomized to receive febuxostat or to remain on allopurinol. For those initiating febuxostat, the starting dose will be 40 mg daily irrespective of prior allopurinol dose. For pre-study allopurinol users randomized to the allopurinol treatment arm, patients will continue with their current dose until scheduled for dose escalation based on the above schedule. For example, a patient on allopurinol 300 mg daily randomized to the allopurinol treatment arm would remain on 300 mg until week 9 of the study at which time they would be eligible for dose escalation. For a similar patient 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 as a consequence of sUA fluctuations and to ensure the same intensity of follow-up for all participants.

Recognizing that true equivalency doses have never been established for allopurinol and febuxostat, the dose titration schedule has been generated in order to yield a similar 'velocity' in sUA reduction in the two treatment arms over the first 24 weeks of the study. We have opted for the proposed dosing schedule for febuxostat, recognizing that the drug's package insert recommends starting all patients on 40 mg/day with a dose titration to 80 mg/day after 2 weeks for those with sUA ≥ 6.0 mg/dl (≥5.0 mg/dl if

tophi present). Given the lifelong nature of gout, our study outcomes have focused on longer-term reductions in gout flares and sUA rather than the 'time to achieve goal'. We believe that the slower dose escalation in febuxostat will reduce treatment-related gout flares in this arm, thus increasing participant adherence and ensuring a similar follow-up intensity between study arms. Recognizing that no comparative effectiveness trials of these two agents have been conducted using allopurinol doses exceeding 300 mg/day, the urate lowering properties of allopurinol 300 mg/day appear to be similar to that of febuxostat 40 mg/daily. In the CONFIRMS trial (12), 45% of patients receiving febuxostat 40 mg daily achieved a serum urate < 6.0 mg/dl over the six-month trial compared to 42% of those receiving allopurinol 300 mg/day. Patients initiated on allopurinol 100 mg daily will be titrated to 200 mg daily at week 3 prior to the first follow-up sUA that is planned for week 6. Although this could lead to 'overshooting' the sUA target in some patients, we believe this will be quite uncommon based on data from Schumacher et al (13) demonstrating that among gout patients with CKD receiving allopurinol 100 mg daily none achieved a sUA < 6.0 mg/dl.

In the event that a participant temporarily stops taking the study medication, it is generally not necessary to re-titrate. At the discretion of the site investigator, patients who were on a stable dose of study drug can be re-started at their prior dose. Participants who interrupted the study medication during the titration phase should be restarted at the dose at which they stopped and titration continued based on sUA results. During the titration phases of the study, a participant who stops and restarts the study medication should be on the study drug for a minimum of 7 days before SUA is drawn for titration purposes. While interruptions in study drug treatment should be avoided as much as possible, short-term (≤10 days) discontinuation of study medications during the Dose Titration Phase or a longer period of discontinuation during the Maintenance/Observation Phases which may occur due to participant non-adherence, adverse events, or other reasons is not generally regarded as a protocol deviation. The LSI may consult with the study team if clarification is necessary.

Prophylaxis:

Prophylactic therapy will be initiated either prior to or concomitant with study medication for all randomized participants.

One or more prophylactic/flare treatments including naproxen, colchicine, or prednisone will be dispensed based on prescriber judgment and individual participant need. While it is important that all participants will be on some flare prophylaxis the LSI may use their judgement if adverse events require changes or short term (≤10 days) interruption of the prophylactic medication. In circumstances where the LSI has additional questions or concerns the Study Chair should be consulted.

For patients with normal kidney function or mild renal impairment (defined as an estimated glomerular filtration rate [eGFR] ≥ 60 ml/min/1.73 m^2), the primary options for anti-inflammatory prophylaxis will be:

- Naproxen 250 mg p.o. twice daily with the possibility of dose escalation to 500 mg twice daily for patients experiencing breakthrough flares
- Colchicine 0.6 mg p.o. once daily with the possibility of dose escalation to 0.6 mg p.o. twice daily for patients experiencing breakthrough flares OR a dose decrease (0.6 mg p.o. every other day) for patients experiencing gastrointestinal intolerance

Based on patient-specific factors about the likelihood of breakthrough flares, intolerance, or other factors, it may be appropriate to initiate naproxen and colchicine at higher or lower doses in accordance with clinical judgment.

Precautions or contraindications for the use of low-dose naproxen include: a history of NSAID or aspirin allergy, CKD Stage 3 (see below), a history of peptic ulcer disease, ongoing anticoagulation (e.g. warfarin or heparin), moderate to severe anemia, poorly controlled hypertension, or cardiovascular disease. Precautions or contraindications with the use of colchicine include the use of high-risk medications that may heighten the risk for colchicine-related toxicity, including clarithromycin, telithromycin, nefazodone, diltiazem, verapamil and certain anti-retrovirals and azole antifungals. Refer to the Drug Information Report (DIR) for more detailed information on drug interactions.

The choice of which prophylactic agent to use (naproxen vs. colchicine) for gout patients with preserved kidney function (eGFR ≥ 60 ml/min/1.73 m^2) will be made at the discretion of the site investigator. A study participant may be switched to the alternative prophylactic strategy if the patient is intolerant to the first agent selected. For patients receiving naproxen, proton pump inhibitor (PPI) therapy may be considered or other effective suppression therapy for peptic ulcer disease at the discretion of the investigator. For certain patients, including those with contraindications or intolerance to both naproxen and colchicine, prednisone may be used as a second-line prophylactic agent with daily doses not to exceed 10 mg. For patients receiving prednisone, calcium/vitamin D supplementation in addition to anti-resorptive therapy may be considered at the discretion of the investigator. Prednisone should be used with caution in patients with poorly controlled diabetes mellitus.

For patients with Stage 3 CKD (eGFR of 30 to 59 ml/min), the primary option for acute gout flare prophylaxis will be:

- Colchicine 0.6 mg p.o. once daily with the possibility of a dose decrease (0.6 mg p.o. every other day) for patients experiencing gastrointestinal intolerance; note that colchicine doses exceeding 0.6 mg daily are not allowed for patients with Stage 3 CKD.
- Prophylaxis will stop for all participants at week 48.
- Low-dose naproxen will not be allowed for use in gout patients with Stage 3 CKD.
- For patients with Stage 3 CKD demonstrating contraindications or intolerance to low-dose oral colchicine, prednisone may be used as a second-line prophylactic agent with daily doses not to exceed 10 mg.

During phase 1-2 of the study, consistent with American College of Rheumatology (ACR) Gout Management Guidelines (61) the duration of prophylaxis will be the greater of:

- Six months' duration (24 weeks)
- Three months (12 weeks) after achieving a target urate goal < 6.0 mg/dl for a patient without tophi at enrollment (i.e., continued prophylaxis in patients with unresolved tophi)
- Six months (24 weeks) after achieving a target urate goal < 5.0 mg/dL, where there has been resolution of tophi that were present at enrollment

- In the event that flares continue after achieving the above criteria in a given patient, prophylaxis will be continued for a minimum of three months after the flare (i.e., prophylaxis continued or restarted for patients who experience a flare).

If the above criteria for stopping prophylaxis have been met the investigator is encouraged to do so. However, in select cases, prophylaxis may be extended beyond these time frames at the discretion of the investigator until the start of phase 3.

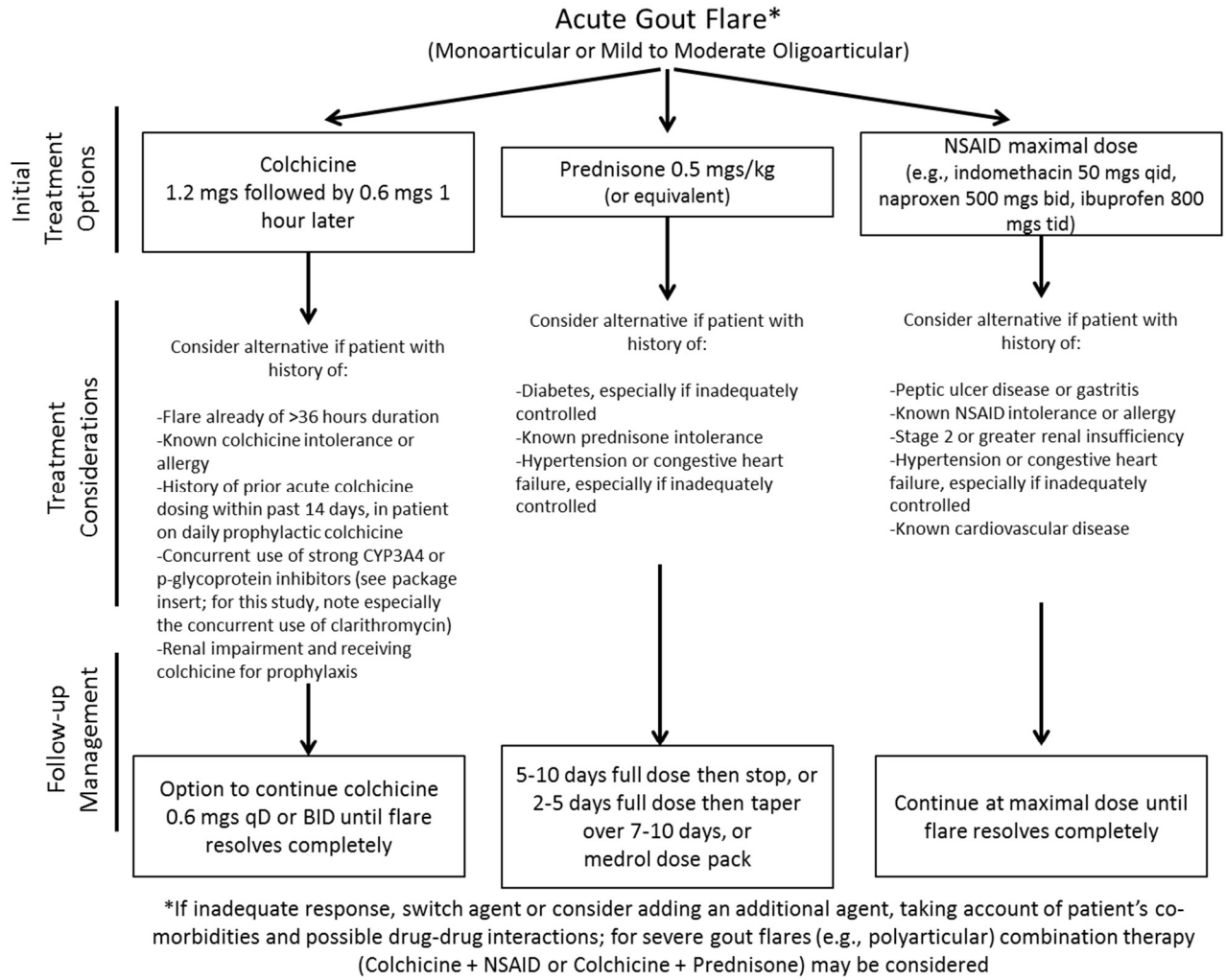
At 48 weeks (start of study phase 3), investigators will discontinue prophylaxis for all participants who are still receiving it. Should an acute flare occur, it should be managed as discussed below and the investigator may elect to reinstitute prophylactic treatment.

Management of Acute Gout Flares During the Study:

Should a patient in the study experience an acute gout flare, the management of the case is left to the discretion of the investigating physician and/or his/her local rheumatologic consultants. For the purposes of providing guidance some broad recommendations, based largely on the recent 2012 ACR gout treatment guidelines are included below (7).

The ACR recommends that all patients experiencing acute gout flares be treated with pharmacologic intervention, ideally within 24 hours of the onset of attack. For patients who can take oral medication, NSAIDs, glucocorticoids and colchicine may all be efficacious. If the patient is experiencing a monoarticular flare in a single large joint, or the involvement of one or several small joints (e.g., toes) only, monotherapy is appropriate. If the flare is particularly severe (e.g., is polyarticular or oligoarticular involving multiple large joints), initial combination therapy with two classes of anti-inflammatory agent may be considered. The ACR does not give instructions on adjustment for co-morbidities and/or drug-drug interactions but expects that the physician will take these into account. Some of those issues are discussed further below. *A simplified schema for managing routine gout flares is provided in Figure 3.*

Figure 3: Management of routine gout flares



Standard agents

Colchicine—Colchicine is an effective drug for gout flare treatment but ideally should be given within the first 36 hours of the flare, as it may be less efficacious after that time. The standard dose for colchicine for this purpose is 1.2 mg, followed by 0.6 mg 1 hour later; no further dose is given on the day of the flare, as higher doses cause toxicity without increased efficacy. This regimen may be used even in patients with mild-to-moderate renal insufficiency. In patients who have no contraindication, colchicine may or may not be continued at 0.6 mg once or twice daily until the flare is fully resolved; this follow-up dose is at the discretion of the physician. Patients who are already on daily colchicine prophylaxis may also receive this regimen, but only if they have not already been treated with colchicine for an acute flare in the last 14 days. In that case, an alternative therapy should be selected.

Treatment considerations include the potential for increased adverse event rates in patients with renal insufficiency and or concurrently taking drugs that affect colchicine metabolism by inhibiting the CYP3A4 or p-glycoprotein enzyme systems. For participants with stage 3 CKD who are on colchicine prophylaxis additional colchicine for flares is not recommended. Drugs that require a dose adjustment of colchicine when administered concurrently include clarithromycin and many anti-retroviral agents (strong interaction); and diltiazem, verapamil and others (moderate interaction). For simplicity's sake practitioners may want to consider using alternative flare treatment regimens in these patients, or consult the package insert for dose adjustment guidelines.

Glucocorticoids—the standard oral glucocorticoid therapy for gout is prednisone, typically starting at 0.5 mg/kg (i.e., typically about 25-40 mg) daily. The medication should either be continued at this dose until gout resolution, or may be tapered and then discontinued. The use of a Medrol dose pack may provide a simple tapering alternative. Patients may also receive an IM injection of triamcinolone 60 mg, but in this case the ACR recommends follow-up with an oral glucocorticoid. For patients who can't take oral medication, direct injection of a single joint is a possibility but requires expertise that is not presumed for the purposes of this study. Other alternatives include methylprednisolone, 0.5-2.0 mg/kg once IV or IM, and repeated daily as needed.

Short-term treatment considerations for glucocorticoids include the potential for promoting hyperglycemia, hypertension, stomach ulcer (particularly in patients already on an NSAID), agitation and avascular necrosis, among others. Practitioners may want to consider using a different agent in patients at higher risk for any of these or other steroid-related complications.

Non-steroidal anti-inflammatory agents—All NSAIDs are considered to effectively treat acute gout, but these agents must be used at their maximal, anti-inflammatory doses (e.g., indomethacin 50 mg every 6 hours, ibuprofen 800 mg every 8 hours, naproxen 500 mg every 8 to 12 hours, etc.). The selection of a particular NSAID should therefore be based on availability, patient convenience, and importantly, the side effect profile of the individual NSAID in the individual patient. COX-2 selective NSAIDs (e.g., celecoxib) are also effective for gout flares at their highest dosages and may be of value in selected patients with high GI risk; addition of a concurrent proton pump inhibitor may also be a consideration, even for short-term use. The selected NSAID should be used at the maximal dose until the flare is fully resolved, then discontinued. Short-term treatment considerations for NSAIDs include the potential for promoting hypertension, renal insufficiency, gastrointestinal intolerance and peptic ulcer disease, bleeding and potentially cardiovascular events; practitioners may consider using an alternative therapy if the patient is at high risk for any of these problems, particularly if their co-morbidities (e.g., hypertension) are presently not adequately managed. The simultaneous use of an NSAID plus daily aspirin may cause more gastrointestinal intolerance than either agent alone; if these are used together a PPI is probably warranted. NSAIDs will not be used to treat acute gout flares in patients with stage 3 CKD.

Specific situations

Severe flares—as noted above, combination therapy should be considered in a patient with a particularly severe gout flare. While all three classes of agents described above can theoretically be combined, we would recommend that first consideration be given to a glucocorticoid or an NSAID plus colchicine. The combination of an NSAID and a glucocorticoid may have synergistic effects in worsening hypertension and gastrointestinal events, especially in high risk patients, and should probably be reserved for special cases.

Treatment of a patient with normal renal function already on prophylaxis—Patients who experience acute gout flares while already on prophylaxis may be treated by advancing the dose of the prophylactic agent from its prophylactic low dose to its acute treatment higher dose (e.g., instituting acute colchicine therapy in a patient already on colchicine, raising the NSAID dose temporarily in a patient already on a low-dose daily NSAID). Alternatively, the prophylaxis may continue with a second agent added. In some cases, it may be advisable to hold the prophylactic agent temporarily while instituting the acute treatment agent (e.g., consideration of temporarily discontinuing a prophylactic NSAID dose while starting an acute gout flare dose of prednisone), to reduce the risk of adverse events.

Failure to respond—Patients who fail to respond to a single agent should be considered for combination therapy. As noted above, we recommend colchicine plus an NSAID, or colchicine plus a glucocorticoid, as a first-line combination, with combinations of NSAID plus a glucocorticoid reserved for special circumstances only. If combination therapy with these agents fails to induce a response, consideration may be given to the use of off-label anti-IL-1 therapy (e.g., anakinra 100mg subcutaneously daily until flare resolution). In that case, participation of a rheumatologist is strongly advised.

XI. Baseline and Follow-up Assessment

After enrollment all patients will be followed in a 'ULT clinic', implemented specifically for CSP594.

ULT clinic visits will occur every six weeks throughout Phase 1 and Phase 2 (weeks 0 to 48) of the study with patients followed by monthly telephone encounters during Phase 3 (weeks 49 through 72). A gout flare questionnaire will be administered during each of these encounters, as described above in Section VII. SUA will be measured at baseline, week 6, and then every three weeks during Phase 1 of the study (0 to 24 weeks) until target sUA levels have been reached and then with each ULT clinic visit after that. SUA will be measured at the time of all Phase 2 visits (weeks 30, 36, 42, and 48) (See Table 5 below). Additional surveillance laboratory, including serum creatinine, ALT and complete blood count (CBC, including platelet count) will be drawn at every ULT clinic visit.

As outlined above in Section VII, patients reporting the occurrence of a new rash (outside the context of the ULT clinic visit), will be asked to present for an in-person evaluation by a study investigator. Structured data will be collected for each rash reported.

After each sUA draw, study personnel will contact the patient (in-person for ULT clinic visits; by telephone for blood draws not coinciding with visit) and adjust the study medication as described above to reach target sUA levels. Information pertinent to adverse events will be collected every 3 weeks for all study participants during Phase 1 (0 to 24 weeks) either at the time of ULT clinic or during telephone encounters. During Phase 2 of the study (24 to 48 weeks), adverse event information will be collected every 6 weeks during ULT clinic visits. For additional information about adverse event surveillance, see Section XVI. Increased surveillance frequency scheduled during Phase 1 of the study is predicated on data demonstrating that serious adverse events (particularly serious dermatologic adverse events related to allopurinol) are most common during this early period of drug initiation. As part of a recent retrospective case-control study, investigators observed that 90% of allopurinol hypersensitivity syndrome (AHS) occurs in the first 6-months of treatment (59).

Post Study Care:

In this study all patients will return to standard care – in some cases this will be primary care providers and in other cases this will be rheumatologists specifically for gout related follow-up. At the end of the study (week 72) the participant will return for their final study visit and the LSI and SC will inform the participant of the study drug that they have been taking. In addition, the study team will send a letter to the treating physician and if applicable, a CPRS note will be completed. Treatment decisions after the study will be up to the primary care doctor's discretion. For participants who choose to withdraw from the study early or have been lost to follow-up (who received drug and have neither revoked consent or HIPAA authorization) the study team will unblind them at what would have been their expected week 72 visit via a letter to their PCP and a note in CPRS. If at any point during the study a subject passes away, the unblinding process listed above is not required. Since gout is a major part of the metabolic syndrome which has a marked increase and morbidity and mortality, particularly from cardiovascular events a 10-year passive follow-up will provide extremely valuable insights in how long-term control of hyperuricemia modifies risks for cardiovascular events, hypertension and renal failure. The 10-year passive follow-up is being sought to explore the impact of improved gout management on long term effects related to gouty arthritis/disability and progression of renal and cardiovascular disease (refer to page 8, section titled "Other Objectives" for a detailed outline). This follow-up will only be in VA patients and will explore meaningful clinical outcomes such as dialysis, MI, stroke and death which are resident in the electronic health record.

Schedule of Events:

A schedule for all study-related procedures including ULT clinic visits, telephone contacts, and laboratory surveillance are shown in the table below:

Table 5: Study follow-up and procedures[1]

		Phase 1 – Dose Titration									Phase 2 – Optimization and Maintenance				Phase 3 – Steady State Flare Observation			
	SC[2]	0	3	6	9	12	15	18	21	24	30[3]	36	42[3]	48[4]	Every 4 weeks	Week 60	Every 4 weeks	72[4]
Informed Consent	X																	
ULT Clinic visit	X	X		X		X		X		X		X		X		X		X
Telephone contact			X		X		X		X		X		X		X		X	
Gout Flare[5]				X		X		X		X		X		X	X	X	X	X
sUA blood draw	X	X		X	†	X	†	X	†	X	X	X	X	X		X		X
Creatinine	X	X		X		X		X		X		X		X		X		X
CBC, ALT	X	X		X		X		X		X		X		X		X		X
CRP		X								X				X		X		X
Blood pressure		X		X		X		X		X		X		X		X		X
Weight		X												X				
Comorbidities[6]	X	X																
Tophi area		X								X				X				
Tophi location		X																
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-3L & VR-12		X								X				X				X
Alcohol intake questions		X												X				X
Concomitant Medications[7]		X		X		X		X		X		X		X		X		X
Patient Reported Adherence[5]				X		X		X		X		X		X	X	X	X	X
Pill Counts Adherence[8]				X		X		X		X		X		X		X		X
Provide Participant with Diaries[5]		X		X		X		X		X		X		X Phase 3 Diary		X		

[1]Study visits will have a window of +/- one week in Phase 1 and +/- two weeks in Phase 2 and 3 with the exception of weeks 48 and 72 which are +/- four weeks.

[2]Tests done at screening do not need to be repeated at baseline if visits occur within 2 weeks of each other

[3]During **weeks 30 and 42** the patient does not come in for a clinic visit but will need to go to the local lab or CBOC to have a **sUA blood draw**.

[4] Early terminations: request participant come in to complete week 48 for participants currently in Phase 1 or 2, or week 72 for patients currently in Phase 3, if feasible.

[5]Patient Diaries (Gout Attack Diary and Medication Adherence Diary): Diaries will be collected from participants ~~at all clinic visits~~. During phase 1 & 2 phone visits remind participants to continue to complete their diaries and to bring them to the next scheduled clinic visit. **At week 48** participants will be given a gout attack diary and a new Phase 3 study drug diary. Participants should be instructed on how to complete the diaries and should have their diary available to review during all visits in phase 3. The patient reported response over the phone and at the clinic visits (weeks 60 & 72) will be collected using the phone script, if feasible.

[6] Comorbidities is listed in both the SC and Baseline Visit (0) because it can be started at the SC visit and finished at the baseline visit.

[7] Concomitant Medication: Use of medications known to impact sUA concentration (e.g. diuretic use, aspirin) will be collected at weeks 0, 24 and 48; screening for use of medications known to cause drug-drug interactions with study drugs will be completed during all ULT clinic visits starting with week 6

[8]Participants will bring in their bottles at all clinic visits. Pill counts will be completed at all ULT clinic visits starting with week 6;

† sUA drawn at weeks 9, 15, and 21 **only** if prior sUA level not at target threshold (target threshold is defined as sUA < 6.0 mg/dl or < 5.0 mg/dl for tophi);

XII. Potential Pitfalls of the Proposed Study Design and Strategies to Address Them

A major concern of the Planning Committee on the initial submission was for the proposed open-label design. Randomized, double-blind, placebo-controlled trials are regarded as the "gold standard" study design to evaluate efficacy, therefore we have switched to this design. The development of skin rash could "break the blind" if it occurred more commonly in one group, however skin rash has been reported with similar frequency with both of our ULT agents in other blinded trials. To minimize unnecessary withdrawal for all skin rashes, the protocol requires investigators to evaluate all rashes and provides guidelines for study drug discontinuation. Investigators will receive extensive training regarding these guidelines. Specific reporting forms for rash will help document all rashes.

Although we will include patients with stage 3 CKD (eGFR 30-59 mL/min/1.73 m^2), we will exclude patients with more severe kidney disease. While stage 3 CKD comprises 7.6% of the most recent NHANES cohort (corresponding to more than 23 million US adults) and more than 10.3% of the VA population, patients with stage 4 CKD comprise less than 0.4% of the US population and less than 0.7% of VA patients (46). Thus, the ability to recruit a sufficient number of patients with advanced CKD and gout to provide a meaningful analysis in this subpopulation is doubtful. In addition, pharmacokinetic studies of febuxostat demonstrate increased concentrations of both parent drug and active drug in patients with severe renal impairment (creatinine clearance <30 mL/min) and there are insufficient data regarding drug dosage and safety in this population (104). Dose reduction of allopurinol is also recommended in patients with severe renal impairment (105), which may necessitate an adjusted dose titration if patients with more severe CKD were included in the study. Moreover, both NSAID and colchicine prophylaxis are contraindicated in patients with more severe CKD (stages 4 or 5), which may skew results in that subset of patients. For these reasons we will have targeted recruitment to include patients with stage 3 CKD but will exclude patients with more severe degrees of renal impairment at study enrollment.

Gout flares are nearly ubiquitous with initiation of effective ULT. Bias could occur if one treatment group has more gout flares than the other leading to a differential change in treatment recommendations or adherence. Indeed, these expected flares are one of the major reasons why patients and clinicians fail to continue effective therapies or to use them at appropriate doses. In order to assure protocol compliance and to avoid early withdrawal, participants will be provided with appropriate anti-inflammatory gout prophylaxis. Anti-inflammatory prophylaxis will conform to recently published guidelines in gout management (61).

XIII. Feasibility of Recruitment

We propose to enroll 950 participants from 20 VA sites. Based on national data from 2009 to 2012, Table 6 below shows the 40 VA sites with the largest estimated number of 12-month prevalent gout patients. The 12-month prevalence is the number of patients on a particular day plus the number of new patients expected within 12 months. The national data indicate that the point prevalence pool increased by about 20% during the last year. The mean pool size among the top 40 VA sites is 398. Data from VISN#1 indicate that about 50% of these patients have a sUA level > 6.8 mg/dl, and thus would be eligible. Hence, these sites need to enroll 25% of the eligible patients.

Table 6: VA sites with largest estimated number of 12-month prevalent gout patients without AKI

Site	Number of Patients	Site	Number of Patients
Buffalo, NY	786	Denver, CO	344
Kansas City, MO	657	Charleston, SC	341
St. Louis, MO	586	Boston, MA	334
Minneapolis, MN	556	Portland, OR	334
Atlanta, GA	555	Orlando, FL	330
Gainesville, FL	549	Indianapolis, IN	322
Nebraska-Western Iowa, NE	525	Loma Linda, CA	321
Tampa, FL	492	Puget Sound HCS, WA	316
Columbia, SC	490	Philadelphia, PA	311
Cleveland, OH	488	Connecticut HCS, CT	310
Richmond, VA	485	Durham, NC	309
Greater Los Angeles, CA	441	N. California HCS, CA	307
Dallas, TX	426	Albuquerque, NM	304
Milwaukee, WI	397	Washington, DC	304
Bay Pines, FL	393	Chicago HCS, IL	302
Pittsburgh, PA	386	Hines, IL	302
Mid Tennessee HCS, TN	378	Memphis, TN	298
Baltimore, MD	373	Birmingham, AL	295
Southern Arizona HCS, AZ	359	Central Texas HCS, TX	293
Houston, TX	252	Salt Lake City, UT	290

From the survey of providers mentioned above we already know they endorse the importance of the question we are asking and both the provider and patient survey support the primary end-point. This endorsement by both providers and patients will certainly help with recruitment. CSPCC conducted a site survey to obtain information on the interest in and feasibility of recruitment for the study. The 26 sites contacted include the CSP NODES sites, CSP551 VA sites (60), sites involved in a Musculoskeletal Mini-Residency education initiative, and sites with a large gout population suggested by the Planning Committee. Twenty-three of the 25 sites contacted (92%) expressed interest in participating in this study. The vast majority of sites have previously participated in CSP trials and rheumatology studies. Only three sites had open studies that would compete for this patient population. Mechanisms to

facilitate recruitment from primary care clinics existed at 87% of sites. The CSP NODES sites were given detailed information on the study design, inclusion/exclusion criteria and the visit schedule, and agreed that the schedule and recruitment goals were feasible for both participants and coordinators.

Table 7 below shows site responses to questions regarding gout patients seen at their site over the past year. The sites were queried about: 1) the number of gout outpatients; 2) those receiving a prescription for ≤300mg daily allopurinol; 3) those receiving a first-time prescription for allopurinol; 4) those who received ≤300mg allopurinol and had a uric acid level measured; and 5) those who had a uric acid level <6mg/dl.

Table 7: Site survey results

VA Site	1. Gout outpatients*	2. Allopurinol scripts	3. New Allo. scripts	4. UA available	5. UA <6
Boston, MA	100	70	50	70	42
Dallas, TX	3412	3468	955	2215	958
Durham, NC	2128	2037	516	1022	610
Fargo, ND	5-10	>40	>20	vast majority	vast majority
Los Angeles, CA	2245	1659	205	1493	600
Hines, IL	83	216	54	62	30
Loma Linda, CA	approx. 150	approx. 100	approx. 30	>100	approx. 80
Long Beach, CA	1148	906	about 800	612	230
Miami, FL	1400	1229	161	85%	66%
Milwaukee, WI	1954	846	unable to discern	590	354
Minneapolis, MN	2994	726	305	2482	1315
Omaha, NE	3598	1665	187	823	466
Orlando, FL	3253	2724	1463	1495	595
Philadelphia, PA	477	170	96	147	61
Portland, OR	3064	2120	517	1421	658
Salt Lake City, UT	1297	1210	167	630	354
San Diego, CA	1700	1400	220	1000	400
San Francisco, CA	>2000	1033	approx. 100	>400	approx. 30%
St. Louis, MO	1668	1596	426	approx. 80%	approx. 25%
Tampa, FL	3840	2124	927	1494	722
Washington, DC	2200	576	150	220	64
White River Junction, VT	1011	530	110	314	180

* Sites were asked to estimate total patients using ICD 9 codes for gout or the number of allopurinol prescriptions given at their site

To assure complete and timely recruitment, we will engage the RAIN to supplement VA recruitment. RAIN was established in 1989 and is recognized internationally for its innovative investigator-initiated research in rheumatic diseases (60, 106, 107). This group recruited at 141% of target for CSP 551 (60). RAIN participants will provide data from non-veteran patients, thus enhancing the generalizability of our findings. Participants recruited from the RAIN network will augment the eligible pool of patients. During 2012, the Omaha RAIN site had 477 gout patients taking ≤300mg of allopurinol daily. Data from other RAIN sites shows similar numbers of potentially eligible gout patients. If RAIN recruits 100 participants the VA recruitment rate decreases from 25%to 22.5% of eligible participants.

With the above information and with the ability to identify potential patients for the sites using the national VA database were are confident that we will be able to recruit the necessary numbers of patients for this important study.

XIV. Anticipated barriers to recruitment and strategies to address potential under-enrollment

To ensure adequate recruitment, it will be critical to have access to patients where clinicians are considering starting ULT and to existing gout patients on ULT with sUA levels > 6.8mg/dl. Since most gout patients are seen and treated by primary care providers rather than rheumatologists, it is critical to engage these clinicians. The common misconceptions of many clinicians in regards to renal dosing of allopurinol must also be dispelled. In our recent national survey of VA providers (n = 179), a majority reported routinely using maximum daily allopurinol doses of 300 mg among patients with stage 3 CKD (unpublished) despite the substantial aforementioned evidence suggesting that allopurinol is both safe and well tolerated in such patients. Education regarding guidelines for gout management, including "treat to target" dosing and appropriate use of ULT in CKD, may be needed. Site investigators may be supplied with educational materials to inform, update and engage clinicians and pharmacists. We will leverage materials used by the VA Musculoskeletal Mini-Residency education initiative. This initiative has been used to educate primary care clinicians regarding the diagnosis, work-up, and management of common musculoskeletal disorders, including gout. The site survey affirms that 87% of the surveyed sites had mechanisms in place to engage primary care, and suggests that this strategy will be highly successful.

To minimize potential patient-centered barriers to recruitment, this protocol avoids onerous study procedures, offers reimbursements for travel to study visits, and provides medications for prophylaxis against and treatment of acute gout flares. Educational materials about gout and its treatment may also be provided to all potential participants to enhance enrollment and adherence once enrolled.

Along with the inclusion of the RAIN centers to augment enrollment, an increase in FTE for VA sites that meet or exceed recruitment targets will be used as an incentive to enhance timely recruitment. Sites that succeed in recruiting 25 participants within their first 6 months will receive an

additional FTE research assistant. A half time research assistant will be given to sites between 6 and 12 months once they achieve enrollment of 30 participants. The additional FTE will enable successful sites to continue recruitment while assuring completion of trial procedures, and, if successful, allow for a shortened trial recruitment period.

We will also plan to leverage the program's investment into Point of Care (POC) Randomization and engage the POC team to explore possible use of alerts in the VA electronic medical record system, which could provide point of care identification of patients. Alerts that inform clinicians about the trial when they initiate or renew either ULT or colchicine could assist in the identification of potential participants. In addition data will be gathered from VA databases to identify eligible participants.

In addition, we will initiate 6 more sites (i.e., approximately 25% more) than what is needed for successful enrollment into the study. In the event that sites fail at recruitment or as the potential patient pool decreases at the vanguard sites, enrollment into CSP 594 will be started at these additional sites. Should this event occur, the financial support for the failing sites will be transferred to the newly initiated sites.

XV. Human Rights and Informed Consent

CSP follows the principles of medical research involving human subjects as outlined in the Declaration of Helsinki.

Informed consent will be obtained from all CSP study participants prior to participation in this study. Informed consent requires that the participant understand and agree to the study procedures, treatments, and risks. The participant will be explained the voluntary nature of participation in the research study and can withdraw from participation without penalty at any time. It will be communicated that the current treatment, future medical care, and benefits will not be dependent on participation in the research. The participant must have sufficient time to read the informed consent document prior to signing.

Informed consent must occur verbally with the study participant. In discussion of the consent form with the participant, the investigator (or other study personnel identified on the Delegated Responsibilities Log to conduct the informed consent process) may provide additional details beyond those contained in the consent form. Additional information may not represent any significant additions, deletions or modifications to the information in the informed consent document. The research participant will be provided with a paper copy of the consent form and any supplementary materials to read and review prior to consent.

The informed consent document will contain all elements as outlined in VHA Handbook 1200.05 as required by the Common Rule. The consent will be documented on VA Form 10-1086 Research Consent Form. The consent form will be approved by the VA CIRB or other IRB of record for the study prior to its use.

The informed consent must be signed and dated by the study participant and the person obtaining the informed consent. The original signed informed consent document will be placed in the investigator's research file. Copies of the signed informed consent document will be provided to the patient at the time of consent.

A signed copy of the informed consent (either hard copy or a scanned version within the participant's medical record) will be made available to the VA pharmacist dispensing the investigational drug or product under investigation for this research prior to the patient receiving any study medication.

The informed consent process will be documented in a detailed progress note prior to study participation. The following elements should be included in the progress note:

1. Name of the study
2. Name of the person obtaining informed consent
3. Statement that the participant was capable of understanding the informed consent process
4. Statement that the study was explained to the participant and the participant was given the opportunity to ask questions

5. Statement that consent was obtained before participation in the study began
6. Information on possible drug interactions and/or toxicity of the study medications
7. A copy of the signed and dated informed consent form and HIPAA authorization

A separate written HIPAA authorization for the use of individually identifiable health information must be signed by the research participant.

In this research study, a waiver of informed consent and HIPPA authorization will be submitted for recruitment purposes in order to access information on potentially eligible patients. In addition consent will be obtained for continued access to participant electronic health records for ten years following completion of the study in order to examine long-term outcomes. Sites will maintain a log of all potentially eligible patients, kept in a secure location and not transmitted to CSPCC. CSPCC will only collect patient information on those who have provided informed consent. A plan to protect patient identities and destroy patient identifiers after use is in place and is described in Section XVII of the protocol.

XVI. Monitoring Adverse Events

Overview of Adverse Event Reporting

Timely and complete reporting of safety information assists study management in identifying any untoward medical occurrence thereby allowing: 1) protection of study patients' safety; 2) a greater understanding of the overall safety profile of the study interventions and therapeutic modalities; 3) appropriate modification of the study protocol; 4) improvements in study design or procedures; and 5) compliance with regulatory requirements. All reporting of protocol related events will include CIRB, FDA, CSP as indicated by rules and regulations.

The local Site Investigator will be responsible for the AE and SAE reporting requirements as described in this protocol outlined below:

- Closely monitoring research participants during the study for the development of new AEs and SAEs.
- Reviewing the accuracy and completeness of all AEs and SAEs reported.
- Reporting all SAEs to the CSPCRPCC and MAVERIC CSPCC within 3 calendar days of the site becoming aware of the event
- Complying with VA Central IRB policies for reporting adverse events and other VA policies as detailed in VHA Handbook 1058.01
- Implementing plans the Study Group and Executive Committee may develop in response to safety concerns

Adverse Events

Adverse Events (AEs) are defined by the VHA Handbook 1058.01, paragraph 4(b) as "… any untoward physical or psychological occurrence in a human subject participating in research." An AE can be any unfavorable and unintended event, including an abnormal laboratory finding, symptom, or

disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research.

For the purpose of CSP 594, the study interventions are allopurinol/matching placebo (100 mg, 300 mg and 400 mg capsules) and febuxostat/matching placebo (40 mg and 80 mg tablets). Prophylactic medications, including those provided for the study, have well established safety profiles and are not the primary topic of interest in this study; therefore, these medications are not considered study interventions for purposes of AE reporting.

Local site investigators, with assistance from their study coordinators, are responsible for collecting AE information regarding the participants at their sites. During the study, data on adverse events will be collected spontaneously through patient reports, actively elicited during visits through open-ended questioning and examination, and gathered at the time of telephone contact and medical record reviews during the follow-up period.

Beginning at informed consent and continuing until the end of participation in the study, all AEs identified for a participant must be recorded on a CSP #594 AE Tracking & Evaluation Record provided by SMART. Each event must be evaluated by the SI/sub-I to determine if the event is:

1. Severe
2. Likely attributable to the Study Intervention
3. Anticipated or unanticipated (expected or unexpected)
4. Serious

After completing the evaluation, the SI/sub-I must initial and date the event on the record, which then serves as a source document for safety evaluation and oversight.

In addition to completing the tracking and evaluation log, AEs which are non-serious but which are judged to be severe or likely attributable (possibly related or related) to the study intervention will be recorded on an adverse event form and documented in source records (e.g., electronic VA medical record and/or the participant's study record). Determination of attributability involves an assessment by the site investigator of the degree of causality between the study interventions (allopurinol or febuxostat) and the event. All AEs with a reasonable causal relationship to the investigative treatment will be considered "possibly related" or "related." A definite relationship does not need to be established. In this way the site creates a permanent record that provides information on the participant's clinical course while in the study.

Related adverse event data will be collected from the time of consent until the end of participation in the study. If a patient receives care at a non-VA facility for an adverse event they experience, research personnel will obtain the requisite release of information form(s) from the patient and once received, acquire the pertinent medical records from the facility.

Adverse events which are or develop into Serious Adverse Events (SAEs), as defined below, will be reported as such and followed to the SAE resolution, stabilization, or study discontinuation.

Serious Adverse Events (SAEs)

SAEs are a subset of adverse events. As defined in VHA Handbook 1058.01, a serious adverse event (SAE) is an untoward occurrence in human research that results in:

- Death
- A life-threatening experience
- Inpatient hospitalization
- Prolongation of hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect, or
- Requires medical, surgical, behavioral, social or other intervention to prevent such an outcome

All SAEs will be collected and reported via DataLabs and to CSPCRPCC and MAVERIC CSPCC within 3 calendar days of knowledge, regardless of whether or not they are considered related to the study interventions. SAEs with a reasonable causal relationship to the study interventions and associated medications will be reported as "possibly related" or "related." A definite causal relationship does not need to be established.

While additional evidence about febuxostat's cardiovascular risks continues to accumulate, side effect profiles for both study medications (allopurinol and febuxostat) and all the supplemental medications (prednisone, colchicine and naproxen) are generally well established and will be used as the basis to determine what are expected and unexpected events. Local site investigators will determine the relatedness to the study medications for any reported event. These local site investigators, with assistance from their study coordinators, are responsible for collecting SAE information regarding the participants at their sites. SAEs will be collected from the time of consent until 30 days after the end of participation in the study. During the study, data on SAEs will be collected spontaneously through patient reports, actively elicited during visits through open-ended questioning and examination, and gathered at the time of telephone contact and medical record reviews during the follow-up period. If a patient receives care at a non-VA facility for a SAE they experience, research personnel will obtain the requisite release of information form(s) from the patient and once received, acquire the pertinent medical records from the facility.

SAEs are a subset of AEs; thus they will be recorded on the AE tracking and evaluation log as described in the previous section. SAEs that are reported to research personnel will be documented in source records (e.g., the electronic VA medical record and/or the participant's study record). In this way, the site creates a permanent record that provides information on the participant's clinical course while in the study. Research personnel at the site will ask follow-up questions to determine the exact nature of the SAE and obtain appropriate medical records, if needed. All unresolved SAEs must be followed up at least every 30 days until resolved or when no further change is expected. All SAEs are followed until no changes are expected or the study is discontinued. The follow up reports will be entered into the EDC system by the site coordinators in a timely manner.

CSP Global SOP 3.6 sets forth situations in which safety events must be reported by individuals within CSP (primarily the PCC clinical research pharmacist) to various parties, including the FDA and VA Central Office. This study will adhere to the most current approved version of this SOP.

SAE reporting will start at the time of patient consent and continue until 30 days after the patient's involvement in the study. All SAEs must be entered in to the EDC system by site personnel within 3 calendar days of the local site staff becoming aware of the event. The site should notify MAVERIC CSPCC, Chair's Office, and CSPCRPCC of the event by encrypted email upon entering the SAE into the EDC system. All unresolved SAEs will be followed up at least every 30 days until resolved or when no further change is expected (i.e. event is ongoing recovering/resolving or not recovered/not resolved. No changes to the event will occur in the future). All SAEs are followed until no changes are expected or the study is discontinued. When the participant's study involvement ends, the investigator will be responsible to arrange for continued follow up.

Site Investigators will review all SAEs to determine their relatedness to participation in VA CSP #594 and whether they are expected in the study population. SAEs that meet VA Central IRB expedited reporting requirements will be reported as detailed on the CIRB website (http://www.research.va.gov/vacentralirb/). All SAEs that are considered related and unanticipated must be reported in writing to CIRB within 5 business days of the site becoming aware of the event. Any participant death that is considered related and unanticipated must be immediately reported orally to CIRB and followed with a written notification within 5 business days of the site becoming aware of the event. All SAEs that are not considered related and unanticipated must be reported to CIRB at the time of continuing review. In addition, all AEs must be reported to CIRB at the time of continuing review.

Emergency Breaking of the Blind

The CSPCRPCC will not provide Emergency Code Envelopes to the Research Pharmacy for CSP #594. Emergency unblinding will be managed through the 24-hour emergency call service (505-248-3203). This number is also listed on the participant ID cards given to each patient participating in CSP #594. The system managed by the CSPCRPCC will electronically capture up-to-date study drug assignment information gathered from the CSP #594 IWRS.

Authorization to Break the Blind:

Under unusual circumstances, chiefly related to participant safety, unblinding may be necessary. This is usually done after consultation with the Study Chair (James O'Dell, MD). If Dr. O'Dell is unavailable, the PCC Clinical Research Pharmacist (Annie Davis-Karim or another Clinical Research Pharmacist), the Study Biostatistician (Hongsheng Wu, Ph.D.), or the medical project director (Mary Brophy, M.D.) should be contacted.

In life-threatening emergencies, the PCC is available through the 24-hour emergency call service. If the PCC receives a request for unblinding information from anyone other than the LSI or SC, the PCC will refer the requester to the LSI or SC, or, in his or her absence, the PCC will attempt to contact the parties above. If unblinding is required in an emergency, the treating physician may contact the PCC through the 24-hour emergency call service to obtain study drug assignment information. The PCC will notify the Study Chair's Office and the Boston CSPCC by telephone as soon as possible after an unblinding has occurred.

If the toxicity is severe enough to require removal of the patient from the study and the blind is broken, the participant and physician will be informed of the drug they were receiving.

XVII. Data Management and Data Security Plans

The Boston CSPCC will manage the trial data using a web-based Electronic Data Capture (EDC) system. The EDC system allows direct entry of case report forms (CRF) into a web-based study database and thus allows site coordinators to manage their participants, handle data clarifications, and correct data online. This system makes patient data management easier, timelier, and more efficient. The electronic system will be used to create, modify, maintain and retrieve clinical data for CSP#594 during each step of the data collection process. The EDC system will be validated by the Boston CSPCC Quality Assurance department to ensure the integrity of the data capture software.

Paper CRFs for all data including Quality of Life measures will be provided to site coordinators as a primary means of collecting data. Data entered on paper CRFs will be used as source documentation for EDC entries. All paper-based study records will be kept under lock and key.

The Study Chair and Study Director will prepare an Operations Manual. A training session at the study kick-off meeting for all site investigators and site coordinators will be conducted to assure uniformity in patient management, data collection, and study procedures. At this training, site coordinators will be provided with reference materials on the software tool and tasks. Formal training on the use of the EDC system for clinical study management will also be conducted at investigator meetings and on an as-needed basis for new study personnel.

For CSP#594, EDC designers will create a specific database that includes case report forms, the interview schedule, and data queries. The purpose of data clarifications (DCFs) or data queries is to draw attention to data that are inconsistent or potentially erroneous. DCFs will be managed in two ways. Certain queries will be programmed into the forms that are designed to activate upon data entry if data is missing or discrepant with study parameters. Additional DCFs will be programmed using other data analysis tools such as SAS and will be uploaded into the system for study coordinators to address. Furthermore, the system will allow manual DCFs to be entered into the forms by the coordinating center as needed. Updates to the electronic forms and database can be generated during the study without impacting collected data. Study reports can be generated from exported data in order to track the study progress and to monitor adverse events, particularly Serious Adverse Events. Study reports will be circulated to appropriate individuals, including the Site Investigators, the Study Chair, the Study Director, and the DMC.

Study data is housed on secure VA servers, encrypted and protected in accordance with VA policies compliant with FDA requirements, Federal Information Security Management Act and the HIPAA Privacy and Security rules. Boston CSPCC personnel manage the data access request process to ensure that data access is appropriate for each individual and the level of the individual access. VA's Office of Information & Technology (OI&T) is responsible for ensuring the security and integrity of VA information systems, including the databases and servers housing study data. In accordance with VA Handbooks and Directives, OI&T is responsible for ensuring that appropriate firewalls and data security is implemented and maintained, that data backups are performed and that data may be restored in the event of a system malfunction.

Hard copy data will be sent via a traceable mail system (i.e., UPS), via a courier, or via secure fax. Faxes are electronically routed on in-house VA servers located in Boston. DataLabs resides on a VA server in Martinsburg, WV. Access to these secure fax servers is restricted to the Coordinating Center personnel with approved access to the system. All data security incidents will be reported in accordance with VA policy within one hour of discovering the incident to:

1. The District (local) Information Security Officer (ISO)
2. The Boston CSPCC Quality Assurance department
3. The VA Central IRB

Study data will be coded and stored using a unique study identifier for each participant. Identifiable information will be collected for patient tracking and safety purposes, and kept on an encrypted, password protected server to which a small number of people will have access. Access to the cross-walk file linking the participant's identifiers and their study data will be restricted to the clinical site and to the approved personnel at the coordinating center. This file will be destroyed according to CSP policy.

Access to the study data is restricted to individuals with CSP approval. Individuals must be properly credentialed research staff and must be compliant with VA security trainings (e.g. HIPAA, Rules of Behavior, and Good Clinical Practices). Once formal training is completed, user accounts utilizing a URL specific to the study to access and use the system and enter patient data will be activated. Accounts will be password protected and unique to the each user. The account permissions will correspond with the users' functional study group (i.e., those for a site coordinator would differ from those of the coordinating center or site monitors). Furthermore, the permissions of the electronic systems are structured such that individual sites can only see the data for their study participants. They cannot see or access the data for another clinical site or for another participant. Research data will be stored on VA secure servers with restricted permissions for copying and exporting data. Only properly approved Coordinating Center personnel will have the ability to copy and export data. These individuals have received training on the local SOP governing their permissions. Access to protected health information (PHI) will be restricted to individuals approved by CSP to have access to the data.

At the Study Sites, three FTE staff positions will have access to PHI. Individuals in these positions will be able to access all forms of PHI:

1. Site Investigator
2. Site Physician
3. Site Coordinator

At the Boston CSPCC nine staff positions will have access to all forms of PHI:

1. Center Director
2. Study Director
3. Project Manager/Project Coordinator
4. Data Manager
5. Biostatistician
6. Junior Biostatistician
7. Quality Assurance Specialist
8. Data Programmer
9. Research Assistant

At the CSPCRPCC four staff positions will have access to PHI. Individuals in these positions will be able to access de-identified forms of PHI:

1. Clinical Monitors
2. Study Pharmacist
3. Adverse Event Specialist (Regulatory Affairs and Safety Officer)
4. Pharmacy Project Manager

Quality control checks and clinical monitoring will enable the Coordinating Center to survey the study database and the clinical sites to ensure that the data have not been improperly used or accessed. 21 CFR part 11 compliant audit trails and access logs will be checked routinely. In addition, the clinical monitors (SMART) will provide continuing education on good clinical practices and will check clinical site operations for compliance with data security policies and best practices.

At the end of the study, the data for CSP#594 will remain property of the Cooperative Studies Program, and be stored and shared according to VA CSP policies on data transfer and data security. The Boston CSPCC Quality Assurance team will work closely with the local CSPCC research compliance officer, the information security officer, and the VA privacy officer as needed to ensure that data security and data transfers are handled appropriately.

Retention and destruction of data will be conducted according to CSP operating procedures and federal and local VA regulations. This will include paper and electronic data stored at the study sites, the Boston CSPCC, and at the VA facility housing our servers. Identifiable data will be kept according to CSP policy as outlined in the "CSP Guidelines for the Planning and Conduct of Cooperative Studies".

Specifically, identifiers will be kept on site at the MAVERIC CSPCC for a minimum of five years or as dictated by the FDA or other regulatory agency with specific written procedures (i.e., two years after last approval of a marketing application, etc.). At the end of the record retention period, the Boston CSPCC will conduct a review to determine if it is appropriate to archive study data. If it is determined that the study data must be kept active, the Boston CSPCC will retain the database in its entirety until the primary and secondary analyses are completed. At the completion of analyses, study data will be de-identified and stored indefinitely. If, however, the study is archived, the study data will be de-identified and stored indefinitely. Study records maintained at the local sites cannot be destroyed without written permission from Boston CSPCC.

Data Management and Access Plan (DMAP)

Upon final analyses of the stated objectives in this proposal, the study plans to submit results for publication in scientific peer- reviewed journals and provide summary results on ClinicalTrials.gov. After acceptance of the primary and other stated analyses by a journal, CSP will make these publication(s) available via the National Library of Medicine's PubMed Central within a year of the date of publication.

Digital data underlying primary scientific publications from this study will be held as part of data sharing resource maintained by the Cooperative Studies Program (CSP). Study data held for this purpose may include data, data content, format, and organization. The data may contain but are not limited to individually identifiable information, other protected health information, and study codes. The data may be available to the public and other VA and non- VA researchers under certain conditions and consistent with the informed consent and CSP policy which prioritize protecting subject's privacy and confidentiality to the fullest extent possible. A detailed plan for data sharing will be developed in accordance with current technology, infrastructure, best practices, and policies and procedures in place at the time of oversight committee reviews (e.g., Privacy Board, IRB, Information Security, and IT standards). The plan will include how data will be discovered, retrieved, and analyzed, managed and will note the materials that are available in machine readable formats. This plan may be revised to ensure consistency with VA, including CSP, policies and standards for overall data management and sharing.

XVIII. Quality Control Procedures

Training on Study Measures

Prior to the initiation of the study, all site investigators and site coordinators will meet to review the governance and management of the study, study procedures and receive training on collecting data for the study. Much of this will take place during the study kickoff meeting. The protocol and case report forms will be sent to site investigators and coordinators to review prior to the meeting. During the meeting, study personnel will receive training on obtaining and maintaining source documents, and completing study assessments and case report forms. Verbal feedback and discussion will follow to ensure that each coordinator comprehends the proper methodology for assessment. The meeting will also cover an in-depth review of the study operations manual. Such a review will serve to reinforce the training described above and will orient the study personnel to the reference guides for the study.

Protocol deviations

Strict adherence to the protocol will be expected of every participating center and monitored by the DMC, the Executive Committee, and the Study Group. Any protocol violations will be fully documented on the Protocol Deviation form developed by the Boston CSPCC. Any protocol deviation that affects the rights, safety, or welfare of the research participant, the participant's willingness to continue participation; or the integrity of the research data, including VA information security requirements will be reported within 5 business days of the site being made aware of the occurrence to CIRB. Protocol deviations will be summarized for review at each DMC meeting. Any medical center or participant with repeated protocol violations, and after remedial action, may be recommended for termination to the Director of the Cooperative Studies Program after discussion with the CSPCC Director, Study Chair, Executive Committee, and DMC. If any member of the DMC or of the monitoring bodies for CSP#594 feels that adherence to the protocol will be detrimental to a participant's health or well-being, the interest of the participant will take precedence and the participant withdrawn after consultation with the Executive Committee. Site coordinators will be responsible for reporting protocol deviations to the IRB of record as required.

Participant non-compliance (e.g. forgetting to take study medication, losing it, or choosing not to take it) with study drug is *not* considered a protocol deviation. However, if study drug was incorrectly administered, prescribed, or there was a significant misunderstanding of dosing instructions that would constitute a deviation.

Enrollment or Termination issues

I. Guidelines for Early Termination of a Study Site

During the course of a study, it may be necessary to drop one or more participating medical centers from the study. Such action must have the prior approval of the CSPCC Director and the CSP Director. Early termination is usually based on recommendations from the Executive Committee and the Data Monitoring Committee and most often reflects inadequate patient intake or serious noncompliance with Good Clinical Practices. This action should always be based on the best interests of the study and study participants and does not necessarily imply poor performance on the part of the site investigator or the medical center. Termination will be conducted per CSP guidelines.

II. Enrollment Issues

The Study Chair and the study biostatistician will monitor the intake rate and operational aspects of the study. Participating medical centers will continue in the study only if adequate participant intake is maintained. The Executive Committee may take action leading to the discontinuation of enrollment at a center with the concurrence of the CSPCC Director. If recruitment is not proceeding at an appropriate rate, the Study Chair and study biostatistician will scrutinize the reasons for participant exclusions and other barriers to recruitment. Based on this information, the Executive Committee may choose, with the approval of the DMC and the Director, VA CSR&D, to drop centers, add additional centers, make minor modifications to the inclusion/exclusion criteria, or extend the recruitment period.

The following performance measures will be used to determine whether sites are at risk of being placed on probation or should be placed on probation:

1. Noncompliance with the protocol, ICH, or applicable federal regulations.
2. Recruitment rate: Recruitment rate will be calculated by dividing the number of randomized patients by the number of expected patients (each site is expected to recruit approximately 3 patients per month). This measure will be continuously monitored and sites between 75% and 90% of expected recruitment will be subject to remediation such as action plans or mentoring. Sites under 75% cumulative recruitment after a 3-month ramp-up period will be recommended for probation. Assessment for probation will occur on a monthly basis.
3. Follow-up rate: Follow-up rate will be calculated by dividing the number of patients with follow-up forms completed by the expected number of patients with visits due. Both the numerator and denominator will be subject to a 4-week delay in order to allow for scheduling of visits and completion of forms. Sites with cumulative follow-up rates below 90% will be recommended for probation. Assessment for probation will occur on a monthly basis.
4. Forms completion rate: Forms completion rate will be calculated by dividing the number of completed forms by the number of expected forms, excluding forms marked "not collected". Forms completion rates will be calculated both by patient and by form. Sites with cumulative forms completion rates under 90% will be recommended for probation. Assessment for probation will occur on a monthly basis.

If a medical center is placed on probation, the Study Chair will confer with the site personnel and may visit the site, if necessary, to help improve the rate of recruitment. Once a site is placed on probation, failure to meet the requirements specified by the end of the probation period will result in a recommendation for termination. Additionally, sites that fail to meet two or more of the above performance measures, and sites that habitually under-perform by any of these measures, will be at risk of termination.

To plan for the possible termination of a site(s) and the addition of a new site(s), back-up sites with IRB approval will be identified prior to study initiation to minimize the delay in adding a new site. The Executive Committee will take actions leading to discontinuation of a site only with the concurrence of the CSPCC Director. If a site is terminated from the trial, resources will be reallocated to other medical centers or used to start up a back-up site.

III. Premature Termination of the Study

The Director, CSP, can terminate a cooperative study before completion. The DMC makes recommendations as to whether the study should continue or be terminated. The decision to terminate a study prematurely is a complex one involving many factors. The DMC may consider the following circumstances as grounds for early termination:

1. If patient accrual falls far below that which is predicted (e.g., 75% of expected accrual), it will be necessary to reassess the study design and the potential value of its continuation.
2. If patient accrual far exceeds the predicted, this study could be completed at an earlier date.
3. If serious adverse events or mortality are noted to be excessive in either treatment group.

Termination by recommendation of the DMC will be carried out as outlined in CSP Guidelines.

Quality Control through the Boston CSPCC Quality Management System

The quality management system (QMS) in place at the CSPCC will ensure further quality control for CSP 594. The Quality Assurance Department of the CSPCC will subject the data to risk based audits and monitoring that will verify and validate data elements according to internal SOPs. In brief, a sample of the data will be verified at routine intervals. If errors are identified they will be referred to the data management team for resolution. If the error level rises to a predefined threshold, then the entire record or data element type will be subjected to verification and validation. Further, the CSPCC will conduct internal audits to ensure the quality of the clinical trial processes and procedures. If deviations or non-conformances are identified they will be remedied through the internal corrective action/preventive action system of the QMS.

Risk based monitoring and auditing will also allow for the early systematic identification of problems that require remediation at the clinical site level. If problems are identified, the CSPCC will work with the clinical site to create a remediation plan to address the issues. If the problems persist after remediation, the site may be recommended for closure to the executive committee.

XIX. Good Clinical Practice (GCP)

Role of GCP

This trial will be conducted in compliance with Good Clinical Practices (GCP) regulations. The intent of these regulations is to safeguard participants' welfare and assure the validity of data resulting from the clinical research. The VA Cooperative Studies Program will assist LSIs in complying with GCP requirements through its Site Monitoring, Auditing and Resource Team (SMART) based in Albuquerque, NM. SMART serves as the Quality Assurance arm of CSP for GCP compliance. Study site personnel will receive a GCP orientation at the study kickoff meeting. SMART will provide training, manuals, and materials to assist study personnel in organizing study files and will be available throughout the trial to advise and assist LSIs regarding GCP issues.

Summary of Monitoring and Auditing Plans:

Monitoring Visits

- Initial visits at each site soon after study start-up
- Subsequent monitoring will be conducted yearly.
- Final monitoring visit to each site during last year of the study
- Additional monitoring visits may be conducted as deemed necessary by study leadership or SMART.

Audits

- Routine audits –independent site visits to one or more sites per year as determined by SMART
- For-Cause audits – independent audits of a site as requested by study leadership or CSP Central Office.

Note: Audits may be scheduled or unannounced

XX. Study Organization and Administration

A. Administration

The administrative structure of this study is similar to others in CSP and includes:

The Cooperative Studies Program (VA Central Office) establishes overall policies and procedures that are applied to all VA cooperative studies through the Study Chair's office and the CSPCC.

The CSPCC and the **Study Chair's office** jointly will perform the day-to-day scientific and administrative coordination of the study. These include developing and revising the study protocol, Operations Manual, and case report forms; ensuring the appropriate support for the participating centers; scheduling meetings and conference calls; answering questions about the protocol; conducting site visits; publishing newsletters; preparing interim and final progress reports; and archiving study data at the end of the study. Study progress reports will be produced every 6 months. Patient accrual, patient safety, and data quality will be monitored closely to ensure that the study is progressing satisfactorily.

The CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) manages the pharmaceutical aspects of multicenter pharmaceutical and device clinical trials including patient safety monitoring. CSPCRPCC acts as a liaison between the study participants, the FDA, and the manufacturers of the study drug(s) or device(s) in all VA Cooperative Studies that involve drugs or devices. The CSPCRPCC develops Drug Treatment and Handling Procedures, obtains and distributes the study drug(s), prepares a Drug Information Report for the study drug, and provides advice and consultation about drug-related matters during the study. CSPCRPCC is responsible for monitoring and reporting the safety of trial participants through the review, assessment, and communication of adverse events and serious adverse events reported by study personnel with reviewing responsibilities occurring through ongoing communication with the Study Chair, Executive Committee, CSPCC, and CSP Central Office. The reporting activities include filing regulatory documents involving adverse events with the FDA and manufacturers to meet federal regulations and CSP policies. In conjunction with the CSPCC, the CSPCRPCC trends and analyzes safety data to prepare reports for various committees including the DMC, VA Central IRB (CIRB), Executive Committee(s), and Study Group meetings.

Each **participating VA medical center** will designate a site investigator (SI) to be responsible administratively and scientifically for the conduct of the study at the center. SIs will be expected to attend all annual Study Group meetings, as well as to hire and supervise personnel. By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the DMC, the CSPCC Human Rights Committee, and the CSSEC.

The Clinical Sciences Scientific Evaluation Committee (CSSEC) reviews the scientific merit of all new cooperative study proposals and all ongoing cooperative studies every 3 years. The committee is composed of both VA and non-VA clinical research scientists, most of whom have had experience in managing their own cooperative studies.

The Study Group will be composed of the SIs from each participating center, the Study Chair, Study Director, and CSP staff (biostatistician, project manager, clinical research pharmacist, and others).

The Study Chair will head the group, which will meet once a year to discuss the progress of the study, any problems that the investigators have encountered, and any suggestions for improving the study.

B. Monitoring

The following groups monitor the various aspects of the study. These committees will meet according to current Cooperative Studies Program guidelines. In addition, the CSP SMART will monitor the trial for GCP compliance as indicated above.

The Executive Committee is responsible for the operations of the study, including protocol amendments, and overall management of the study. It will be headed by the Study Chair and Study Director and consist of the study biostatistician, study project manager, clinical research pharmacist, selected participating investigators, and outside consultants as needed. This committee will meet regularly to review blinded data (not broken down by treatment group), decide upon changes in the study, determine the fate of hospitals whose performance is substandard, initiate any sub protocols, and discuss publication of the study results. This Committee must grant permission before any study data may be used for presentation or publication.

The Data Monitoring Committee (DMC) will review the progress of the study and will monitor patient intake, outcomes, adverse events, and other issues related to patient safety. Interim, independent, and unbiased reviews of the study's ongoing progress will be provided. The DMC will consist of experts in the study's subject matter field(s), clinical trials, biostatistics, and ethics. These individuals will not be participants in the trial and will not have participated in the planning of the protocol. The DMC will consider safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or the unfeasibility of addressing the study hypothesis (e.g., poor patient intake, poor adherence to the protocol).

At each of its meetings during the study period, the DMC will review the randomization rates and assess the difference between the actual and the projected rates, as well as the impact of these assessments on overall trial size. If the study enrollment is inadequate, the reasons for exclusion may be scrutinized and actions may be suggested. An assessment of whether the trial should be continued will be made followed by recommendations, as appropriate. All serious adverse events will be reported regularly to the DMC for review. Unexpected, related serious adverse events will be reported to the DMC as soon as they become known based upon the consensus of the Study Chair, the study biostatistician, the Study Director, and the study pharmacist. The study biostatistician will provide the appropriate data to the DMC at specified intervals for this purpose. Conditional power estimates will be provided to the DMC to assist them in making their decisions and recommendations. To help them make their assessment, the Study Chair and study biostatistician will furnish the Data Monitoring Committee with appropriate monitoring data before each meeting. The DMC makes recommendations after each meeting to the CSP Director about whether the study should continue or be stopped.

The VA Central IRB will be the IRB of record for all VA sites. They will monitor the study's serious adverse events and review deviations on a continual basis. They will conduct annual reviews of the study. All local sites may be required to submit reports to their local Research and Development and/or Safety Committee for approval. In addition, some study materials (such as participant correspondence and protocol changes) will have to be reviewed by the VA CIRB, and approved prior to implementation.

The **CSPCC Human Rights Committee (HRC)** is composed primarily of lay people and is responsible for ensuring that patients' rights and safety are upheld prior to study initiation and during the conduct of the study. The committee reviews all new protocols, periodically makes site visits to participating centers to monitor firsthand the progress of the study, and may be asked to review any ethical and human rights issues that arise during the conduct of the study.

The CSP Site Monitoring, Auditing and Resource Team (SMART), located at the CSPCRPCC in Albuquerque, will monitor the trial for compliance with Good Clinical Practices (GCP). GCP monitors from SMART will visit participating sites shortly after enrollment is initiated and subsequent monitoring will be conducted yearly thereafter to ensure investigator regulatory and protocol compliance and to evaluate research practices. SMART will provide an orientation to GCP at the study kick-off meeting and provide GCP tools to enhance compliance. Additionally, SMART will conduct periodic routine audits throughout the course of the study and for-cause audits as requested by study leadership or CSP VACO.

XXI. Publications

Publication policy

It is the policy of the CSP that outcome data will not be revealed to the participating investigators until the data collection phase of the study is completed. This policy safeguards against possible biases affecting the data collection. All presentations and publications from this study will be done in accordance with current CSP Guidelines, including the Authorship Policy. The most current version of the Guidelines should be referenced when planning any study publication.The presentation or publication of any or all data collected by participating investigators on patients entered into the VA Cooperative Study is under the direct control of the study's Executive Committee. No individual participating investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any or all of the data other than under the auspices and approval of the Executive Committee.

The Executive Committee has the authority to establish one or more publication subgroups of investigators and members of the Executive Committee for producing scientific presentations and publications. Authors with VA appointments must list their VA affiliation first. The VA contributions to the research project should be acknowledged in all written and oral presentations of the research results, including scientific articles, news releases, news conferences, public lectures, and media interviews.

All study reports and journal manuscripts must be reviewed and approved by the Boston CSPCC Director prior to submission for publication. After approval for submission is granted by the Boston CSPCC Director, VA Central Office must be notified upon acceptance of any publications. This includes minor publications such as abstracts and poster presentations.

XXII. References

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011;63(10):3136-41.

2. Arromdee E, Michet CJ, Crowson CS, O'Fallon WM, Gabriel SE. Epidemiology of gout: is the incidence rising? J Rheumatol. 2002;29(11):2403-6.

3. Krishnan E. Chronic kidney disease and the risk for incident gout among middle aged men: A seven-year prospective observational study. Arthritis Rheum. 2013.

4. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR, Jr., Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990-1999. Ann Rheum Dis. 2005;64(2):267-72.

5. Perez-Ruiz F, Martinez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, Krishnan E. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. Ann Rheum Dis. 2013.

6. Singh JA, Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. Ann Rheum Dis. 2008;67(9):1310-6.

7. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64(10):1431-46.

8. Mikuls TR. Quality of care in gout: from measurement to improvement. Clin Exp Rheumatol. 2007;25(6 Suppl 47):114-9.

9. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Saag KG. Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia: results from the UK General Practice Research Database (GPRD). Rheumatology (Oxford). 2005;44(8):1038-42.

10. Singh JA, Hodges JS, Toscano JP, Asch SM. Quality of care for gout in the US needs improvement. Arthritis Rheum. 2007;57(5):822-9.

11. Becker M, Schumacher HJ, Wortmann R, MacDonald P, Eustace D, Palo W, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005;353:2450-61.

12. Becker MA, Schumacher HR, Espinoza LR, Wells AF, Macdonald P, Lloyd E, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Res Ther. 2010;12(2):R63.

13. Schumacher HR, Jr., Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum. 2008;59(11):1540-8.

14. Abdellatif AA, Elkhalili N. Management of Gouty Arthritis in Patients With Chronic Kidney Disease. Am J Ther. 2012.

15. U.S. Department of Veterans Affairs. 2001 National Survey of Veterans. Available at: http://www.virec.research.va.gov/DataSources/NationalSurveyVeterans/2001NationalSurveyofVeterans.html. Accessed 11 Sept 2006.

16. Abbott RD, Brand FN, Kannel WB, Castelli WP. Gout and coronary heart disease: the Framingham Study. J Clin Epidemiol. 1988;41(3):237-42.

17. Bickel C, Rupprecht HJ, Blankenberg S, Rippin G, Hafner G, Daunhauer A, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. Am J Cardiol. 2002;89(1):12-7.

18. Breckenridge A. Hypertension and hyperuricaemia. Proc R Soc Med. 1966;59(4):316-9.

19. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation. 2007;116(8):894-900.

20. Cohen SD, Kimmel PL, Neff R, Agodoa L, Abbott KC. Association of incident gout and mortality in dialysis patients. J Am Soc Nephrol. 2008;19(11):2204-10.

21. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med. 1999;131(1):7-13.

22. Darmawan J, Rasker JJ, Nuralim H. The effect of control and self-medication of chronic gout in a developing country. Outcome after 10 years. J Rheumatol. 2003;30(11):2437-43.

23. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA. 2000;283(18):2404-10.

24. Hoieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int. 2004;65(3):1041-9.

25. Ioachimescu AG, Brennan DM, Hoar BM, Hazen SL, Hoogwerf BJ. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. Arthritis Rheum. 2008;58(2):623-30.

26. Krishnan E. Hyperuricemia and incident heart failure. Circ Heart Fail. 2009;2(6):556-62.

27. Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH. Long-term cardiovascular mortality among middle-aged men with gout. Arch Intern Med. 2008;168(10):1104-10.

28. Lehto S, Niskanen L, Ronnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. Stroke. 1998;29(3):635-9.

29. Chao J, Terkeltaub R. A critical reppraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. Curr Rheumatol Rep. 2009;11:135-40.

30. Hande K, et al. Severe allopurinol toxicity. Description of guidelines for prevention in patients with renal insufficiency. Am J Med. 1984;76:47-56.

31. Stamp LK, O'Donnell JL, Zhang M, James J, Frampton C, Barclay ML, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum. 2011;63(2):412-21.

32. Garg R, Sayles HR, Yu F, Michaud K, Singh J, Saag KG, et al. Gout-related health care utilization in US emergency departments, 2006 through 2008. Arthritis Care Res (Hoboken). 2013;65(4):571-7.

33. Kleinman NL, Brook RA, Patel PA, Melkonian AK, Brizee TJ, Smeeding JE, et al. The impact of gout on work absence and productivity. Value Health. 2007;10(4):231-7.

34. Brook RA, Kleinman NL, Patel PA, Melkonian AK, Brizee TJ, Smeeding JE, et al. The economic burden of gout on an employed population. Curr Med Res Opin. 2006;22(7):1381-9.

35. Wu EQ, Patel PA, Mody RR, Yu AP, Cahill KE, Tang J, et al. Frequency, risk, and cost of gout-related episodes among the elderly: does serum uric acid level matter? J Rheumatol. 2009;36(5):1032-40.

36. Wu EQ, Patel PA, Yu AP, Mody RR, Cahill KE, Tang J, et al. Disease-related and all-cause health care costs of elderly patients with gout. J Manag Care Pharm. 2008;14(2):164-75.

37. Halpern R, Fuldeore MJ, Mody RR, Patel PA, Mikuls TR. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. J Clin Rheumatol. 2009;15(1):3-7.

38. Luk AJ, Levin GP, Moore EE, Zhou XH, Kestenbaum BR, Choi HK. Allopurinol and mortality in hyperuricaemic patients. Rheumatology (Oxford). 2009;48(7):804-6.

39. Kesselheim AS, Solomon DH. Incentives for drug development--the curious case of colchicine. N Engl J Med. 2010;362(22):2045-7.

40. Sarawate CA, Brewer KK, Yang W, Patel PA, Schumacher HR, Saag KG, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. Mayo Clin Proc. 2006;81(7):925-34.

41. Cottrell E, Crabtree V, Edwards JJ, Roddy E. Improvement in the management of gout is vital and overdue: an audit from a UK primary care medical practice. BMC Fam Pract. 2013;14:170.

42. Roddy E, Zhang W, Doherty M. Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. Ann Rheum Dis. 2007;66(10):1311-5.

43. Stamp L, Gow P, Sharples K, Raill B. The optimal use of allopurinol: an audit of allopurinol use in South Auckland. Aust N Z J Med. 2000;30:567-72.

44. Reinders MK, Haagsma C, Jansen TL, van Roon EN, Delsing J, van de Laar MA, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day in patients with gout. Ann Rheum Dis. 2009;68(6):892-7.

45. Juraschek SP, Kovell LC, Miller ER, 3rd, Gelber AC. Association of kidney disease with prevalent gout in the United States in 1988-1994 and 2007-2010. Semin Arthritis Rheum. 2013;42(6):551-61.

46. Center for Disease Control and Prevention. Chronic Kidney Disease Surveillance System. Atlanta, US Department of Health and Human Services, 2011. Available at: http://www.cdc.gov/ckd.

47. Hoshide S, Takahashi Y, Ishikawa T, Kubo J, Tsuchimoto M, Komoriya K, et al. PK/PD and safety of a single dose of TMX-67 (febuxostat) in subjects with mild and moderate renal impairment. Nucleosides Nucleotides Nucleic Acids. 2004;23(8-9):1117-8.

48. Mayer MD, Khosravan R, Vernillet L, Wu JT, Joseph-Ridge N, Mulford DJ. Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. Am J Ther. 2005;12(1):22-34.

49. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincon A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010;5(8):1388-93.

50. Momeni A, Shahidi S, Seirafian S, Taheri S, Kheiri S. Effect of allopurinol in decreasing proteinuria in type 2 diabetic patients. Iran J Kidney Dis. 2010;4(2):128-32.

51. Whelton A, MacDonald PA, Chefo S, Gunawardhana L. Preservation of renal function during gout treatment with febuxostat: a quantitative study. Postgrad Med. 2013;125(1):106-14.

52. Whelton A, Macdonald PA, Zhao L, Hunt B, Gunawardhana L. Renal function in gout: long-term treatment effects of febuxostat. J Clin Rheumatol. 2011;17(1):7-13.

53. Dalbeth N, Stamp L. Allopurinol dosing in renal impairment: walking the tightrope between adequate urate lowering and adverse events. Semin Dial. 2007;20(5):391-5.

54. Lee HY, Ariyasinghe JT, Thirumoorthy T. Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction? Singapore Med J. 2008;49(5):384-7.

55. Vazquez-Mellado J, Morales EM, Pacheco-Tena C, Burgos-Vargas R. Relation between adverse events associated with allopurinol and renal function in patients with gout. Ann Rheum Dis. 2001;60(10):981-3.

56. Paisansinsup T, Breitenstein MK, Schousboe JT. Association between adverse reactions to allopurinol and exposures to high maintenance doses: implications for management of patients using allopurinol. J Clin Rheumatol. 2013;19(4):180-6.

57. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee For International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;65:1312-24.

58. Jordan KM, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology (Oxford). 2007;46(8):1372-4.

59. Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum. 2012;64(8):2529-36.

60. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369(4):307-18.

61. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012;64(10):1447-61.

62. Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020: Workshop Summary. Washington, DC: The National Academies Press; 2012.

63. Gaffo AL, Schumacher HR, Saag KG, Taylor WJ, Dinnella J, Outman R, et al. Developing a provisional definition of flare in patients with established gout. Arthritis Rheum. 2012;64(5):1508-17.

64. Mitha E, Schumacher HR, Fouche L, Luo SF, Weinstein SP, Yancopoulos GD, et al. Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial. Rheumatology. 2013;52(7):1285-92.

65. Rubin BR, Burton R, Navarra S, Antigua J, Londono J, Pryhuber KG, et al. Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. Arthritis Rheum. 2004;50(2):598-606.

66. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis. 2012;71(11):1839-48.

67. Schlesinger N, Mysler E, Lin HY, De Meulemeester M, Rovensky J, Arulmani U, et al. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Ann Rheum Dis. 2011;70(7):1264-71.

68. Schumacher HR, Berger MF, Li-Yu J, Perez-Ruiz F, Burgos-Vargas R, Li C**.** Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. J Rheumatol. 2012;39(9):1859-66.

69. Schumacher HR, Jr., Sundy JS, Terkeltaub R, Knapp HR, Mellis SJ, Stahl N, et al. Rilonacept (interleukin-1 trap) in the prevention of acute gout flares during initiation of urate-lowering therapy: results of a phase II randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2012;64(3):876-84.

70. So A, De Meulemeester M, Pikhlak A, Yucel AE, Richard D, Murphy V, et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: Results of a multicenter, phase II, dose-ranging study. Arthritis Rheum. 2010;62(10):3064-76.

71. Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA. 2011;306(7):711-20.

72. Sundy JS, Schumacher HR, Kivitz A, Weinstein SP, Wu R, King-Davis S, et al. Rilonacept for gout flare prevention in patients receiving uric acid-lowering therapy: results of RESURGE, a phase III, international safety study. J Rheumatol. 2014;41(8):1703-11.

73. Chagoya de Sanchez V, Hernandez-Munoz R, Suarez J, Vidrio S, Yanez L, Aguilar-Roblero R, et al. Temporal variations of adenosine metabolism in human blood. Chronobiol Int. 1996;13(3):163-77.

74. Statland BE, Winkel P, Bokelund H**.** Factors contributing to intra-individual variation of serum constituents. 2. Effects of exercise and diet on variation of serum constituents in healthy subjects. Clin Chem. 1973;19(12):1380-3.

75. Kanabrocki EL, Third JL, Ryan MD, Nemchausky BA, Shirazi P, Scheving LE, et al. Circadian relationship of serum uric acid and nitric oxide. JAMA. 2000;283(17):2240-1.

76. Perez-Ruiz F, Alonso-Ruiz A, Calabozo M, Herrero-Beites A, Garcia-Erauskin G, Ruiz-Lucea E**.** Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout. Ann Rheum Dis. 1998;57(9):545-9.

77. Stamp LK, Zhu X, Dalbeth N, Jordan S, Edwards NL, Taylor W**.** Serum urate as a soluble biomarker in chronic gout-evidence that serum urate fulfills the OMERACT validation criteria for soluble biomarkers. Semin Arthritis Rheum. 2011;40(6):483-500.

78. Coons SJ, Rao S, Keininger DL, Hays RD**.** A comparative review of generic quality-of-life instruments. Pharmacoeconomics. 2000;17(1):13-35.

79. Singh JA, Taylor WJ, Simon LS, Khanna PP, Stamp LK, McQueen FM, et al. Patient-reported outcomes in chronic gout: a report from OMERACT 10. J Rheumatol. 2011;38(7):1452-7.

80. Dalbeth N, Schauer C, Macdonald P, Perez-Ruiz F, Schumacher HR, Hamburger S, et al. Methods of tophus assessment in clinical trials of chronic gout: a systematic literature review and pictorial reference guide. Ann Rheum Dis. 2011;70(4):597-604.

81. Singer JZ, Wallace SL**.** The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. Arthritis Rheum. 1986;29(1):82-7.

82. Rothenbacher D, Primatesta P, Ferreira A, Cea-Soriano L, Rodriguez LA**.** Frequency and risk factors of gout flares in a large population-based cohort of incident gout. Rheumatology. 2011;50(5):973-81.

83. Shoji A, Yamanaka H, Kamatani N**.** A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum. 2004;51(3):321-5.

84. Wortmann RL, Macdonald PA, Hunt B, Jackson RL**.** Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. Clin Ther. 2010;32(14):2386-97.

85. Neogi T, Hunter DJ, Chaisson CE, Allensworth-Davies D, Zhang Y**.** Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. J Rheumatol. 2006;33(1):104-9.

86. Chow S-C, Wang H, Shao J**.** *Sample size calculations in clinical research*. 2nd ed. London: Chapman & Hall; 2012.

87. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls TR**.** Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. Curr Med Res Opin. 2009;25(7):1711-9.

88. Harrold LR, Andrade SE, Briesacher B, Raebel MA, Fouayzi H, Yood RA, et al. The dynamics of chronic gout treatment: medication gaps and return to therapy. Am J Med. 2010;123(1):54-9.

89. Harrold LR, Andrade SE, Briesacher BA, Raebel MA, Fouayzi H, Yood RA, et al. Adherence with urate-lowering therapies for the treatment of gout. Arthritis Res Ther. 2009;11(2):R46.

90. Solomon DH, Avorn J, Levin R, Brookhart MA**.** Uric acid lowering therapy: prescribing patterns in a large cohort of older adults. Ann Rheum Dis. 2008;67(5):609-13.

91. Dalbeth N, House ME, Horne A, Petrie KJ, McQueen FM, Taylor WJ**.** Prescription and dosing of urate-lowering therapy, rather than patient behaviours, are the key modifiable factors associated with targeting serum urate in gout. BMC Musculoskelet Disord. 2012;13:174.

92. Cannon GW, Mikuls TR, Hayden CL, Ying J, Curtis JR, Reimold AM, et al. Merging Veterans Affairs rheumatoid arthritis registry and pharmacy data to assess methotrexate adherence and disease activity in clinical practice. Arthritis Care Res (Hoboken). 2011;63(12):1680-90.

93. Little RJA, Rubin DB**.** *Statistical analysis with missing data*. 2nd ed. New York: John Wiley and Sons; 2002.

94. Daniels MJ, Hogan JW**.** Missing data in longitudinal studies: strategies for Bayesian modeling and sensitivity analysis. Boca Raton: Chapman and Hall; 2008.

95. Neogi T, Jansen T, Dalbeth N, et al. 2015 Gout Classification Criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arth Rheumat 2015;67:2557-68.

96. National Kidney Foundation**.** K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266.

97. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20-9.

98. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group**.** KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Supplements. 2013;3:1-150.

99. Cockcroft DW, Gault MH**.** Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

100. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D**.** A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461-70.

101. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-54.

102. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

103. Becker MA, Schumacher HR, Jr., Wortmann RL, MacDonald PA, Palo WA, Eustace D, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. Arthritis Rheum. 2005;52(3):916-23.

104. Uloric [package insert]**.** Deerfield, IL: Takeda Pharmaceuticals America Inc; February 2009.

105. Zyloprim [package insert]**.** San Diego, CA: Promethius Laboratories Inc; October 2003.

106. O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med. 1996;334(20):1287-91.

107. O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002;46(5):1164-70.

108. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, Hunt B, Castillo M, Gunawardhana L; CARES Investigators. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. N Engl J Med. 2018 Mar 29;378(13):1200-1210. doi: 10.1056/NEJMoa1710895.