CSP594 Comparative Effectiveness in Gout: Allopurinol vs. Febuxostat

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CSP 594
Comparative Effectiveness in Gout: Allopurinol vs. Febuxostat

Statistical Analysis Plan

Abbreviations

ACR = American College of Rheumatology
AE = Adverse Event
AHS = Allopurinol Hypersensitivity Syndrome
CKD = Chronic Kidney Disease
CRF = Case Report Forms
CSP = Cooperative Studies Program
eGFR = estimated Glomerular Filtration Rate
RAIN = Rheumatology and Arthritis Investigational Network
SAE = Serious Adverse Event
sUA = serum Uric Acid
SAP = Statistical Analysis Plan
ULT = Urate Lowering Therapy

1. Introduction

This document outlines the statistical methods for the analysis of data collected in the Department of Veterans Affairs Cooperative Studies Programs (CSP) study #594 entitled "Comparative Effectiveness in Gout: Allopurinol vs Febuxostat". The purpose of this document is to provide guidelines from which the analysis will proceed. Deviations from these guidelines will be documented and filed electronically in the study central file SharePoint site.

The following documents were used in preparation of this statistical analysis plan (SAP):

- Clinical Study Protocol CSP #594
- Case Report Forms (CRF) from above entitled Protocol
- Global CSP SOP 2.9: "Developing and Conducting Statistical Analyses"
- Local Work Instruction WI 201 Statistical Analysis Plan and Biostatistical Research Data Processing Plan Creation and Amendment
- Local Job Aid No. 036: Guide to Writing Statistical Analysis Plans

2. Overview of the Study Design and Objectives

The proposed study is a double-blinded, two-arm intervention trial testing whether appropriately titrated allopurinol is non-inferior to appropriately titrated febuxostat.

Participants will be recruited from 19 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. A total of 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.

The 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 Objective:

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 < 6.0 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 phase 3 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 and then extend this analysis to the entire 72-week period.

7) To explore the tolerability/toxicity of the two ULT dosing regimens.

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

3. Investigational Plan

3.1. Description of the Study Population

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 already taking 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 trail is approved for dual enrollment by VACO

3.2. Description of the Intervention Strategy

Eligible patients who consent to participate will be randomized in a 1:1 ratio to receive either allopurinol or febuxostat.

Specified titration of ULT dosing, adhering to the currently recommended initial dosing in gout patients with both normal renal function and CKD stage 3 [1] will be used in Phase 1 (see Table 1 for dose titration schedule).

Specified dose titration will occur until:

1) achievement of sUA concentrations at target level < 6.0 mg/dl (5.0 for participants with tophi);
2) an adverse event occurs mandating drug discontinuation or dose reduction;
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 [2] will be used in Phase 1 and 2.

Table 1: Phase 1 Dose Titration for 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

3.3. Definition of Intention to Treat Sample

All consented and randomized subjects will be accounted for and reported in the CONSORT diagram for the study. By definition, all those randomized subjects will be considered as an intention to treat (ITT) subjects. And all subjects who initiated intervention (i.e., did not drop out or withdraw prior to start of the allocated intervention) will be included in the Data Monitoring Committee (DMC) reports. However, in keeping with clinical practice, only subjects who can tolerate the medications will be considered as our primary analysis subjects. They belong in the phase 3 comparison wherein participants are asked to maintain their level of medication for 24 weeks.

Thus, our primary hypothesis evaluates response during phase 3, while treating phases 1 and 2 as the induction period which identifies those who can tolerate the medications at more than minimum doses. In the secondary analyses we will re-analyze the data using the ITT population to determine if dropout patterns during the induction phases appear to change the results of the comparison. We anticipate that participants who experience severe side effects or who struggle to maintain the medication regimen will drop out during these early phases. Thus, in phase 3 nearly all the remaining patients should find the regimen easy to maintain and have only minor side effects.

Moreover, the ITT analysis that regards any gout flare as a treatment failure is not interpretable. Typically, during titration and stabilization many participants experience flares as the medications reduce sUA level and bring long-term disease under control. These flares are not treatment failures, but instead expected side effects of the titration. Thus, the phase 2 stabilization period is a time buffer that allows us to assert that failures during phase 3 are solely due to treatment (as opposed to titration).

Two analytic sample files consisting of the “ITT” subjects and “Primary Analysis” subjects as defined above will be created and maintained throughout the study. These files will be called the “CSP594_ITT” file and “CSP594_PA” file.

3.4. Definition of per-Protocol sample

Participant adherence to protocol-directed study treatment will be assessed via dosage review 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 in phase 3 of the study with 80% adherence.

We will compare the primary results with the analogous results for the per-protocol participants.

3.5. Description of the Efficacy Endpoints

3.5.1. Primary outcomes

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; this approach is consistent with the approach used in gout RCTs. 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%. 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.

3.5.2. Secondary outcomes

The secondary outcomes will include:

1) The efficacy and tolerability in patients with CKD 3.

    i. 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 in this patient subset.

ii. 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 < 6.0 mg/dl during Phase 2 (mean level assessed at weeks 36, 42, and 48) across treatment groups.

3) The proportion of having at least one 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.

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, 48 and 72 weeks.

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

   We anticipate that ~20% of study participants will have tophi at enrollment. 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).Change in tophi area will be examined at week 24, week 48, and week 72 as a secondary outcome among this informative subset of patients with tophaceous gout.

6) The impact of treatment on the flare rate over time.

   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) The tolerability/toxicity of the two ULTs.

   Toxicity data will be carefully collected throughout the 72 weeks of the study and compared across treatment arms. Toxicity data include rises in sUA levels, serum creatinine, CBC, liver function tests (LFTs), blood pressure, cardiovascular safety events of interest, hospitalization,

and reports of skin rashes.

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

3.6. Description of Baseline Data

Demographic details (e.g., age, sex, race, ethnicity, military service), medical history (e.g., co-morbidities), and baseline labs will be evaluated overall, and by intervention group.

3.7. Safety Data

The safety information to be collected for this study include the description of the event, distinction between serious and non-serious adverse event, severity and expectedness of the event, relatedness to the study intervention, and outcome of the event. In addition, data on all events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.0) coding dictionary.

Related AE data will be collected for all consented subjects 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.

SAE reporting will start at the time of patient consent and continue until 30 days after the patient's involvement in the study.

For reporting to the DMC and inclusion in the final report safety data will be aggregated for the sample as described in **3.3**. Data will be summarized as follows.

- Frequency and percentages of all non-serious and serious adverse events overall and by intervention group
- Frequency and percentages of all unique subjects with non-serious and serious adverse events overall and by intervention group
- Rates of non-serious and serious adverse events overall, by intervention group, and by center, calculated as # events/ person-time in years
- Tabulation of event type, MEDRA classification, severity, expectedness, relatedness and outcome of all events overall and by intervention group

4. Sample Size and Power

The results for the primary hypothesis will be analyzed by using a one-sided 95% confidence interval on the difference in proportion of participants with one or more gout flare events during phase 3. The test of the difference between proportions will have one-sided type I error of 5%.

Starting with a total of 950 participants and allowing up to 10% dropout, the test has 90% power to reject the null hypothesis of inferiority with a total of 850 participants, 425 participants per treatment arm.

Sample recruitment and subsequent event rates will be summarized and presented to the DMC bi-annually. These reports will be used for monitoring the progress of the study and any modification to the recruitment schedule or the statistical analysis plan will be at the recommendation of the DMC.

5. Statistical Methods

5.1. Handling of Missing Data in Analysis

During phase 3, 2% of subjects have been estimated to drop out. This is less than the dropout rate in phase 1 and 2 because no one is having dose titration. For purpose of making the power calculation conservative, the rate of attrition has been estimated as being up to 10%, and sample size has been adjusted accordingly to maintain 90% statistical power for the primary analysis.

The high dropout rate reflects clinical practice and not the more vigilant patient monitoring in a clinical trial. Distribution of participants lost to follow-up and missing data on key variables across the treatment groups will be monitored throughout the study. Missing primary endpoint data will not be imputed. All those with missing endpoint data either due to attrition or active withdrawal of consent will be excluded from primary analysis. Missing covariate data will be imputed in selected circumstances as described in [3]. We will explore the possibility of non-random dropout on endpoint data [4].

5.2. Balancing During Randomization

Simple 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;
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 current receipt of allopurinol.

Furthermore, to guarantee enrollment of a sufficient number of gout participants with CKD stage 3 (eGFR ≥30 but <60 ml/min/1.73 m^2) to address a key secondary objective (see Section 2), we will randomize at least one participant with CKD Stage 3 for every two participants with preserved renal function (eGFR ≥ 60 ml/min/1.73 m^2).

Distribution of all these variables across the treatment groups will be closely monitored throughout the study. If any unbalancing happens on one or more characteristics listed above, a biased coin algorithm will be implemented to remedy the condition.

5.3. Univariate and Bivariate Distributions of Baseline, Safety and Follow-up data

- In general, the number of observations, mean, median, standard deviation, minimum, and maximum will be calculated for continuous variables. The number of decimals places will be two decimal places.
- Frequencies and percentages will be calculated for categorical data.
- Distribution of continuous variables and proportions of categorical variables will be tabulated by intervention group, and t-test and chi-square tests will be performed to evaluate if these variables are balanced between 2 intervention groups.
- For the primary analysis, baseline is defined as the starting date of Phase 3.

5.4. Primary Efficacy Analysis

Primary efficacy analysis will include patients who remain on study when phase 3 begins.

The primary outcome is the difference (D) in proportion of patients with one or more gout flares during Phase 3. Seven rheumatologists on our Planning Committee, selected for their expertise in gouty arthritis and clinical trial design, chose B = 8%.

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 (lower gout flare proportion). To test the null hypothesis, we will compute the upper limit of a one-sided 95% confidence interval for D:

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

The graphic below displays the decision process. In **Figure 1** the upper limit (U) is less than B, and we reject the null 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

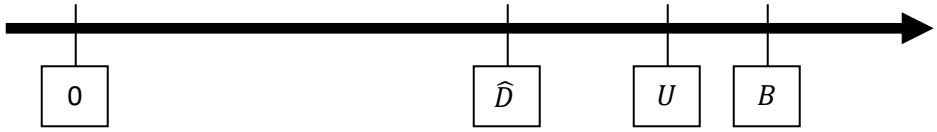
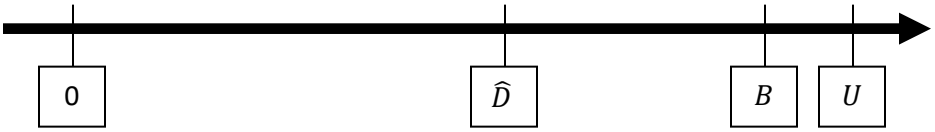


Figure 2: One-Sided 95% Confidence Interval for the Non-inferiority Test Depicting 'Acceptance' of the Null Hypothesis



SAS 9.4 will be used to carry out the analysis. Analytic reports will provide the proportions, the differences among proportions, and the upper limit of a one-sided 95% confidence interval, the bound, followed by a report of the results.

5.4.1. Sensitivity Analysis

(1) The primary analysis will be repeated on the "per-Protocol" sample with adherence as defined in **3.4** to evaluate efficacy among those adherent to the protocol. We will compare the primary results with the analogous results for the per-protocol participants.

(2) On the "Primary Analysis" cohort assuming all allopurinol patients with missing primary outcome had at least one gout flare during phase 3 of our study while none of febuxostat patients with missing primary outcome had any gout flare during phase 3 (the worst-case scenario).

(3) On the "Primary Analysis" cohort assuming all febuxostat patients with missing primary outcome had at least one gout flare during phase 3 of our study while none of allopurinol

patients with missing primary outcome had any gout flare during phase 3 (the best case scenario).

5.5. Secondary Analysis

All secondary analyses are descriptive exploratory analyses and will be done with and without covariate adjustment (age, sex, disease severity, comorbidities, etc.). In some secondary analyses, we will impute values to explicitly explore the effect of missing data.

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.

    a. We will carry out the analogues non-inferiority analysis proposed for the primary objective but restricted to participants with stage 3 CKD, using only gout flares observed during Phase 3. 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 with a logistic regression model.

    b. Tolerability of the two treatments will also be compared in this patient subset and will include comparisons of proportions of adverse events, serious adverse events, and related study withdrawal during the whole study using logistic regression.

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.

    a. The 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.

    b. We will run the same analysis using the biological threshold of sUA < 6.8 mg/dl at the end of phase 2.

3) To determine if there are 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.

   The binary outcome for this logistic regression analysis will be the presence of gout flares in phase 3. The analysis will use gout flares in phase 1 and phase 2 as baseline covariates.

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.

   a. EQ-5D-3L & VR-12 instruments will be administered at baseline, 24, 48, and 72 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.

   b. With outcome change from baseline to later weeks, we will compare mean changes by treatment group with and without covariates using linear regression.

   c. We will carry out a repeated measures analysis using all time points. Missing data methods will address potential censoring of events among patients who fail to complete the instrument at a particular time.

   d. 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.

   a. Tophi area will be assessed at baseline, 24, 48, and 72 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.

   b. With area change from baseline to later weeks, we will compare mean changes by location with and without covariates using linear regression.

   c. We will carry out a repeated measures analysis using all time points. Missing data methods will address potential censoring of events among patients who fail to complete the instrument at a particular time.

   d. 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.

    a. We will model the number of gout flares, which can have substantial variation, as Poisson random variables. We will use Poisson regression to compare treatments using a longitudinal repeated measure (PROC GLIMMAX and GENMOD in SAS). Missing data methods will address potential censoring of events among patients who appear to fail to report flares.

    b. 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.

    c. Phase 2 analysis will consider prophylactic treatment after a gout flare and severe side effects of treatment as predictors of subsequent counts.

    d. 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 AR(1) variance-covariance to model the series of events.

    e. 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.

    a. 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 will also be included in this analysis.

    b. 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 week 48 sUA level. As in the sixth secondary analysis the same statistical methods for Poisson counts will be used.

    c. At each clinic visit we will assess the count of each type of major side effect episodes between visits. 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.

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

   a. We will carry out logistic regression analyses adjusting for covariates and use GEE model.

   b. 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.

   c. Time-dependent variables include data obtained after baseline include sUA measures, titration levels, and side effects.

   d. All data obtained before Phase 3 may be used as baseline factors for Phase 3 analyses.

6. Data Monitoring Committee Reports

Data and study progress will be monitored by the study executive committee and by the Data Monitoring Committee. The DMC will review the study progress and safety semiannually with additional meetings and communications as needed.

All reports will be generated in conjunction with the Data Management department using SQL and SAS.

6.1. Analytic Sample for DMC Reports

All subjects randomized more than six weeks prior to the DMC meeting date who initiated intervention (i.e., did not drop out or withdraw prior to start of the allocated intervention) will be included in the analytic cohort for the upcoming DMC report, and all data collected up to four weeks prior to the DMC meeting date will be analyzed. This allows for two weeks lag time for submission of data from sites.

6.2. Outline of DMC Reports

The report is divided into four sections to cover subject disposition, baseline assessment, follow-up assessment, and safety assessment.

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Table D5. Serious Adverse Events by System Organ Class and Preferred Term

7. Shell DMC Tables (subject to change)

Figure A1. CONSORT Diagram

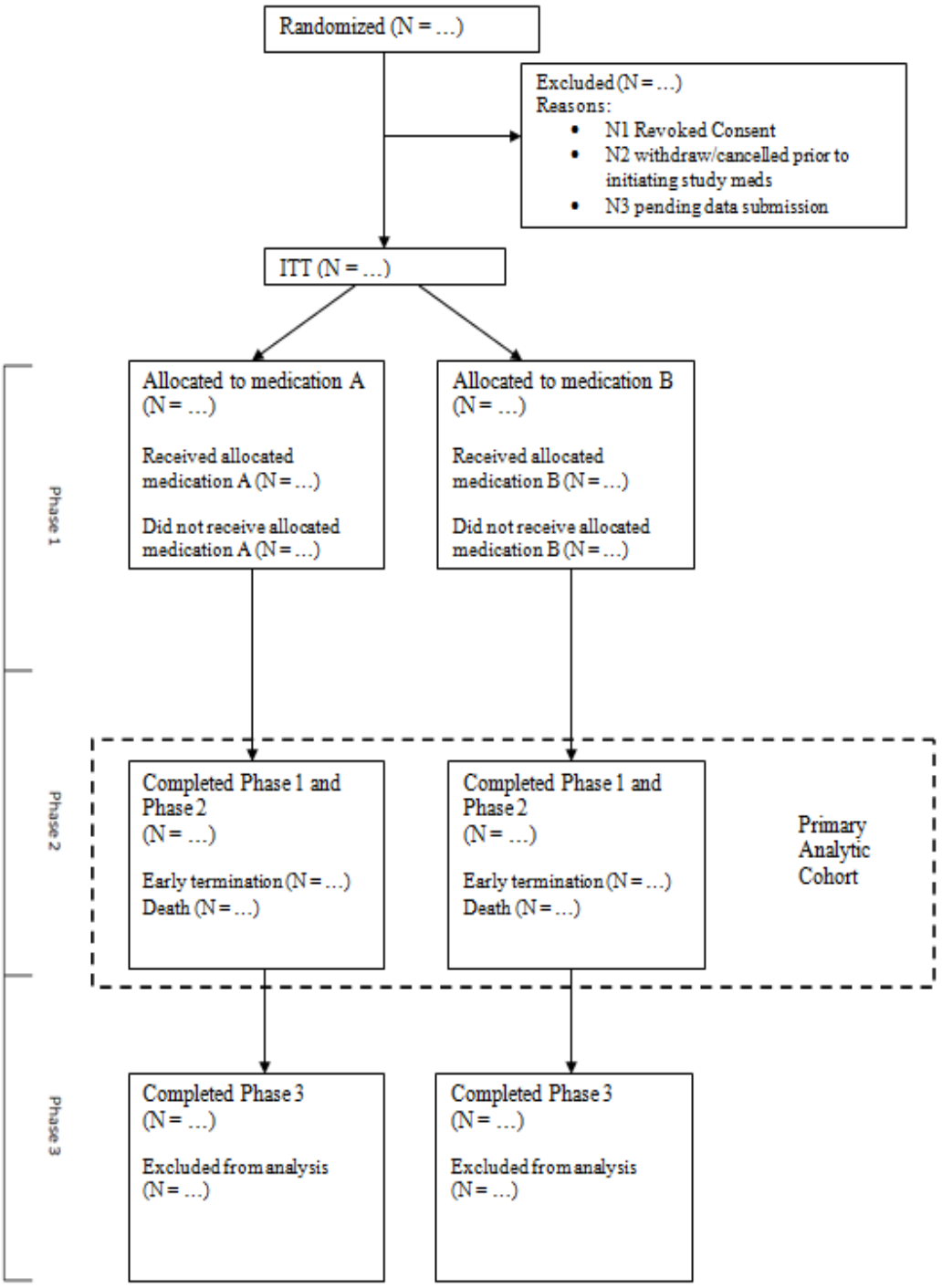


Table A2. Recruitment by Site

Site ID	Site Name	Actual Accrual	Expected Accrual	Percentage of Expected
101	Nebraska-WesternIowa	N	N	XX%
102	CharlesGeorge	N	N	XX%
103	RAIN5-UNMC	N	N	XX%
104	Portland	N	N	XX%
105	RAIN1-Mayo	N	N	XX%
106	Pittsburgh	N	N	XX%
107	SaltLakeCity	N	N	XX%
108	Salem	N	N	XX%
109	SanFrancisco	N	N	XX%
110	SanDiego	N	N	XX%
111	EdwardHines	N	N	XX%
112	NYU	N	N	XX%
113	Philadelphia	N	N	XX%
114	Cincinnati	N	N	XX%
116	Minneapolis	N	N	XX%
117	KansasCity	N	N	XX%
118	RAIN3-Yankton	N	N	XX%
119	Dallas	N	N	XX%
120	LomaLinda	N	N	XX%
121	WhiteRiverJunction	N	N	XX%
122	Miami	N	N	XX%
123	Boston	N	N	XX%
124	RAIN2-Bismark	N	N	XX%
125	WRJ-Manchester	N	N	XX%

Figure A2. Overall Study Enrollment

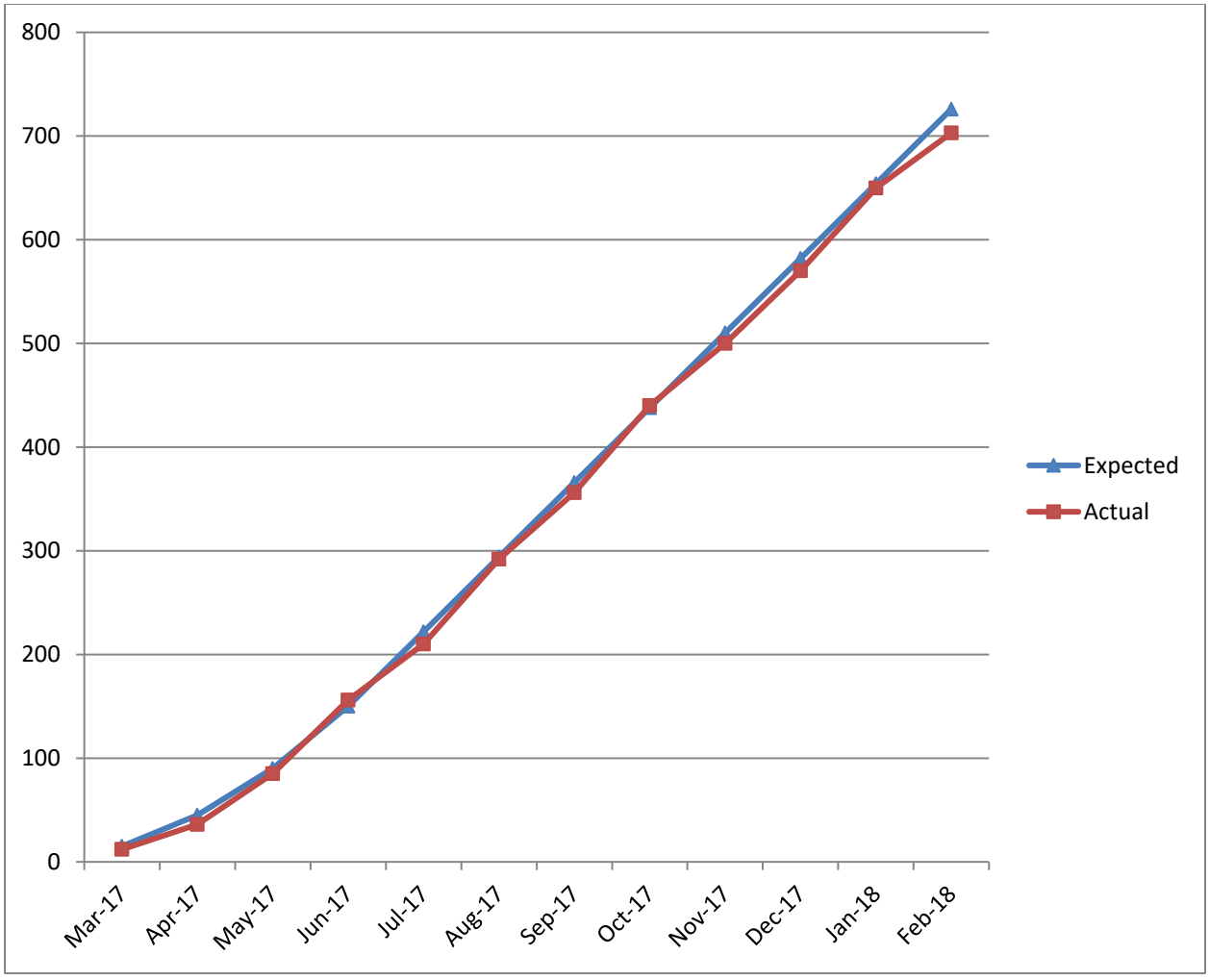


Figure A3. Enrollment by Site

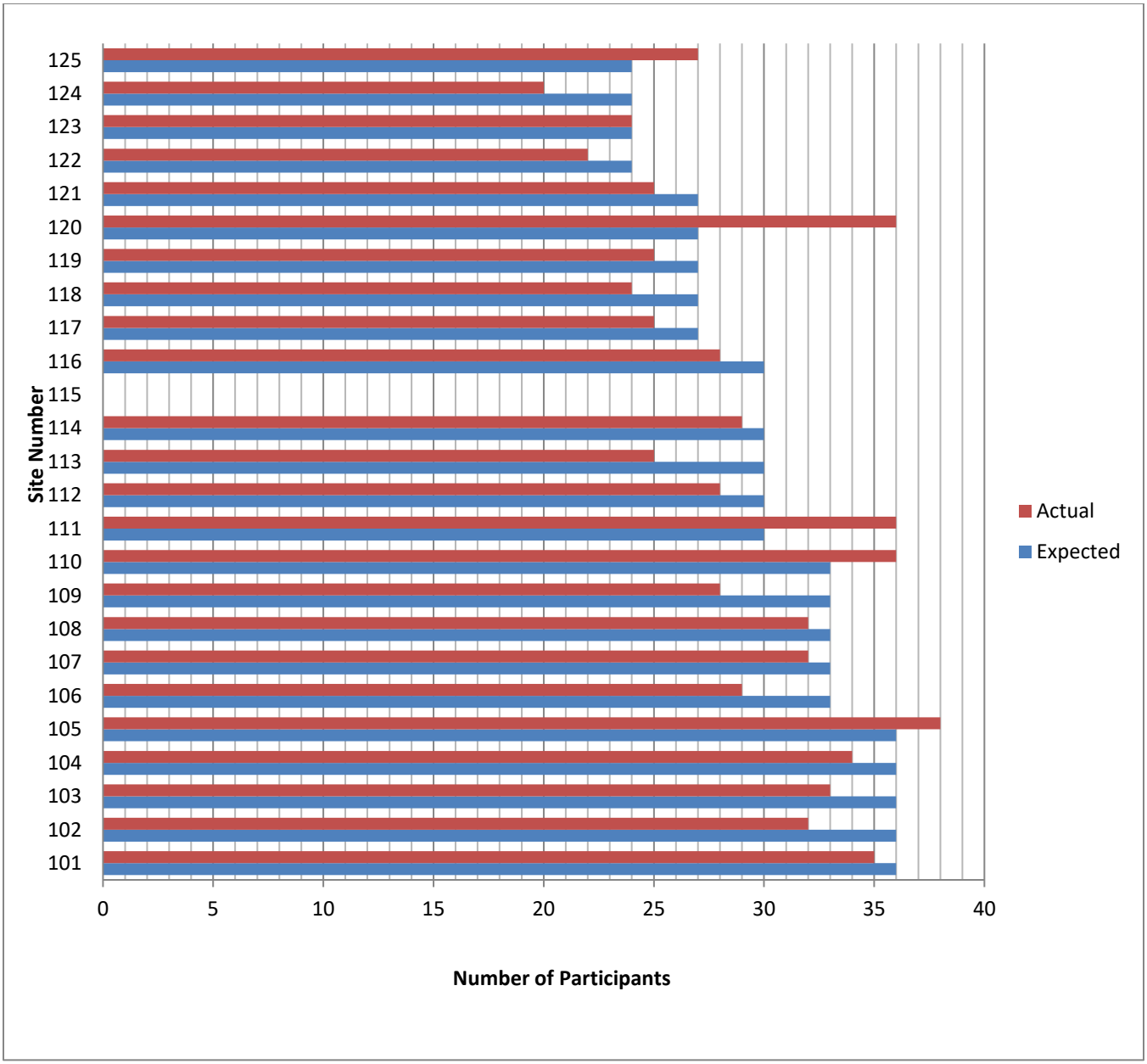
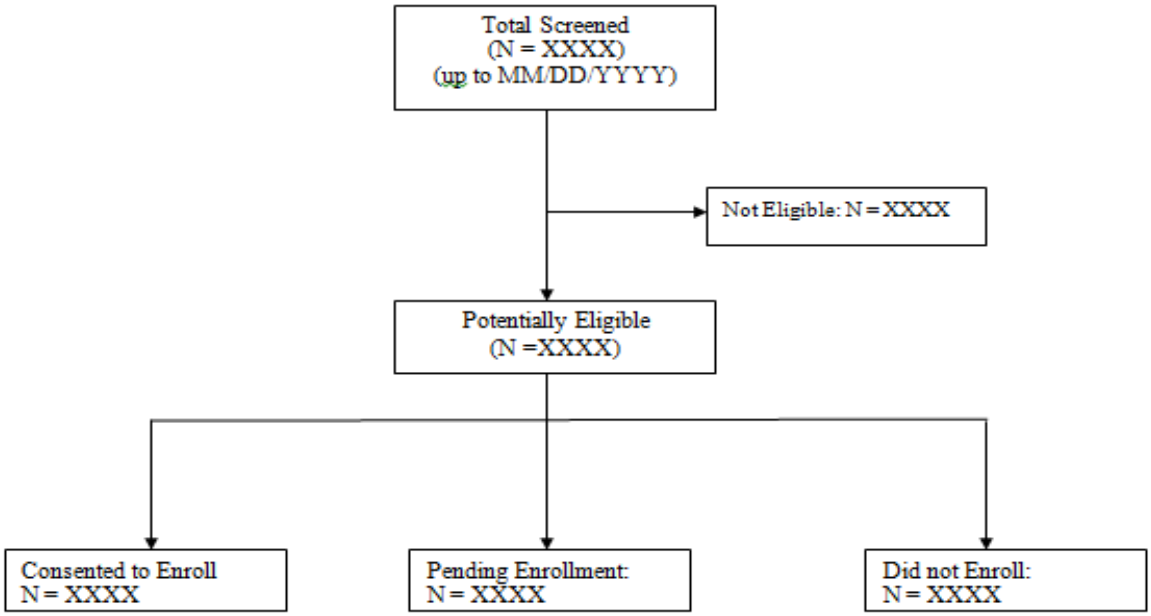


Table A4. Pre-Screening Log Data.



Reason Why no tEnrolled	Eligible but did not enroll (N=)	%	Cumulative %
A. Refusal	N	%	%
B. Provider decision	N	%	%
C. Dual Enrollment Issue	N	%	%
D. Missing – No reason given	N	%	100%

Table A5. Protocol Deviations

Description of Protocol Deviation	Sample (N=)	Form Location	Element Codes
Informed consent and/or HIPAA authorization not signed until after study procedures started	N (%)	PD	DVDECOD=1
Eligibility criteria violated	N (%)	PD	DVDECOD=2
Allopurinol/Febuxostat not prescribed and/or not dispensed as per protocol	N (%)	PD	DVDECOD=3
Required study procedure not completed	N (%)	PD	DVDECOD=4
SAE not reported per protocol	N (%)	PD	DVDECOD=5
Lab blood draws not obtained as per protocol	N (%)	PD	DVDECOD=6
Participant took Probenecid and or/ Lesinurad	N (%)	PD	DVDECOD=7
Participant took other excluded medication after randomization	N (%)	PD	DVDECOD=8
Required source documentation could not be obtained	N (%)	PD	DVDECOD=9
Patient seen outside visit window (Study visits will have a window +/- 1 week in Phase 1 and +/- 2 weeks in Phase 2 and 3)	N (%)	PD	DVDECOD=10
Other protocol deviation[1]	N (%)	PD	DVDECOD=11

[1]See Appendix B.

Table A6. Early Terminations

Reason for Termination	Sample (N=)	Form Location	Element Codes
Death	N (%)	EOS	DSDECOD=1
Side effects with study medications	N (%)	EOS	DSDECOD=2
Provider decision	N (%)	EOS	DSDECOD=3
Participant decision	N (%)	EOS	DSDECOD=4
Participant lost to follow-up	N (%)	EOS	DSDECOD=5
Study site closure	N (%)	EOS	DSDECOD=6
Participant required to take exclusion medication on a regular basis	N (%)	EOS	DSDECOD=7
Other reasons for early termination	N (%)	EOS	DSDECOD=8

[1]See Appendix C.

Table A7. Form Completion, by Form Type

Form Name	#Forms Expected	#Forms Completed
Adverse Event Follow Up	N	N (%)
Adverse Event	N	N (%)
Alcohol Use Questionnaire	N	N (%)
Change in Study Medication Dosage	N	N (%)
Clinical Biochemistry Laboratory Test	N	N (%)
Concomitant Medications	N	N (%)
Demographics	N	N (%)
Eligibility and Randomization	N	N (%)
End of Study	N	N (%)
EQ5D-3L	N	N (%)
Gout Attack Diary and Questionnaire	N	N (%)
Index Tophus Location and Area	N	N (%)
Military History	N	N (%)
Participant Contact Information	N	N (%)
Protocol Deviation	N	N (%)
Rash Adverse Event Form	N	N (%)
Relevant Medical History	N	N (%)
Serious Adverse Event Follow Up	N	N (%)
Serious Adverse Event	N	N (%)
Study Medication Adherence	N	N (%)
sUA unscheduled	N	N (%)
Vital Signs	N	N (%)
VR-12	N	N (%)

*Expectation: >=90% submission

Table A8. Form Completion, by Site

Site#	Site Name	#Forms Expected	#Forms Completed
101	Nebraska-WesternIowa	N	N (%)
102	CharlesGeorge	N	N (%)
103	RAIN5-UNMC	N	N (%)
104	Portland	N	N (%)
105	RAIN1-Mayo	N	N (%)
106	Pittsburgh	N	N (%)
107	SaltLakeCity	N	N (%)
108	Salem	N	N (%)
109	SanFrancisco	N	N (%)
110	SanDiego	N	N (%)
111	EdwardHines	N	N (%)
112	NYU	N	N (%)
113	Philadelphia	N	N (%)
114	Cincinnati	N	N (%)
116	Minneapolis	N	N (%)
117	KansasCity	N	N (%)
118	RAIN3-Yankton	N	N (%)
119	Dallas	N	N (%)
120	LomaLinda	N	N (%)
121	WhiteRiverJunction	N	N (%)
122	Miami	N	N (%)
123	Boston	N	N (%)
124	RAIN2-Bismark	N	N (%)
125	WRJ-Manchester	N	N (%)

*Expectation: >=90% submission

Table B1. Patient Characteristics

Characteristic	Sample *VA* (N=)	Sample *RAIN* (N=)	Form Location	Element Codes
Age (years)				
Mean ± SD	Mean ± SD	Mean ± SD	Eligibility and Demographics	Average, Stddev (floor(Randdt-Brthdat)/365.25)
Range	(Range)	(Range)	Eligibility and Demographics	Range=(min-max(Randdt-Birthdat))
Sex				
Male	N (%)	N (%)	Demographics	SEX = 1
Female	N (%)	N (%)	Demographics	SEX = 2
Race				
American Indian/Alaskan Native	N (%)	N (%)	Demographics	RaceAI = 1
Asian	N (%)	N (%)	Demographics	RaceAs = 1
Black/African American	N (%)	N (%)	Demographics	RaceAA=1
Native Hawaii/Pacific Islander	N (%)	N (%)	Demographics	RacePI=1
White / Caucasian	N (%)	N (%)	Demographics	RaceW=1
Other / Multiple Selected	N (%)	N (%)	Demographics	RaceO=1
Ethnicity				
Not Hispanic or Latino	N (%)	N (%)	Demographics	Ethnic=1
Hispanic or Latino	N (%)	N (%)	Demographics	Ethnic =2
Participant chose not to answer	N (%)	N (%)	Demographics	Ethnic =-99
Education				
Less than High School Diploma	N (%)	N (%)	Demographics	Educatn = 1
High School Diploma	N (%)	N (%)	Demographics	Educatn = 2
Some College credit but no Degree	N (%)	N (%)	Demographics	Educatn = 3
Associate's Degree	N (%)	N (%)	Demographics	Educatn = 4
Bachelor’s Degree	N (%)	N (%)	Demographics	Educatn = 5
Master’s Degree	N (%)	N (%)	Demographics	Educatn = 6
Doctoral Degree	N (%)	N (%)	Demographics	Educatn = 7
Other	N (%)	N (%)	Demographics	Educatn = 8
Marital Status				
Married	N (%)	N (%)	Demographics	Marital=1

Divorced	N (%)	N (%)	Demographics	Marital=2
Civil Commitment	N (%)	N (%)	Demographics	Marital=3
Never Married	N (%)	N (%)	Demographics	Marital=4
Widowed	N (%)	N (%)	Demographics	Marital=5
Separated	N (%)	N (%)	Demographics	Marital=6
Cohabitating	N (%)	N (%)	Demographics	Marital=7

Table B2. Military Service, VA sites only

Characteristic	Sample* (N=)	Form Location	Element Codes
Military Service			
Army	N (%)	Military History	MilBranchA =1
Navy	N (%)	Military History	MilBranchN =1
Air Force	N (%)	Military History	MilBranchAF =1
Marine Corps	N (%)	Military History	MilBranchM =1
Coast Guard	N (%)	Military History	MilBranchCG =1
Other	N (%)	Military History	MilBranchOth =1
Service Periods			
Prior to World War II (Nov 1941 or earlier)	N (%)	Military History	MilWartimePWW =1
World War II Era (Dec 1941-Dec 1946)	N (%)	Military History	MilWartimeWW =1
Jan 1947-June 1950	N (%)	Military History	MilWartime47 =1
Korean Conflict Era (July 1950-Jan 1955)	N (%)	Military History	MilWartimeK =1
Feb 1955-July 1964	N (%)	Military History	MilWartime55 =1
Vietnam Conflict Era (Aug 1964-April 1975)	N (%)	Military History	MilWartimeV =1
May 1975-July 1990	N (%)	Military History	MilWartime75 =1
Persian Gulf War Era(Aug 1990-Feb 1991)	N (%)	Military History	MilWartimePG =1
March 1991-Sep 2001	N (%)	Military History	MilWartime91 =1
Afghanistan/Iraq Conflict Era (Oct 2001-Present)	N (%)	Military History	MilWartimeAI =1

*Number of subjects from VA sites only

Table B3. Relevant Medical History

	Does participant currently have the problem?	Is participant currently receiving treatment?	Does it limit the participant's activities?	
Characteristic	**(N=)**	**(N=)**	**(N=)**	**Form Location**
Congestive Heart Failure				
Coronary Artery Disease or Myocardial Infarctions.	N (%)	N (%)	N (%)	Relevant Medical History
High Blood Pressure	N (%)	N (%)	N (%)	Relevant Medical History
Lung Disease	N (%)	N (%)	N (%)	Relevant Medical History
Diabetes	N (%)	N (%)	N (%)	Relevant Medical History
Gastrointestinal Disease	N (%)	N (%)	N (%)	Relevant Medical History
Kidney Disease	N (%)	N (%)	N (%)	Relevant Medical History
Liver Disease	N (%)	N (%)	N (%)	Relevant Medical History
Blood Disorder				Relevant Medical History
Cancer (with exception of non-melanoma skin cancer)	N (%)	N (%)	N (%)	Relevant Medical History
Arthritis or Musculoskeletal Disorder (other than Gout)	N (%)	N (%)	N (%)	Relevant Medical History
Thyroid Disease	N (%)	N (%)	N (%)	Relevant Medical History
Chronic Rash				Relevant Medical History

Table B4. Baseline Labs and Assessment

Characteristic	Sample (N=)	Form Location
Creatinine (mg/dl)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
White Blood Cell (K/CMM)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Platelet Count (K/CMM)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Hemoglobin (Hgb) (g/dl)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
C-reative Protein (CRP) (mg/dl)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Alanine Aminotransferase (ALT) (U/L)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Weight (kg)		
Mean ± SD (N)	Mean ± SD (N)	Vital Signs
Range	(Range)	Vital Signs
Systolic BP		
Mean ± SD (N)	Mean ± SD (N)	Vital Signs
Range	(Range)	Vital Signs
Diastolic BP		
Mean ± SD (N)	Mean ± SD (N)	Vital Signs
Range	(Range)	Vital Signs

Table B5. Week 24 Labs and Assessment

Characteristic	Sample (N=)	Form Location
Creatinine (mg/dl)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
White Blood Cell (K/CMM)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Platelet Count (K/CMM)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Hemoglobin (Hgb) (g/dl)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
C-reative Protein (CRP) (mg/dl)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Alanine Aminotransferase (ALT) (U/L)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Weight (kg)		
Mean ± SD (N)	Mean ± SD (N)	Vital Signs
Range	(Range)	Vital Signs
Systolic BP		
Mean ± SD (N)	Mean ± SD (N)	Vital Signs
Range	(Range)	Vital Signs
Diastolic BP		
Mean ± SD (N)	Mean ± SD (N)	Vital Signs
Range	(Range)	Vital Signs

Table B6. Week 48 Labs and Assessment

Characteristic	Sample (N=)	Form Location
Creatinine (mg/dl)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
White Blood Cell (K/CMM)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Platelet Count (K/CMM)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Hemoglobin (Hgb) (g/dl)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
C-reative Protein (CRP) (mg/dl)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Alanine Aminotransferase (ALT) (U/L)		
Mean ± SD	Mean ± SD	Clinical Bio Lab
Range	Range	Clinical Bio Lab
Weight (kg)		
Mean ± SD (N)	Mean ± SD (N)	Vital Signs
Range	(Range)	Vital Signs
Systolic BP		
Mean ± SD (N)	Mean ± SD (N)	Vital Signs
Range	(Range)	Vital Signs
Diastolic BP		
Mean ± SD (N)	Mean ± SD (N)	Vital Signs
Range	(Range)	Vital Signs

Table B7. Study Medication Adherence

Adherence[1]	Baseline (n=)	Form Location
Phase 1		
<80%	N (%)	Study Medication Adherence
>= 80%	N (%)	Study Medication Adherence
Phase 2		
<80%	N (%)	Study Medication Adherence
>= 80%	N (%)	Study Medication Adherence
Phase 3		
<80%	N (%)	Study Medication Adherence
>= 80%	N (%)	Study Medication Adherence
Overall		
<80%	N (%)	Study Medication Adherence
>= 80%	N (%)	Study Medication Adherence

[1]Adherence is compusted as (Total capsules/Tablets taken/Total capsules/tablets given) * 100

Table B8. Study Medication Dose Change

Adherence[1]	Baseline (n=)	Form Location
Baseline		
< 100/40mg	N (%)	Change in Study Medication dosage
= 100/40mg	N (%)	Change in Study Medication dosage
> 100/40mg	N (%)	Change in Study Medication dosage
3 weeks		
< 200/40mg	N (%)	Change in Study Medication dosage
= 200/40mg	N (%)	Change in Study Medication dosage
> 200/40mg	N (%)	Change in Study Medication dosage
6 weeks		
< 300/40mg	N (%)	Change in Study Medication dosage
= 300/40mg	N (%)	Change in Study Medication dosage
> 300/40mg	N (%)	Change in Study Medication dosage
9 weeks		
< 400/80mg	N (%)	
= 400/80mg	N (%)	
> 400/80mg	N (%)	

Table B9. Concomitant Medications

Characteristic	Baseline (n=)	Form Location
Probenecid	N (%)	**Concomitant Medications**
Lesinurad	N (%)	**Concomitant Medications**
Angiotensin Converting Enzyme (ACE) Inhibitor	N (%)	**Concomitant Medications**
Alpha Blocker	N (%)	**Concomitant Medications**
Angiotensin Receptor Blocker (ARB)	N (%)	**Concomitant Medications**
Losartan	N (%)	**Concomitant Medications**

Table C1. Study Primary Outcome Events

Outcome Event Type	Sample (N=)	Element Code
Primary Outcome		
# Subjects with more than one gout flare Phase 3	N(%)	Gout flare Questionnaire and diary
Secondary outcome 1		
# Subjects with CKD3 in Phase 3	N(%)	Clinical Biochem Lab
# Subjects with more than one gout flare in Phase 3	N(%)	Gout flare Questionnaire and diary
Secondary outcome 2 and 3		
# Subjects with mean sUA < 6.0 at the end of Phase 2	N(%)	Clinical Biochem Lab
# Subjects with mean sUA < 6.8 at the end of Phase 2	N(%)	Clinical Biochem Lab
Secondary outcome 4		
EQ-5D-3L		
Mean ± SD	Mean ± SD	EQ5D-3L
Range	(range)	EQ5D-3L
VR-12		
Mean ± SD	Mean ± SD	VR-12
Range	(range)	VR-12

Table C2. Study Secondary Outcome Events – Part I

Outcome Event Type	Sample (N=)	Element Code
Secondary outcome 1		
# Subjects with CKD3 in Phase 3	N(%)	Clinical Biochem Lab
# Subjects with more than one gout flare in Phase 3	N(%)	Gout flare Questionnaire and diary
Secondary outcome 2 and 3		
# Subjects with mean sUA < 6.0 at the end of Phase 2	N(%)	Clinical Biochem Lab
# Subjects with mean sUA < 6.8 at the end of Phase 2	N(%)	Clinical Biochem Lab

Table C3. Study Secondary Outcome Events – Part II

Outcome Event Type	Sample (N=)	Element Code
Secondary outcome 4		
EQ-5D-3L Baseline		
Mean ± SD	Mean ± SD	EQ5D-3L
Range	(range)	EQ5D-3L
VR-12 Baseline		
Mean ± SD	Mean ± SD	VR-12
Range	(range)	VR-12
EQ-5D-3L Week 24		
Mean ± SD	Mean ± SD	EQ5D-3L
Range	(range)	EQ5D-3L
VR-12 Week 24		
Mean ± SD	Mean ± SD	VR-12
Range	(range)	VR-12
EQ-5D-3L Week 48		
Mean ± SD	Mean ± SD	EQ5D-3L
Range	(range)	EQ5D-3L
VR-12 Week 48		
Mean ± SD	Mean ± SD	VR-12
Range	(range)	VR-12

Table C4. Study Secondary Outcome Events – Part III

Outcome Event Type	Sample (N=)	Element Code
Secondary outcome5		
Tophus Baseline		
Mean ± SD	Mean ± SD	Index Tophus Location and Area
Range	(range)	Index Tophus Location and Area
Tophus Week 24		
Mean ± SD	Mean ± SD	Index Tophus Location and Area
Range	(range)	Index Tophus Location and Area
Tophus Week 48		
Mean ± SD	Mean ± SD	Index Tophus Location and Area
Range	(range)	Index Tophus Location and Area

Table C5. Study Secondary Outcome Events – Part IV

Phase	Gout Flare Count	Sample (n=)	Form Location
1	0	N (%)	Gout Attack Diary and Questionnaire
	1-2	N (%)	
	3+	N (%)	
2	0	N (%)	Gout Attack Diary and Questionnaire
	1-2	N (%)	
	3+	N (%)	
3	0	N (%)	Gout Attack Diary and Questionnaire
	1-2	N (%)	
	3+	N (%)	
Overall	0	N (%)	Gout Attack Diary and Questionnaire
	1-2	N (%)	
	3+	N (%)	

Table C6. Study Secondary Outcome Events – Part V

Phase	Toxicity Events	Sample (n=)	Form Location
Rise in sUA levels			
1	Mean ± SD	N (%)	Clinical Biochem Lab
2	Mean ± SD	N (%)	Clinical Biochem Lab
3	Mean ± SD	N (%)	Clinical Biochem Lab
Overall	Mean ± SD	N (%)	Clinical Biochem Lab
Skin Rashes			
1	0	N (%)	Rash Adverse Event
	1-2	N (%)	
	3+	N (%)	
2	0	N (%)	Rash Adverse Event
	1-2	N (%)	
	3+	N (%)	
3	0	N (%)	Rash Adverse Event
	1-2	N (%)	
	3+	N (%)	
Overall	0	N (%)	Rash Adverse Event
	1-2	N (%)	
	3+	N (%)	

Table D1. Rates of Non-Serious Adverse Events (NAEs) and Serious Adverse Events (SAEs), by Site

Site#	# NAEs	#Unique Subjects	Rate per Year*		# SAEs	#Unique Subjects	Rate per Year*
101	N (%)	N (%)			N (%)	N (%)	
102	N (%)	N (%)			N (%)	N (%)	
..	..	..			..	..	
..	..	..			..	..	
125	N (%)	N (%)			N (%)	N (%)	
TOTAL							

*Rate per year computed as [# events /(sum of (data close date - randomization date))], if events are rare, then present as rate per 100 years.

Table D2. Summary of Non-Serious Adverse Events

	Sample (N= Events)	Form Location	Element Codes
#Weeks since Randomization	Mean±SD	Randomization and AE	
Phase 1	N(%)	Randomization and AE	
Phase 2	N(%)	Randomization and AE	
Phase 3	N(%)	Randomization and AE	
Severity of NAE			
Mild AEs	N(%)	AE	AESEV=1
Moderate AEs	N(%)	AE	AESEV =2
Severe AEs	N(%)	AE	AESEV=3
Relatedness			
Possibly or Definitely Related to Study Treatment	N(%)	AE	AEIVREL=yes, possibly
# Unique Subjects with at least 1 NAE that is possibly or definitely related to Study Treatment	N*(%) of N subjects	AE	)

Table D3. Summary of Serious Adverse Events

Characteristic	Sample (N= Events)	Form Location	Element Codes
#Weeks since Randomization	Mean±SD	Randomization and SAE	
Phase 1	N(%)	Randomization and SAE	
Phase 2	N(%)	Randomization and SAE	
Phase 3	N(%)	Randomization andS AE	
SAE category (can be multiple)			
Death	N(%)	SAE	AESDTH=1
Initial or prolonged hospitalization	N(%)	SAE	AESHOSP=1
Life threatening experience	N(%)	SAE	AESLIFE=1
Required medical or surgical treatment	N(%)	SAE	AESMIE=1
Persistent or significant disability or incapacity	N(%)	SAE	AESDISAB=1
Congenital anomaly/birth defect	N(%)	SAE	AESCONG=1
Relatedness (Possibly or Definitely)			
To Study Treatment	N(%)	SAE	
# Unique Subjects with at least 1 SAE that is possibly or definitely related to Study Treatment	N*(%) of N subjects	SAE	
# Unique Subjects with at least 1 SAE that is possibly or definitely related to Study Drug Capsule	N*(%) of N subjects	SAE	
Outcome			
Recovered/resolved	N(%)	SAE	AESOUT =1
Recovered/resolved with sequelae	N(%)	SAE	AESOUT =2
Recovering/resolving	N(%)	SAE	AESOUT =3
Not recovered/not resolved	N(%)	SAE	AESOUT =3
Fatal ***5***	N(%)	SAE	AESOUT =5
Data not available	N(%)	SAE	AESOUT =6

Table D4. Non-Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class	Prefered Term	N (%)

Table D5. Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class	Prefered Term	N (%)

8. References

[1] 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.

[2] 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 anti-inflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012;64(10):1447-61.

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

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