



STATISTICAL ANALYSIS PLAN

(Version 1.09)

Protocol Title: Controlled trial of slowing of **K**idney **D**isease progression
From the **I**nhibition of **X**anthine oxidase (Version 3.0).

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PREFACE

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting for The Australasian Kidney Trials Network (AKTN) protocol 10.02, a Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase: The CKD-FIX Study.

The structure and content of this SAP provide sufficient detail to meet the requirements identified by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.(1) All work planned and reported for this SAP will follow national and international guidelines for statistical practice (2, 3).

The planned analyses identified in this SAP will be included in future manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support planned analyses. Any post-hoc or unplanned analyses not specified in this SAP will be clearly identified as such in the Final Statistical Report (FSR) and manuscripts for publication.

This SAP was written and reviewed by a statistician and clinical investigators from the CKD-FIX Trial Steering Committee (TSC). All contributors were blinded to treatment allocations and treatment-related study results and will remain so until the central database is locked and the final data extracted for analysis. To ensure and maintain blinding, treatment allocations and statistical code for generating them are stored electronically in a separate location accessible only by a designated un-blinded statistician.

The following documents were reviewed when preparing this SAP:

- Clinical Research Protocol for AKTN Trial Number 10.02 (4).
- Electronic case report forms (eCRFs) for AKTN Trial Number 10.02.
- Data Safety Monitoring Board (DSMB) Terms of Reference for AKTN Trial Number 10.02.
- ICH Harmonised Tripartite Guideline on Statistical Principles for Clinical Trials (1).
- ICH Harmonised Tripartite Guideline on Estimands and Sensitivity Analysis in Clinical Trials (5).
- ICH Harmonised Tripartite Guideline on Structure and Content of Clinical Study Reports (6).

Readers of this SAP are encouraged to read the Clinical Research Protocol for further details on the conduct of this study and the operational aspects of clinical assessments and timing for completing a patient in this study.

ABBREVIATIONS

ABBREVIATION	DEFINITION
ACR	Albumin/creatinine ratio
AE	Adverse Event
ANZDATA	Australian and New Zealand Dialysis and Transplant Registry
AKTN	Australasian Kidney Trials Network
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ESKD	End-Stage Kidney Disease
FSR	Final Statistical Report
HRC	Health Research Council of New Zealand
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intention-To-Treat
MAP	Mean Arterial Pressure
MAR	Missing at random
MDRD	Modification of Diet in Renal Disease
MNAR	Missing not at random
NHMRC	National Health and Medical Research Council of Australia
RAAS	Renin-Angiotensin-Aldosterone System
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TSC	Trial Steering Committee
WHO	World Health Organization

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1. INTRODUCTION

1.1 Background

Chronic kidney disease (CKD) is a large and growing public health problem in Australia, New Zealand and worldwide. CKD is associated with progression to end-stage kidney disease (ESKD) requiring dialysis or kidney transplantation. ESKD is associated with cardiovascular events and high mortality. These risks are further enhanced in CKD patients with albuminuria (7-9) and those experiencing rapid decline in kidney function (10-13). CKD consumes disproportionate healthcare resources. In 2011-2012 the Commonwealth of Australia spent 1.6% of the annual health-care budget to provide treatment for ESKD, while ESKD patients represented less than 0.01% of the entire population (14). In New Zealand 0.9% of the health budget is spent on renal replacement therapy (15). However, despite the huge social, medical and financial toll exacted by CKD, there is very little clinical research investigating novel therapeutic targets to slow CKD progression. As a result, therapies that are available to prevent progression of CKD are limited in number and few are effective.

Uric acid has emerged as a promising novel therapeutic target for slowing CKD progression. Empirical evidence from experimental and early clinical studies suggests a possible beneficial effect of allopurinol on progression of CKD but requires evaluation in an adequately powered randomised controlled trial (RCT). There is now a sufficient body of experimental and clinical evidence to justify a RCT of uric acid lowering therapy in patients with CKD (16). In addition, the safety of allopurinol should be evaluated in a RCT, as rare but potentially life-threatening complications of allopurinol, such as Stevens-Johnson syndrome, toxic epidermal necrolysis and aplastic anaemia, are possibly more common in individuals with decreased kidney function due to renal drug elimination (17-21). Therefore, an adequately powered RCT is needed to establish: (1) the effectiveness of allopurinol in slowing the progression of CKD, and (2) the safety of allopurinol use in CKD patients.

Demonstration of a significant attenuation of GFR decline in CKD patients treated with allopurinol will provide clinicians with an important, new and relatively inexpensive strategy for effectively retarding CKD progression leading to improved health outcomes for CKD patients and potential savings to the Australia and New Zealand health budgets of tens to hundreds of millions of dollars annually.

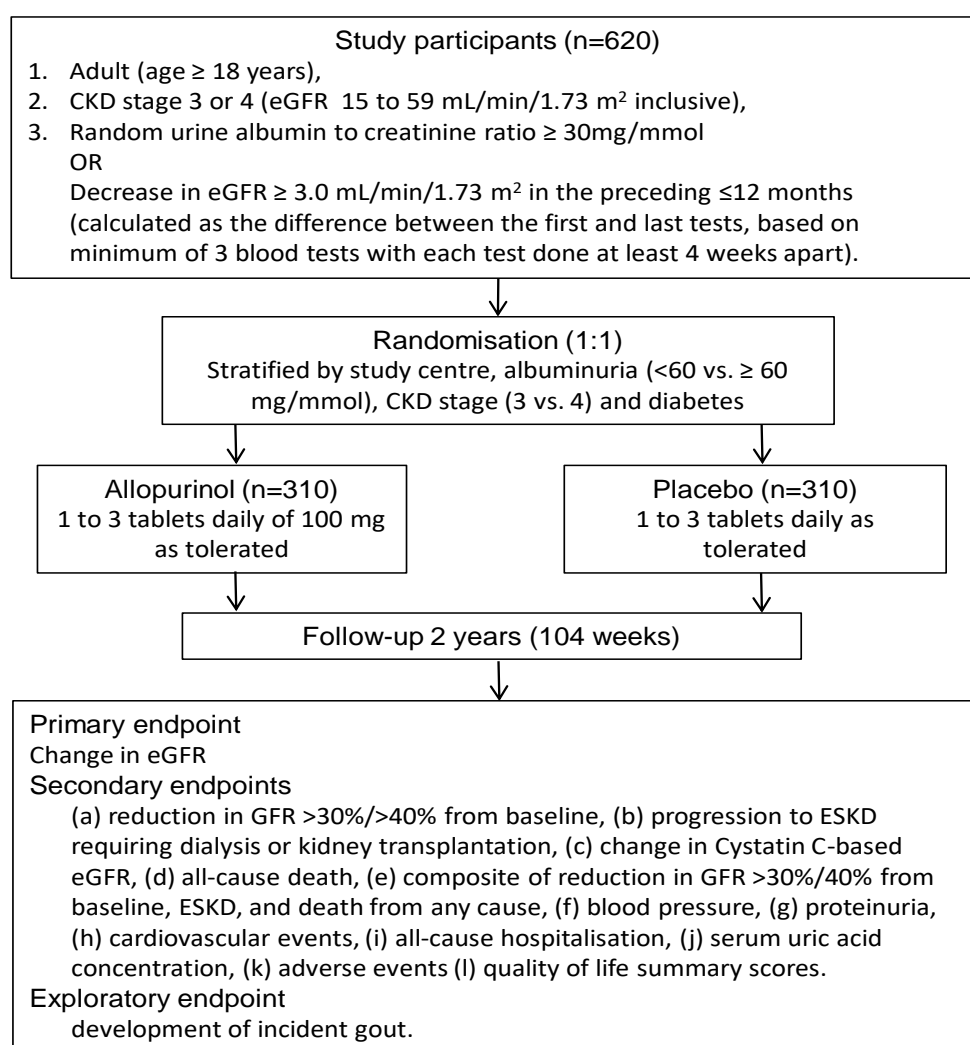
1.2 Study synopsis

The CKD-FIX trial is an investigator-initiated, multi-centre, randomised, placebo-controlled, double-blind, parallel group, superiority trial to evaluate whether allopurinol will slow CKD progression compared to placebo. The primary outcome is change in estimated glomerular filtration rate (eGFR) and the main scientific question concerns the comparison of allopurinol to placebo on change in eGFR from baseline up to 104 weeks after initiation of therapy.

Figure 1 displays the study schema. Eligible patients were randomly assigned to receive either allopurinol (1 to 3 x 100 mg tablets daily as tolerated) or placebo (1 to 3 tablets daily as tolerated). The planned recruitment target was 620 patients (includes upward adjustment for anticipated rates of treatment drop-out and loss to follow-up; further details are given below). The trial recruited its first participant on 21 March 2014 and stopped recruiting on 31 December 2016 before reaching the recruitment target. The last participant was randomised

on 29 December 2016. In total, 369 participants from 29 clinical centres in Australia (23 centres) and New Zealand (6 centres) were randomised, which is 60% of the planned recruitment target. The final study visit for the last enrolled participant was 21 January 2019. The primary outcome data will be obtained from samples sent to a central laboratory and will not be entered into the main trial database. Analysis of central laboratory samples is expected to be completed by the end of May 2019 and the full set of trial data is expected to be clean and available for analysis by the end of June 2019.

Figure 1. Study schema



2. STUDY DESIGN ISSUES

2.1 Overview

The study is a prospective, multi-centre, randomised, placebo-controlled, double-blind, parallel-group, phase 4, superiority trial.

2.2 Study population

The population of interest is adults with CKD. Plans to extend the trial to other countries did not occur due to lack of funding.

2.2.1 Inclusion criteria

Patients were eligible for inclusion in the trial if all of the following criteria were met:

1. Adult (age ≥ 18 years)
2. CKD stage 3 or 4 (eGFR 15 to 59 mL/min/1.73 m² inclusive)
3. Random urine albumin to creatinine ratio (ACR) ≥ 30 mg/mmol **OR** evidence of CKD progression (decrease in eGFR ≥ 3.0 mL/min/1.73 m² in the preceding ≤ 12 months, calculated as the difference between the first and last tests, based on minimum of 3 blood tests with each test done at least 4 weeks apart)*

*For the diagnosis of CKD and determination of eGFR decline, eGFR estimated by either the Modification of Diet in Renal Disease (MDRD) Study equation or the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation could be used according to local practice.

2.2.2 Exclusion criteria

Patients were excluded from the trial if any one of the following conditions was met:

1. Past history of clinically established gout, according to the 2015 ACR/EULAR gout classification criteria¹⁴⁷
2. History of hypersensitivity to allopurinol
3. Kidney transplant recipients
4. Concurrent treatment with azathioprine, 6-mercaptopurine, theophylline, cyclophosphamide, cyclosporine, probenecid, phenytoin, or chlorpropamide
5. Indication for allopurinol, including history of tophus or tophi on clinical examination or imaging study, uric acid nephropathy, uric acid nephrolithiasis or urolithiasis
6. Current non-skin cancer malignancy
7. Unresolved acute kidney injury in last 3 months
8. Current pregnancy, breast feeding
9. Any uncontrolled psychological illness or condition which interferes with the ability to understand or comply with the requirements of the study
10. Elective or imminent initiation of maintenance dialysis or kidney transplantation expected in the next 6 months

2.3 Study design and treatment allocation

Patients were consented then randomised to receive allopurinol (100 mg per tablet, ZYLOPRIM™, Aspen Pharma Pty Ltd, St Leonards, NSW) or matching placebo (Aspen Pharma Pty Ltd, St Leonards, NSW). The starting dose for both medications was one tablet daily for four weeks. The dose was increased to two tablets daily for another four weeks if all the pre-defined dose escalation criteria were met. The dose was further increased to three tablets daily thereafter if all the pre-defined dose escalation criteria were met. The maximally tolerated dose (1, 2 or 3 tablets daily) was continued for the remaining 92 weeks of follow-up (total follow-up of 104 weeks). The final dose of trial medication was at the treating physician's discretion. Physicians were instructed to not titrate dose against serum uric acid or plasma oxypurinol concentrations, for many reasons, including the potential threat to trial blinding. All participants received concomitant CKD-related management as per the standard of care.

A covariate-adaptive allocation algorithm was used to assign patients to treatment groups. The algorithm minimised imbalance across treatment groups in the following variables: trial centre, CKD stage (stage 3 vs. stage 4), albuminuria ($\text{ACR} \geq 60 \text{ mg/mmol}$ vs. $\text{ACR} < 60 \text{ mg/mmol}$), and presence-absence of diabetes mellitus. Randomisation was implemented using a password-protected and encrypted web-based system called Flexetrial™.

2.4. Sample size

The calculations were based on an assumed annual decline in eGFR of $3 \text{ mL/min/1.73 m}^2$ in the control group (22) and an annual reduction in decline of $0.6 \text{ mL/min/1.73 m}^2$ due to allopurinol. This magnitude of improvement is at the lower end of the range of estimates, $0.5\text{--}1.0 \text{ mL/min/1.73 m}^2$ per year, associated with meaningful change in clinical endpoints (23). Based on similar previous studies, additional assumptions were loss to follow-up of 5% and drop-in and drop-out rates of 5% (from the treatment arm to the control arm and in the opposite direction). Given these assumptions, 310 patients per arm or 620 patients in total would have had 90% power to demonstrate a 20% attenuated decline in eGFR (ΔeGFR of $1.2 \pm 4.0 \text{ mL/min/1.73 m}^2$) after 104 weeks of follow up. The difference in the change of GFR for which the CKD-FIX trial is powered is of the same order of magnitude as that demonstrated for ACE inhibitors (compared to placebo) and would likely translate into 29% and 25% relative reductions in the risks of doubling of serum creatinine and ESKD, respectively (24).

2.5 Treatment blinding and allocation concealment

Investigators and participants were blinded to treatment assignment. Biochemistry staff in local laboratories who performed outcome assessments were also blinded to the participant's assigned treatment. Biochemistry staff in the central laboratory will be similarly blinded when analysing samples for the primary outcome. To ensure concealment of treatment allocation, randomisation was performed using a central web-based randomisation system called Flexetrial™ administered by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre in Sydney.

2.6 Schedule of assessments

	Study visit												
Data collection form	Screen/ consent	Base- line	Week 4	Week 8	Week 12	Week 16	Week 24	Week 40	Week 56	Week 72	Week 88	Week 104	Withdr awal [#]
Consent	✓												
History		✓											
B-HCG*, eGFR and spot urine ACR	✓												
Clinical/physical examination/gout history		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓
Serious Adverse Events			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medication dispensed		✓				✓		✓		✓			
Full Blood Count, urea, creatinine, electrolytes (Na, K, Cl and HCO ₃), uric acid, LFT, glucose, eGFR		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ca, PO ₄ , iPTH, lipid profile		✓							✓			✓	✓
Random urine albumin creatinine ratio, creatinine and uric acid		✓					✓	✓	✓	✓	✓	✓	✓
Health survey questionnaires		✓							✓			✓	✓
IL-6, CRP, F ₂ -isoprostane (central laboratory)		✓					✓	✓	✓	✓	✓	✓	✓
Creatinine, cystatin C (central laboratory)		✓				✓	✓	✓	✓	✓	✓	✓	✓
Plasma oxypurinol (central laboratory)						✓	✓	✓	✓	✓	✓	✓	✓
HLA-genotyping/genetic influences on response (central laboratory)		✓											

* Women of child bearing potential only

Permanent withdrawal from study

V1-V5 can be +/- 7 days and V6-V10 can be +/-14 days. Blood and urine tests are within the same timeframe, however for V1-V3 they cannot be after the date of visit

3. STUDY OUTCOME VARIABLES

3.1 Primary outcome

The primary outcome is change in eGFR, with measurements taken at baseline and seven time points after randomisation: 16, 24, 40, 56, 72, 88 and 104 weeks. The CKD-EPI equation will be used to calculate eGFR from serum creatinine concentrations obtained from samples analysed by a central laboratory (25). The CKD-EPI creatinine equations for Australia and New Zealand, as per Australasian Creatinine Consensus Group recommendations (26) are in the Appendix, section 10.1.

3.2 Secondary outcomes

Data are being collected on the following secondary outcomes:

1. Reduction from baseline eGFR of $\geq 40\%$ (no, yes)
2. Reduction from baseline eGFR of $\geq 30\%$ (no, yes)
3. Progression of CKD to ESKD requiring dialysis or kidney transplantation (no, yes)
4. Death from any cause (alive, dead)
5. Composite of reduction from baseline eGFR of $\geq 40\%$, progression to ESKD, or death from any cause
6. Composite of reduction from baseline eGFR of $\geq 30\%$, progression to ESKD, or death from any cause
7. Systolic and diastolic blood pressure (mm Hg, average of three readings) and mean arterial pressure (MAP), measured at baseline and eight time points after randomisation: 8, 16, 24, 40, 56, 72, 88 and 104 weeks.
8. ACR (mg/mmol), measured at baseline and six post-randomisation visits: 24, 40, 56, 72, 88 and 104 weeks.
9. Fatal or nonfatal cardiovascular event (none, at least one)*
10. All-cause hospitalisation (none, at least one)
11. All-cause hospitalisation (rate, per person-years of follow-up)
12. Serum uric acid concentration (mmol/L), measured at baseline and all 10 post-randomisation visits
13. Any adverse drug reaction known to be a complication of allopurinol, such as severe cutaneous adverse reactions- Erythema Multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis; minor skin rash; hypersensitivity syndrome; aplastic anaemia; thrombocytopenia
14. Quality of life as measured by the Short Form 36, with measurements taken at baseline, week 56 and week 104

*Includes myocardial infarction, stroke including intra-cranial haemorrhage, sudden cardiac death, resuscitated cardiac arrest, heart failure, coronary revascularisation procedure, cerebrovascular revascularisation procedure, peripheral arterial revascularisation procedure, amputation of part of limb or digit that is not directly caused by trauma or infection, but where vascular insufficiency is deemed the primary reason for the amputation.

3.3 Exploratory outcomes

The following variables are described in the trial protocol as exploratory outcome variables:

1. F₂-isoprostane (pg/mL), measured at baseline and six post-randomisation visits (weeks 24-104)*
2. C-reactive protein (mg/L), measured at baseline and seven post-randomisation visits (weeks 16-104)
3. Interleukin-6 (IL-6) (pg/mL), measured at baseline and six post-randomisation visits (weeks 24-104)
4. Development of incident gout (no, yes)
5. Pharmacokinetics of allopurinol*
6. Pharmacogenomics of allopurinol (HLA genotyping)*
7. Genetic influence of uric acid transporters and xanthine oxidase on serum creatinine response to allopurinol*

*These outcomes are the focus of designated ancillary studies and the analysis methods will be described elsewhere.

3.4 Safety outcomes

The following safety variables have been recorded:

1. Any SAE
 - a. Death due to any cause
 - b. Any life-threatening event
 - c. Any initial or prolonged inpatient hospitalisation
 - d. Any persistent or significant disability/incapacity
 - e. Any important medical event
 - f. Any congenital abnormality/birth defect
2. SAE organ systems (cardiovascular, respiratory, gastrointestinal, renal, neurological, musculoskeletal, endocrine, cancer/neoplasm, haematology, skin)
3. SAE relationship to study medication (none, unlikely, possible, probable)
4. Any adverse drug reaction (ADR)
5. ADR severity (mild, moderate, severe, life-threatening)
6. ADR relationship to study medication (possible, probable)
7. ADR (rate)

4. SEQUENCE OF PLANNED ANALYSES

4.1 Interim analyses

An independent Data and Safety Monitoring Board (DSMB) comprising experts in clinical trials, biostatistics, and nephrology reviewed un-blinded data on participant characteristics, treatment compliance, trial conduct and participant safety. The DSMB held an orientation meeting (11 September 2013) and five data and safety review meetings (19 June 2014 to 20 February 2018) at which un-blinded trial results were assessed. The DSMB recommended continuation of the trial without modification on each occasion. Only DSMB members and

the statistician compiling closed-session reports for DSMB meetings had access to un-blinded interim data and results.

4.2 Blinded review of primary outcome

Primary outcome eGFR measurements will be obtained from serum samples analysed by a central laboratory at the end of the trial. Because of this, it has not been possible to review actual primary outcome data. Instead, eGFR results obtained from local laboratories at the trial sites were used to conduct a blinded review to assess assumptions on which sample size was estimated. This review was originally planned to take place after 1/3 of participants had completed 104 weeks of follow-up. However, due to slow recruitment, the review was based on just 53 study completions. The review was conducted in June 2016. eGFR was more variable than assumed in the pre-trial calculations, indicating an increase in sample size would have been needed to detect the pre-specified difference in eGFR.

4.3 Final analyses and reporting

Planned analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the week 104 follow-up assessment visit, the REDCapTM database has been cleaned and locked, and results from the central laboratory, which will be received in an Excel spreadsheet and include eGFR for the primary outcome, have been cleaned and declared final. Blinded data review meetings will be held before locking the REDCapTM database and, again, before declaring a final electronic copy of the central laboratory data. There will be no un-blinding and analyses will not commence until this SAP has been approved by the Lead Principal Investigator and Trial Statistician and reviewed and approved by the TSC. Key statistics and trial results from the final analyses will be presented to the TSC for discussion prior to completion of the FSR and subsequent manuscripts. Any post-hoc exploratory analyses performed to provide support for planned analyses but not identified in this SAP will be reported in appendices to the FSR and clearly identified as unplanned analyses. All analyses and their interpretation will be conducted independently of the trial funders: the NHMRC of Australia; the Health Research Council (HRC) of New Zealand; and the manufacturer of allopurinol (ZYLOPRIMTM), Aspen Pharma Pty Ltd.

5. CHANGES TO STATISTICAL INFORMATION IN THE PROTOCOL

The following amendments have been made to statistical information given in the final version of the trial protocol (4):

1. The primary outcome is reported in the trial protocol as “change in eGFR at 104 weeks”. This has been amended in the SAP to change in eGFR from baseline up to 104 weeks. The decision to focus on change in eGFR over the duration of follow-up rather than at the final time point was agreed to by the TSC in response to the proportion of participants (approx.. 16%) with observations truncated due to commencement of renal replacement therapy (RRT; dialysis or kidney transplantation) or death.
2. The protocol lists 12 subgroups, including proteinuria. While there are 12 subgroups listed in this SAP, proteinuria has been replaced by albuminuria (ACR: < 3 mg/mmol, 3-30 mg/mmol, > 30 mg/mmol).

6. ANALYSIS PRINCIPLES

6.1 Intention-to-treat principle and analysis dataset

Tests of the effects of treatment on the primary and secondary outcomes will be conducted as close as possible to the intention-to-treat (ITT) ideal. For the primary outcome, all randomised patients with a baseline eGFR measurement will be included in the “full analysis set” and analysed in the group to which they were randomly allocated regardless of whether they received the assigned treatment and irrespective of any protocol deviations or violations. The full analysis set for continuous secondary outcomes will be similarly defined in terms of availability of a baseline measurement on the particular outcome. For categorical secondary outcomes, the full analysis set will include participants who are assessable on the outcome. Meeting the “assessable” criterion will require 104 weeks of follow-up or a relevant event before discontinuation. All discontinuations will be captured in a figure illustrating participant progression through the trial.

6.2 Multicentre study and heterogeneity

Twenty-nine centres recruited between three and 35 participants. Although included as a variable in the randomisation scheme, study centre will not be adjusted for in the main analysis of the primary outcome because some centres were small (≤ 5 participants). However, if there is a positive treatment effect on the primary outcome, study centres will be combined within four Australian states and New Zealand (five regional strata in total) to assess the homogeneity of the treatment effect across regions. Potential heterogeneity will be tested by including a treatment x time x region interaction term in a multivariable model with treatment, time and region as main effects and a treatment x time interaction as the test of the overall effect of treatment on eGFR decline.

6.3 Multiple comparisons and multiplicity

There will be no adjustments for multiplicity as there is a pre-defined hierarchy of importance of study objectives and outcome variables and the influence of individual results on the overall interpretation of the trial will reflect their level within this hierarchy. Hence, all statistical tests of significance will be two-sided and at the 5% level.

6.4 Covariate adjustment

The main statistical analyses of primary and secondary efficacy outcomes comparing allopurinol with placebo will be unadjusted except for continuous outcomes with baseline measurements (e.g., the primary outcome eGFR will be adjusted for centred baseline eGFR). Supporting analyses will be adjusted for regional location of the clinical site (5 regions) and baseline variables used in the minimisation algorithm: CKD stage (stage 3, stage 4), albuminuria (ACR ≥ 60 mg/mmol, ACR < 60 mg/mmol), and diabetes mellitus (no, yes). The principal reason for not including minimisation variables as covariates in the main analyses is to avoid unnecessarily complicating these models (27). Additional modelling with *ad hoc* adjustments may be performed where baseline characteristics are not sufficiently balanced across the treatment groups.

6.5 Missing data

6.5.1 Missing outcome data

Outcome data will be missing intermittently (non-monotone missing) for participants who miss some study visits but ultimately complete the final study visit. Most missing outcome data will be a consequence of study discontinuation (monotone missing) due to participant death, commencement of RRT (dialysis or kidney transplant), or study withdrawal (encompassing a variety of specific reasons). Blinded analysis of reasons for discontinuation indicates that the majority of monotone missing data will be informatively missing, that is, missing not at random (MNAR) due to RRT or death.

For the eGFR primary outcome, intermittent missing values will be substituted with local laboratory eGFR measurements where these are available. The statistical analysis method of joint modelling (see section 7) was chosen to address the MNAR monotone missing outcomes. For continuous secondary outcomes, the MNAR monotone missing outcomes will be addressed using the same methods. Participants not assessable on categorical secondary outcomes for MNAR reasons will not be included in the analysis for that outcome. The number of excluded participants will vary according to the categorical outcome as several are composite outcomes and include the MNAR reason (e.g., RRT) as one of the components.

6.5.2 Missing baseline covariate data

In the interest of statistical efficiency in the estimation of treatment effects (28), mean imputation will be used to replace any missing values on baseline variables used as covariates in secondary covariate adjusted analyses of treatment effect. While mean imputation can bias statistical estimates in observational studies, this is not the case in a randomised trial where randomisation ensures baseline variables are independent of treatment group (29-31). Mean values will be calculated from the non-missing values for the baseline variable using pooled data from both treatment groups. For binary (coded 0 or 1) variables, the imputed mean will be rounded up to 1 or down to 0, whichever is nearest. For computed variables such as Body Mass Index (BMI), mean imputation will be performed at the level of the component variables of height and weight. The number (percentage) of missing values will be reported for all baseline covariates with missing data. Further, covariate adjusted statistical models will include a missing value indicator (0=observed, 1=missing) for each covariate with missing data (29, 31). It is important to note that there are no missing values on the key adjustment variables – variables used in the minimisation algorithm and region (derived from study centre).

7. STATISTICAL METHODS

7.1 Analysis of the primary outcome

The primary goal of the CKD-FIX trial is to estimate and test treatment differences in change in eGFR after commencement of treatment with allopurinol or placebo. A joint modelling approach will be used to accommodate truncation of data collection due to death or commencement of RRT before completion of the 104 week study visit.

7.1.1 Primary comparison

Joint modelling of longitudinal and survival data is increasingly recommended as a means of accounting for the effect of informative dropout on longitudinal outcomes (32-35). Joint models for this context have two sub-models: a linear mixed model for longitudinal eGFR measurements and a survival model for times to the different reasons for informative study dropout. The two sub-models can be linked in various ways, including via shared random effects in the models. A shared parameter (random effects) model allows appropriate adjustments to the analysis of longitudinal outcomes where there are competing survival (i.e., dropout) events. Measurements of eGFR over time for seven post-randomisation visits will be analysed using a linear mixed model with fixed effects for treatment, continuous time, treatment x continuous time interaction, and centred baseline eGFR and random intercepts and random slopes. Time to discontinuation for one of three reasons (death, commencement of RRT, and withdrawal from the study) will be analysed using a parametric competing risk survival model with random effects. The shared random effects allow adjustment of the fixed effects in the linear mixed model (treatment, continuous time, treatment x continuous time interaction) for informative dropout. The fixed effect of primary interest from the linear mixed model is the interaction between treatment and time.

A key assumption of the linear mixed model is linear time trends in eGFR. This assumption will be assessed graphically via trajectory plots for individual patients and statistically via inclusion of nonlinear terms for time in the linear mixed model. A key assumption of the parametric survival model is the shape of the baseline hazard distribution. Information criterion fit statistics (AIC and BIC) will be used to assist in selecting a function form for the baseline hazard distribution.

Joint modelling can be computationally intensive (34, 35). To minimise the potential for intractable computational issues, the longitudinal and survival models will include only those effects (fixed and random) needed to answer the treatment effect question while adequately addressing MNAR. In the unlikely event of intractable computational issues, a simplified two-step method which avoids the need to maximise the joint likelihood of longitudinal and survival data will be used (34).

7.1.2 Treatment effect heterogeneity

If there is a statistically significant effect of allopurinol on eGFR as indicated by a statistically significant interaction between treatment and time, heterogeneity of the effect will be tested by including a treatment x time region interaction effect in the linear mixed model.

7.1.3 Supporting analyses adjusted for minimisation variables

Robustness of the estimate of the allopurinol treatment effect relative to placebo will be assessed by fitting a linear mixed model which adjusts for region (4 Australian states and New Zealand) and three patient baseline characteristics used in the randomisation algorithm: CKD stage (stage 3 vs. stage 4), albuminuria ($\text{ACR} \geq 60 \text{ mg/mmol}$ vs. $\text{ACR} < 60 \text{ mg/mmol}$), and presence-absence of diabetes mellitus. This adjusted analysis will be viewed as supportive, providing additional context for interpreting the primary unadjusted (except for baseline eGFR) analysis.

7.1.4 Sensitivity to estimation of GFR

Estimation of GFR for the primary outcome uses the creatinine-based CKD-EPI equation. Sensitivity analyses will also employ GFR estimated by the creatinine-based MDRD equation, cystatin C-based CKD-EPI equation, and creatinine and cystatin C-based CKD-EPI equation (Appendix, section 10.1). The primary and supporting analyses of eGFR obtained from the creatinine-based CKD-EPI equation will be repeated on measurements of eGFR obtained by the three alternative equations. During the course of the study, if another equation becomes the standard of practice, a sensitivity analysis will employ that equation as well.

7.1.5 Sensitivity to missing data mechanism

The shared parameter joint modelling approach which will be used to analyse the primary outcome and longitudinally-measured secondary outcomes makes the most conservative assumption that data are missing not at random (MNAR). Some of the missing values, specifically those not due to RRT or death, are very plausibly missing at random (MAR). We will assess the potential loss in efficiency by comparing the shared parameter linear mixed model results to those from a standard linear mixed model.

7.1.6 Subgroup analyses for the primary outcome

Pre-specified subgroups for analysis of the primary outcome are formed by the following baseline characteristics: sex (female, male), age (<65, ≥65 years), CKD stage (stage 3, stage 4), albuminuria (ACR: < 3 mg/mmol, 3-30 mg/mmol, > 30 mg/mmol), diabetes mellitus (no, yes), reason for inclusion (eGFR decline, albuminuria), cause of CKD (diabetic neuropathy, nondiabetic kidney disease, polycystic kidney disease), use of diuretics (no, yes), use of renin-angiotensin-aldosterone system (RAAS) blockade (no, yes), ethnicity (Caucasian, Asian, Indigenous, Other), body mass index (BMI: <18.5, 18.5-24.9, 25.0-29.9, ≥30.0), and metabolic syndrome (no, yes) (36). The main subgroup analyses will be tests of treatment x time x variable interactions in the shared parameter linear mixed models. These analyses will be performed regardless of the result for the treatment x time interaction in the main model for the primary outcome. Treatment group differences in mean slope within each sub-group will be reported along with their 95% confidence limits.

7.2 Analysis of secondary outcomes

Secondary outcome variables are mainly binary outcomes with a single post-baseline measurement per participant or repeatedly measured continuous outcomes. Binary outcomes will be analysed using a log binomial regression model to obtain estimates of risk ratios and 95% confidence intervals. Repeatedly measured continuous outcomes will be analysed using the same joint modelling approach used to analyse the primary outcome. SF-36 total scores will be similarly analysed, except time will be categorical rather than continuous as measurements were taken at only two follow-up visits. The rate of all-cause hospitalisations will be analysed using a Poisson regression model, with the treatment effect reported as a rate ratio and 95% confidence interval.

7.3 Analysis of exploratory outcomes

Exploratory outcome variables that are not part of a designated ancillary study are F₂-isoprostane, C-reactive protein, and IL-6. All three are continuous outcomes measured repeatedly over six study visits in addition to baseline measurements. If distributional characteristics allow, these exploratory outcomes will be analysed using a shared parameter joint modelling approach as per the primary and continuous secondary outcomes. Incident gout is a binary exploratory outcome and the treatment effect will be presented as a risk ratio and 95% confidence interval from a log binomial regression model.

7.4 Analysis of safety outcomes

The relationship of each category of SAE and ADR (present versus absent) to treatment group will be summarised by frequencies and percentages and analysed with chi-square tests. The relationship between treatment group and SAE organ system (cardiovascular, respiratory, gastrointestinal, renal, neurological, musculoskeletal, endocrine, cancer/neoplasm, haematology, skin), SAE relationship to study medication (none, unlikely, possible, probable), ADR severity (mild, moderate, severe, life-threatening), and ADR relationship to study medication (possible, probable) will be summarised by frequencies and percentages and analysed with chi-square tests. ADR rates will be analysed using a Poisson regression model.

7.5 Data manipulation and computing

Most of the trial data are stored in a central REDCapTM database. Some measurements will be obtained from samples analysed by a central laboratory at the end of the trial. These measurements will be stored in an Excel spreadsheet and include measurements of creatinine to be used in the calculation of values for the primary outcome, eGFR. Also included will be measurements of cystatin C, C-reactive protein, IL-6, F₂-isoprostane, and plasma oxypurinol. All data manipulation, tables, figures, listings and analyses will be documented in SAS[®] programs and performed using SAS version 9.4.

8. REPORTING

All results described above as well as tables, listings and figures (TLFs) listed below will be presented in the FSR.

8.1 Trial profile

All patients who provide informed consent will be accounted for in the FSR. A CONSORT-style flow diagram will illustrate patient progression through the trial from initial screening for eligibility to completion of the final primary outcome assessment. Number (percentage) of participants randomised to each treatment group will be given for all randomised patients along with reasons for study withdrawal by treatment group.

8.2 Patient characteristics and baseline comparisons

Demographic and other baseline characteristics, including laboratory investigations, will be summarised by assigned treatment group. Categorical variables will be summarised by

frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator, which will be less than the number of patients assigned to the treatment group, will be reported either in the body or a footnote in the summary table. Continuous variables will be summarised by mean and standard deviation as well as quartiles.

8.3 TABLES, LISTINGS, AND FIGURES (TLFs)

Templates for all planned TLFs are in a separate document titled CKD-FIX SAP Tables, Listings and Figures.

8.3.1 Planned tables

The following are planned summary tables:

- Table 1. Enrolment by study centre stratified by country
- Table 2. Treatment group allocations by study centre
- Table 3. Minimisation variables by treatment group
- Table 4. Protocol deviations by treatment group (stratified by deviation category)
- Table 5. Study medications dispensed by treatment group across study visits
- Table 6. Study medication compliance (pill counts) by treatment group across study visits
- Table 7. Study medication withdrawals by treatment group across study visits
- Table 8. Baseline concomitant medications by treatment group
- Table 9. Baseline demographic and clinical characteristics by treatment group
- Table 10. Baseline blood investigations by treatment group
- Table 11. Baseline urine investigations by treatment group
- Table 12. Clinical assessments by treatment group across study visits
- Table 13. Central laboratory eGFR (CKD-EPI creatinine equation) mean values and standard deviations by treatment group across study visits
- Table 14. Estimates, confidence intervals and p-values from a shared parameter linear mixed model analysis of eGFR (CKD-EPI creatinine equation) (table parts a, b, c, and d for main analysis, supporting analyses, and sensitivity analyses)
- Table 15. Estimates, confidence intervals and p-values from a shared parameter linear mixed model analysis of eGFR for subgroups (12 subgroups)
- Table 16. Central laboratory eGFR (CKD-EPI cystatin C equation) mean values and standard deviations by treatment group across study visits
- Table 17. Estimates, confidence intervals and p-values from a shared parameter linear mixed model analysis of eGFR (CKD-EPI cystatin C equation) (table parts a, b, c, and d for main analysis, supporting analyses, and sensitivity analyses)
- Table 18. Central laboratory eGFR (CKD-EPI creatinine-cystatin C equation) mean values and standard deviations by treatment group across study visits
- Table 19. Estimates, confidence intervals and p-values from a shared parameter linear mixed model analysis of eGFR (CKD-EPI creatinine-cystatin C equation) (table parts a, b, c, and d for main analysis, supporting analyses, and sensitivity analyses)
- Table 20. Central laboratory eGFR (MDRD equation) mean values and standard deviations by treatment group across study visits
- Table 21. Estimates, confidence intervals and p-values from a shared parameter linear mixed model analysis of eGFR (MDRD equation) (table parts a, b, c, and d for main analysis, supporting analyses, and sensitivity analyses)

- Table 22. Estimates of treatment effect, confidence intervals and p-values from log-binomial regression models from analysis of binary secondary outcomes (secondary outcomes 1-6, 9, 10 and 13)
- Table 23. All-cause hospitalisation rates, treatment effect rate ratio, confidence intervals and p-values from a Poisson regression model
- Table 24. Blood pressure mean values and standard deviations by treatment group across study visits (separate table parts for systolic, diastolic, and MAP)
- Table 25. Estimates, confidence intervals and p-values from shared parameter linear mixed model analyses of blood pressure (separate table parts for systolic, diastolic, and MAP)
- Table 26. ACR geometric mean values and standard deviations by treatment group across study visits
- Table 27. Estimates, confidence intervals and p-values from a shared parameter linear mixed model analysis of ACR
- Table 28. Serum uric acid geometric mean values and standard deviations by treatment group across study visits
- Table 29. Estimates, confidence intervals and p-values from a shared parameter linear mixed model analysis of serum uric acid
- Table 30. SF-36 mean total scores and standard deviations by treatment group across study visits
- Table 31. Estimates, confidence intervals and p-values from shared parameter linear mixed model analyses of SF-36 total scores
- Table 32. C-reactive protein mean values and standard deviations by treatment group across study visits
- Table 33. Estimates, confidence intervals and p-values from shared parameter linear mixed model analyses of C-reactive protein
- Table 34. Interleukin-6 mean values and standard deviations by treatment group across study visits
- Table 35. Estimates, confidence intervals and p-values from shared parameter linear mixed model analyses of Interleukin-6
- Table 36. Estimates of treatment effect, confidence intervals and p-values from log-binomial regression analysis of incident gout
- Table 37. Any ADR and ADR categories by treatment group
- Table 38. ADR severity by treatment group
- Table 39. ADR relationship to study medication by treatment group
- Table 40. Any SAE and SAE categories by treatment group
- Table 41. Relationship of SAE to study medication by treatment group
- Table 42. SAE body system by treatment group

8.3.2 Planned listings

The following are planned data and patient listings:

- Listing 1. Reasons for participants withdrawing from the study
- Listing 2. Medication compliance problems requiring participant to come off trial
- Listing 3. Deaths and life threatening events

8.3.3 Planned figures

The following are planned summary figures:

Figure 1. Monthly and cumulative entry of participants into the study

Figure 2. Flowchart of patient progression through the study

Figure 3. Kaplan-Meier plots for time to (a) RRT and (b) death from the shared parameter survival model for the primary outcome.

Figure 4. Primary outcome (eGFR) by treatment group across study visits (baseline & 7 post-randomisation visits)

Figure 5. Forest plot of mean slope differences, 95% confidence intervals and interaction test p-values for subgroup analyses on the primary outcome (eGFR)

8.3.4 Supplementary TLFs

Results from supporting and sensitivity analyses not allocated a specific table number and results from analyses not pre-specified in this SAP will be presented in supplementary tables. Missing data on the primary outcome will be summarised by treatment groups and presented in supplementary tables and figures as appropriate.

8.4 General reporting conventions

All TLFs will be presented in portrait orientation, unless landscape orientation suggests that the information is easier to view. Legends will be used for all figures with more than one variable or item displayed. Figure lines should be wide enough to see the line after being copied.

All titles will be centred on a page. The first title line will be the number of the table, figure, or data listing. The second (and if required, third) line will be the description of the table, figure, or data listing. The ICH numbering convention will be used for all TLFs (6).

All tables, figures, and data listings will have the name of the relevant SAS (or Stata) program and a date-time stamp on the bottom of each output. All analysis programs developed for a table, figure, or data listing will be self-contained to facilitate transfer of programs to multiple computing environments. A separate analysis program will be written to produce each TLF.

8.5 Statistical summary conventions

For tables, sample sizes for each treatment group will be presented as totals in the column header (N=xxx), where appropriate. Sample sizes shown with summary statistics are the number (n) of patients with non-missing values.

Summaries for categorical variables will include only categories that patients had a response in. Percentages corresponding to null categories (cells) will be suppressed. All summaries for continuous variables will include: N, mean, and SD. Other summaries (e.g. median, quartiles, 5%, 95% intervals, coefficient of variation (CV) or %CV will be used as appropriate. All percentages should be rounded and reported to a single decimal place (xx.x%). If percentages are reported as integers, percentages greater than 0% but <1% will be reported as <1%, whereas percentages greater than 99% but <100% will be reported as >99%. A percentage of 100% will be reported as 100%. No value of 0% should be reported. Any computation of percent that results in 0% is to be reported as a blank. Summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). Small p-values less than 0.001 will be reported as <0.001.

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10. APPENDIX

10.1 Equations for estimating GFR

Sex	Serum Creatinine ($\mu\text{mol/L}$)	Serum Cystatin C (mg/L)	Equation†#
CKD-EPI creatinine equation*			
Female	≤ 62		$144 \times (\text{Scr} \times 0.0113/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
Female	> 62		$144 \times (\text{Scr} \times 0.0113/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
Male	≤ 80		$141 \times (\text{Scr} \times 0.0113/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
Male	> 80		$141 \times (\text{Scr} \times 0.0113/0.9)^{-1.209} \times (0.993)^{\text{Age}}$
CKD-EPI cystatin C equation			
Female or male		≤ 0.8	$133 \times (\text{Scys}/0.8)^{-0.499} \times 0.996^{\text{Age}} [\times 0.932 \text{ if female}]$
Female or male		> 0.8	$133 \times (\text{Scys}/0.8)^{-1.328} \times 0.996^{\text{Age}} [\times 0.932 \text{ if female}]$
CKD-EPI creatinine-cystatin C equation*			
Female	≤ 62	≤ 0.8	$130 \times (\text{Scr} \times 0.0113/0.7)^{-0.248} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$
		> 0.8	$130 \times (\text{Scr} \times 0.0113/0.7)^{-0.248} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$
Female	> 62	≤ 0.8	$130 \times (\text{Scr} \times 0.0113/0.7)^{-0.601} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$
		> 0.8	$130 \times (\text{Scr} \times 0.0113/0.7)^{-0.601} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$
Male	≤ 80	≤ 0.8	$135 \times (\text{Scr} \times 0.0113/0.9)^{-0.207} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$
		> 0.8	$135 \times (\text{Scr} \times 0.0113/0.9)^{-0.207} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$
Male	> 80	≤ 0.8	$135 \times (\text{Scr} \times 0.0113/0.9)^{-0.601} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$
		> 0.8	$135 \times (\text{Scr} \times 0.0113/0.9)^{-0.601} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$
MDRD equation*			
Female or male			$175 \times (\text{Scr}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times 0.742 [\text{if female}]$

†Abbreviations: Scr = serum creatinine; Scys = serum cystatin C.

Age = age in years

*Coefficients for black race ($\times 1.159$) for CKD-EPI creatinine equation, $\times 1.08$ for CKD-EPI creatinine-cystatin C equation, and $\times 1.212$ for MDRD equation) are not included as they are appropriate for African Americans and not Australian Aboriginal and Torres Strait Islanders or New Zealand Māori or Pacific ethnicities.