

A Protocol for the Pharmacokinetics of Enteric Coated Mycophenolate Sodium in Lupus Nephritis (POEMSLUN): an open-label, randomised controlled trial

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To cite: Ranganathan D, John GT, Healy H, *et al.* A Protocol for the Pharmacokinetics of Enteric Coated Mycophenolate Sodium in Lupus Nephritis (POEMSLUN): an open-label, randomised controlled trial. *BMJ Open* 2013;**3**:e003511. doi:10.1136/bmjopen-2013-003511

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2013-003511>).

Received 1 July 2013
Revised 8 July 2013
Accepted 10 July 2013

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ABSTRACT

Introduction: Mycophenolate sodium, an enteric-coated tablet (EC-MPS), is as effective and safe as mycophenolate mofetil (MMF) in preventing transplant rejection. EC-MPS and MMF improve the outcome of severe lupus nephritis (LN) and have fewer side effects than pulsed intravenous cyclophosphamide. Blood concentrations of mycophenolic acid (MPA), the active metabolite of EC-MPS, vary between participants despite fixed dosing. Interpatient variability has been studied in transplantation, but not well documented in LN. The relationship between MPA concentration and its clinical effect on LN has not been described.

Methods and analysis: This is a prospective, open-label, randomised controlled trial. ~32 participants with LN who meet the inclusion and exclusion criteria will be randomised into two groups: one receiving a fixed dose of EC-MPS and the second, a dosing regimen that is titrated with therapeutic drug monitoring. Included participants will have blood sampled over a period of 8–12 h on three different occasions. Pharmacokinetic parameters will be calculated using non-compartmental methods.

Ethics and dissemination: The Human Research and Ethics Committee of the Royal Brisbane Women's Hospital have approved this study. The study is registered with Australian and New Zealand Clinical Trials Registry—ACTRN12611000798965 We planned to present the de-identified information at conferences and publish the results in medical journals.

Trial Registration: ACTRN12611000798965

BACKGROUND

Mycophenolate mofetil (MMF), the first prodrug of mycophenolic acid (MPA), has been used in kidney transplant recipients for the prevention of acute rejection in combination with steroids and calcineurin inhibitors

ARTICLE SUMMARY

Article focus

- Interpatient variability of blood concentrations of mycophenolic acid (MPA), the active metabolite of enteric-coated mycophenolate sodium (EC-MPS), has been studied in transplantation, but not well documented in lupus nephritis (LN).
- This article describes a protocol for a single centre, open label, randomised controlled trial, using a two-arm design to determine whether exposure-guided dosing (therapeutic drug monitoring—TDM) of EC-MPS results in a higher proportion of participants achieving targets of MPA exposure compared with fixed drug dosing in participants with LN.

Key messages

- This study determines whether TDM-guided dosing of EC-MPS results in a higher proportion of participants in achieving established targets of MPA exposure compared with the standard fixed dosing in participants with biopsy-proven LN.
- This study also determines whether there is a difference in the complete and partial remission rates between participants on fixed drug dosing and exposure-controlled dosing of MPS in LN in induction group and renal relapse in the maintenance group.
- This study will try to validate a limited blood sampling protocol to measure exposure to MPA using a 0–12 h, 17 sample-based area under curve.

Strengths and limitations of this study

- This prospective randomised study is designed specifically to test whether exposure controlled dosing results in a higher proportion of participants achieves target exposure levels of MPA compared with exposure controlled dosing.
- Size of the sample studied limits the power of observations.

since 1995 in the USA and 1996 in Europe.¹ A second MPA product, the enteric-coated mycophenolate sodium (EC-MPS) became available subsequently. Clinical trials have shown that EC-MPS is therapeutically equivalent to MMF with comparable safety profiles and equimolar doses of the two drugs producing equivalent MPA exposures.^{2–3} The favourable experience with MMF in transplant recipients resulted in it being used in trials involving participants with autoimmune and other immunologically mediated renal diseases.^{4–8} The Aspreva Lupus Management Study group (ALMS) found rates of adverse events, particularly infection, between MMF and intravenous cyclophosphamide to be similar in lupus nephritis (LN).⁹ Furthermore, a recent meta-analysis of randomised controlled trials showed that MMF was superior in inducing remission in severe LN and had fewer side effects compared with pulsed cyclophosphamide.¹⁰ Other clinical trials reported similar results with EC-MPS.^{11–14} The Therapeutic Goods Administration of Australia approved EC-MPS-Myfortic (<http://www.novartis.com.au/DownloadFile.aspx?t=pf=myf.pdf>) for the treatment of classes III, IV, V and V LN.¹⁵

Dosing and therapeutic drug monitoring of MMF/MPS

MMF is usually administered at a fixed dose of 1000 mg twice daily in transplant recipients (independent of weight) and modified according to clinical tolerance. The randomised controlled trial, the Adaption de Posologie du MMF en Greffe Renale (APOMYGRE) and the fixed dose versus concentration controlled (FDCC) studies investigated the benefit of using therapeutic drug monitoring (TDM) but results were not consistent.^{16–17} APOMYGRE showed a reduction in acute rejection whereas the FDCC study had a neutral effect. To date, there is currently no consensus on using TDM of MPA to optimise MMF use in patients with transplants.^{18–21}

The dose of MMF for induction and maintenance therapy in LN varies from 2 to 3 g daily.²² In the ALMS study, the median MMF dose was 42 mg/kg body weight by 20–24 weeks and 91.3% of participants tolerated daily doses of 2.5–3 g daily.²³ In a study by Pietruck *et al*, 720 mg of MPS and 1000 mg of MMF were found to deliver near equimolar exposures of MPA.²⁴

Interindividual variability of MPA

Factors affecting the interpatient variability of MPA have been extensively investigated in transplant recipients and are likely to be similar in LN.^{25–26} The clearance of MPA depends on its non-protein bound fraction.²⁶ Therefore, patients with reduced renal function and hypoalbuminaemia have higher free fractions of MPA, theoretically resulting in higher MPA clearance and a lower MPA exposure. Furthermore, cotherapy with calcineurin inhibitors, phosphate binders, steroids and rifampicin may affect MPA pharmacokinetics.²⁶ Nonetheless, the MPA concentration–effect relationship is more likely to be linear in LN patients treated with MMF and

steroids, as opposed to transplant recipients who are treated with many immunosuppressive agents.²⁷

TDM of MPA in LN

Neumann *et al*^{28–29} reported on the value of measuring MPA plasma concentrations in patients with autoimmune diseases. In their study, there was a weak correlation between the 12 h trough (C₀) MPA concentrations and the area under the curve (AUC), with remission being associated with higher MPA trough concentrations (≥ 3.5 mg/L). There was a clustering of adverse events in participants with a high MPA exposure, thus refining the therapeutic window. In contrast, studies in renal transplant participants showed tolerability correlated poorly with MPA concentrations. Neumann *et al* proposed in their exploratory study that MPA trough levels between 3.5 and 4.5 mg/L be used for maintenance of remission and prevention of adverse events. Roland *et al*,³⁰ in a prospective pharmacokinetic study of MMF in patients treated for systemic lupus erythematosus, found a high interindividual variability of MPA AUC levels. The therapeutic range of MPA has to be better defined with the clinical response to exposure-controlled dosing in patients with LN.

Limited sample strategy

Measurement of AUC 0–12 h has been well documented in transplant literature and a target AUC 0–12 of 30–60 mg/L/h is advised to reduce the risk of rejection.^{31–32} For treatment with MMF, LSS was suggested as an alternative because MPA AUC 0–12 was laborious and expensive.^{33–34} LSS has been trialled for EC-MPS showing that time points from the initial half of the full concentration time profile produced near identical results.³⁵ Neuman *et al* found that MPA exposure expressed as MPA AUC_{0–12} was comparable in patients with autoimmune diseases and renal patients with transplants treated with EC-MPS.³⁶ They suggested an LSS for estimating MPA exposure could be valid in autoimmune disorders. A recent study using MPS suggested an AUC over 8 h could be calculated with four blood samples, correlating favourably with an AUC_{0–12}.³⁷

Our study will include participants who have blood sampled over a period of 8 or 12 h. For the 8 h sampling period, the AUC_{0–12} will be calculated imputing the predose sample value for the 12 h sample value. With few studies in LN treated with MPS formulations measuring the relationship of MPA levels to efficacy and toxicity, this prospective randomised controlled trial will add more information on the pharmacokinetics and pharmacodynamics of MPA in LN.^{38–39}

AIM

This study is to determine whether TDM-guided dosing of EC-MPS results in a higher proportion of participants achieving targets of MPA exposure in LN compared with fixed drug dosing.

METHODS/DESIGN

Study design and setting

The study is a prospective, open-label, randomised controlled trial. Participant population: Participants will be selected from either inpatients at Royal Brisbane and Women's Hospital (RBWH) Renal and Rheumatology Departments or patients attending the Renal Rheumatology Lupus Vasculitis Clinic. This study will be carried out in collaboration with the Burns, Trauma and Critical Care Research Centre, School of Medicine, The University of Queensland and Department of Chemical Pathology, Pathology Queensland, Queensland Health.

The interventions will comprise of two groups:

Intervention: control

Group 1: Fixed dose regime—oral EC-MPS 30 mg/kg body weight to induce remission. MPS dosage will be reduced by 180 mg twice daily on achieving complete remission or if there are side effects such as diarrhoea or leucopenia (total white cell count $<3500/\text{mm}^3$ or opportunistic infections).

Intervention: experimental

Group 2: Exposure controlled dose—oral EC-MPS dose will be titrated according to the AUC_{0-12} adjusted to a target AUC_{0-12} of 40–60 mg/L/h. The dosage will be reduced if the AUC_{0-12} is above 60 mg/L/h and once there is complete remission, an AUC of 30–50 mg/L/h will be maintained.

All participants in the control and intervention groups will undergo pharmacokinetic analysis of MPA.

Other than EC-MPS dosing, both groups will be given similar management of LN including treatment with corticosteroids. The illustration of the study design is presented in Figure 1.

Identification of eligible participants

Participants with biopsy-proven classes III/IV/V LN who fulfil the inclusion and exclusion criteria are eligible for the study. The inclusion criterion has been kept as broad as possible to represent the participant population and the exclusion criteria as restricted as possible to maximise validity and generalisability of findings.

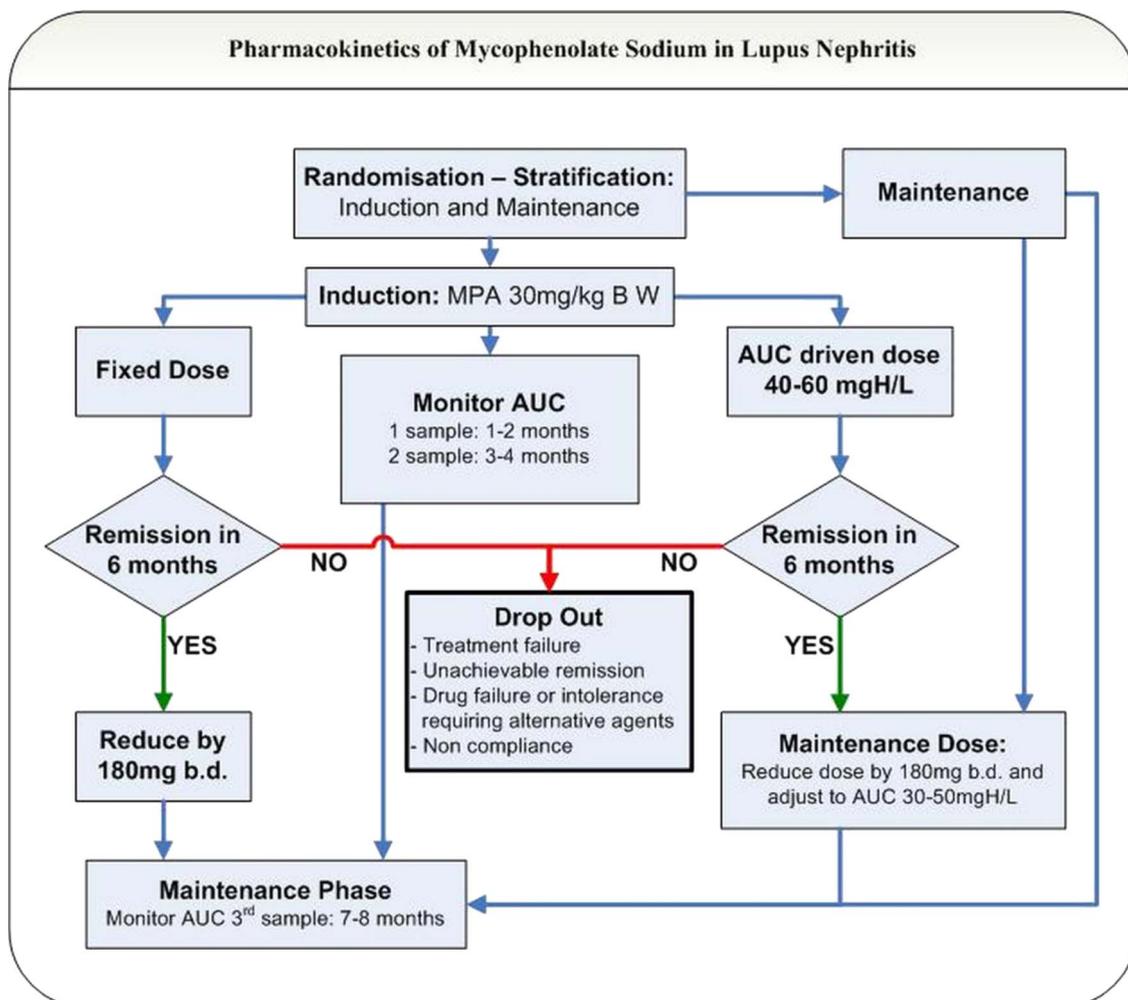


Figure 1 Pharmacokinetics of mycophenolate sodium in lupus nephritis (POEMSLUN) study design.

Inclusion criteria

All participants 18 years of age and above with classes III/IV/V LN proven by renal biopsy and have been on EC-MPS for more than 2 weeks either as maintenance or induction therapy will be eligible for this study.

Exclusion criteria

Participants will be excluded if there is a history of psychological illness, a condition which interferes with their ability to understand or comply with the requirements of the study or who are unable to give consent. Pregnant, nursing (lactating) women and women planning on getting pregnant during the study period and not using contraception will be excluded. Finally, those with a history of malignancy treated or untreated within the past 5 years (with the exception of localised basal or squamous cell carcinomas of the skin) regardless of local recurrence or metastases will also be excluded from the study.

Informed consent

At the recommendation of the treating clinician who will seek permission from the participant or authorised surrogate to be approached by the investigator, the investigator/s will seek informed consent or assent from potential trial participants or authorised surrogate. This will occur through a verbal presentation of the written consent document, which the participant or authorised surrogate would then be given sufficient time to consider before consenting to the study or not.

Participants

Participants are randomised in permuted block sizes of 2 and 4 with the 33% and 66%, respectively, and stratified for induction and maintenance therapy with EC-MPS. Masking of investigators and participants will not be possible. Nonetheless, the laboratory staff analysing the pharmacokinetics of MPS will be masked to the treatment allocation. An individual's participation in the study will cease at the end of the study period, which will be 12 months after the last participant is recruited. The recruitment period is 36 months. It is anticipated that the average follow-up time will be 24 months, assuming a steady recruitment rate of 12 participants per year.

The participants will have regular clinic appointments and follow-up to improve adherence. A trial pharmacist will be involved with the study and will detail the changes in medication doses and monitor participant adherence.

Adverse events

Adverse events are defined as any untoward medical event (clinical or laboratory) experienced by a participant during the course of this clinical trial and considered by the investigator to be related to the study. All adverse events will be recorded on the Adverse Event page of the case report form and reported immediately

to the Human Research and Ethics Committee in writing.

Adverse events will be reported from the day of consent. The responsible investigator will determine whether the degree of any untoward event warrants removal of any participant from the study. They will institute appropriate diagnostic and therapeutic measures and keep the participant under observation for as long as is medically indicated.

OUTCOME MEASURES

Primary

This is a study to determine whether TDM-guided dosing of EC-MPS results in a higher proportion of participants achieving established targets of MPA exposure compared with the standard empirical dosing in participants with biopsy-proven LN.

Secondary

This study will also determine whether there is a difference in the complete and partial remission rates between participants on fixed drug dosing and exposure controlled dosing of MPS in LN in induction group and renal relapse in the maintenance group.

Complete remission is defined as a decrease in urinary protein measured over 24 h to less than 0.3 g/24 h, a urine protein/creatinine ratio of less than 0.3 g/g (30 mg/mmol) with a normal urinary sediment, normal serum albumin and stabilisation ($\pm 25\%$) or improvement in serum creatine levels at week 24 from the first sample. Partial remission is defined as stabilisation ($\pm 25\%$) or improved renal function (but still not to normal with reduction of proteinuria by more than 50% ranging between 0.3 and 3 g/24 h and a serum albumin of more than 30 g/L.⁴⁰ Renal relapse is defined as "recrudescence of renal disease after an initial response demonstrated by a recent increase in serum creatine by $>50\%$ with active urinary sediment and or increase in proteinuria to 3.5 g/day or greater."⁴¹ Proteinuria will be measured using the urine protein to creatine ratio or by measuring the 24 h urinary protein excretion. The urine protein-to-creatinine ratio is numerically equal to 24 h urinary protein excretion in grams.

Secondary outcome measures include the time required to achieve complete or partial remission, the assessment of improvement with the SLE Disease Activity Index (SLEDAI) score as well as C3, C4 and anti-double-stranded DNA (anti-dsDNA) levels, the development of a pharmacokinetic model that can be used to develop MPS dosing recommendations in LN participants treated with MPS, validating the LSS for determining AUC_{0-12} , and the evaluation of the cost effectiveness of TDM analysis of MPS.

An individual who is masked to the study allocation and not involved in the clinical care of the participant will adjudicate outcome measures.

Data collection

Clinical and demographic data are collected for each participant, including age, gender, weight, height, allergies, clinical information, other comorbidities, concomitantly prescribed drugs, serious adverse events, safety and treatment outcomes (clinical and/or immunological improvement) including SLEDAI scores (Table 1).

Laboratory investigations are performed consisting of renal function assessments, urine sediment examination, 24 h urinary protein and creatine measurement, estimated-glomerular filtration rate (modification of diet in renal disease-glomerular filtration rate (mL/min/1.73 m²) = 175 × (S. Cr)−1.154 × (age)−0.203 × (0.742 if female) × (1.212 if African-American) (conventional units)⁴²), liver function tests, complement components C3 and C4, antinuclear antibody (ANA), anti-dsDNA and pharmacokinetic analysis of MPA.

The above information will be collected every 12 weeks and the presence of any serious adverse effects will be continually monitored and recorded during the study period. It is anticipated that the average follow-up time will be 18 months assuming a constant recruitment rate.

Data analysis

Blood samples will be collected by a dedicated research nurse at 15 time points for the 8 h group and 17 samples for the 12 h group, including the time points from previously described LSS data for MPS at 0, 1.5, 4 and 8 h postdose, on three different occasions. Blood samples for the 8 h group will be collected at half hourly intervals initially until the 7 h and the last sample at the eighth hour. Blood samples for the 12 h group will be collected as for the 8 h group along with further samples at the 10th and 12th hour. Samples will be kept on ice until centrifugation (3000 rpm for 10 min) and will then be analysed by high-performance liquid chromatography at Pathology Queensland (Royal Brisbane and Women's Hospital, Herston, Australia).

Induction phase. Blood sampling at three different time points; first sample at 1–2 months, second at 3–4 months and the third at 7–9 months.

Maintenance phase: Pharmacokinetic study will be performed only once at the time of entry. The pharmacokinetic values will be calculated using non-compartmental methods. The AUC_{0–12} will be calculated using the trapezoidal rule; CL = Dose/AUC; C_{max} will be the observed value; apparent terminal elimination rate constant (λ_z) will be determined from log-linear least squares regression analysis of concentrations from 4 to 8 h. Vz = CL/ λ_z ; apparent elimination half-life = ln²/ λ_z .

Statistical methods

A sample size of 32 participants is projected with 16 in each group. The sample required to test the ability for TDM-guided dosing to achieve target MPS exposure compared with no TDM, is based on pharmacokinetic data from patients with LN by Lertdumrongluk *et al.*⁴³

Test	Study visit							
	1 (Baseline)	2 (4–6 weeks)	3 (12th week)	4 (14–16 weeks)	5 (24 weeks)	7 (28–32 weeks)	8 (36th week)	End of study (48th week)
Demographics	X		X		X		X	X
Medical history	X		X		X		X	X
Clinical assessment	X		X		X		X	X
SLEDAI assessment	X		X		X		X	X
Renal Function assessment	X		X		X		X	X
Immunological Study	X		X		X		X	X
Adverse event assessment		X		X		X		
Pharmacokinetic analysis—total 3 sampling occasions								

Table 1 Visit schedule

Using a 95% CI, predicting that 50% of patients will have exposures under the target range requires a total sample of 30 participants. We will collect data from 32 participants assuming that there was less than a 10% attrition rate.⁴⁴

Comparisons between groups for the outcome variable for complete and partial remission will be performed using χ^2 or Fisher's exact tests followed by a multivariable logistic regression analysis to estimate the association between outcome and the groups. The secondary outcome of interest, namely, time to complete/partial remission will be evaluated using Kaplan-Meier survival curves, log-rank test. Multivariable Cox regression models will be used to estimate the effect of group adjusting for other covariates. Student t test or Mann-Whitney U test are used to compare the continuous variables. Differences in infection rates (number of infections/total follow-up time) and serious adverse events between the two groups will be analysed by Z tests. All data will be analysed on an intention-to-treat basis, and a significance level of 0.05 will be assumed.

Ethical considerations and dissemination

The Human Research and Ethics Committee of the RBWH have approved this study. The investigators will comply with and conduct the study in accordance with Good Clinical Practice Guidelines, the principles that have their origins in the 'Declaration of Helsinki' adopted by the World Medical Association in October 1996, the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (2007) or replacement, and or other relevant NHMRC publication or guideline that relate or may relate to clinical trials.⁴⁵

Withdrawal of study medication may be made at the discretion of the treating physician or investigator following an adverse event. However, participants will continue to be followed for the duration of the study if possible, even if they have stopped treatment. This will include attendance at scheduled trial visits, and data collection, particularly of outcomes. The investigator may withdraw a participant from study medication at any time if it is felt to be in the best interests of the participant, where there is disease progression or non-adherence to study medication. Under such circumstances, participants will continue to be monitored for outcome events and will attend scheduled trial visits so that results can be analysed on an intention to treat basis. If a participant withdraws consent for the study they shall be withdrawn from the study. Any participant is free to withdraw their consent at any time without the need to justify their decision.

We plan to publish the results in medical journals and present the de-identified information at conferences.

Protection of participant confidentiality

Participants' records and the data generated by the study will be confidential in line with the

recommendations of the Australian NHMRC and locally applicable laws. Standardised case report forms will be provided for each participant on this study. The participants in this study will be identified only by initials and subject number on these forms. Any information that may identify a participant will be excluded from data presented in the public arena. Data will only be shared among the investigators. Individual participant's medical information may be given to the treating clinician where deemed clinically necessary. De-identified information will not be released. Data collected as part of this trial will be stored on a computer data base held by the principal investigator in a secure, lockable location. The data will be stored for 15 years after completion of the project in accordance with the revision of the Joint NHMRC/Australian Vice Chancellors' Committee (AVCC) statement and guidelines on research practice.⁴⁵

DISCUSSION

Several studies have demonstrated that MMF/MPS is effective at gaining control of severe LN. The variations in pharmacokinetics of MPA/MPS and the factors causing these differences have been studied in transplant recipients but are not well documented in those with LN. The primary objective of this study is to examine whether exposure controlled MPS dosing results in higher proportion of participants achieving targets of MPA exposure compared with standard empiric dosing in participants with LN. Secondary objectives include the efficacy of exposure-controlled MPS dosing in LN with TDM, the relationship between the disease activity of LN and MPA blood concentrations (pharmacodynamics), and using the data to develop dosing recommendations for MPS in LN. Defining the optimal therapeutic range for MPA is likely to help improve outcomes in participants with LN treated with MPS. The consequences of failure of immunosuppression in LN can be severe and can lead to end-stage renal failure. By personalising MPS dosing for participants with LN using TDM, it may be possible to maximise therapeutic efficacy while preventing significant complications, therapeutic failure and toxicity.

CURRENT STATUS OF THE STUDY

The study has started and is in its early stages. The recruitment rate will be assessed periodically and if the target is unlikely to be met, we will invite other nephrology centres in Queensland to participate in the study.

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Acknowledgements The authors would like to thank Dr Sree Krishna Venthurupalli and Dr Jennifer Martin, members of Data Safety monitoring board and Dr Shankar Viswanathan for advice on statistical methods.

Contributors DR, GTJ and JAR designed the study and wrote the protocol. HH, JL and RGF advised and reviewed the study protocol and ethics application. PK provided input and will be involved with the recruitment component of the study. JAR, JU and BCMcW will be involved in the analysis of samples. AL, MLP, MJR and RR will be involved in the collection of blood samples and data collection. AL assisted in preparing the manuscript. All authors read and approved the final version of the manuscript.

Funding This study is funded by a Research grant from the RBWH Research Foundation and an unrestricted grant Novartis Australia. The study funders have no role in study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication. The investigators will have ultimate authority over each of these activities.

Competing interests DR and GTJ were principal investigators for Ascertain study sponsored by Novartis Australia (pte) limited and Novartis India (pte) limited, respectively.

Ethics approval Human Research & Ethics Committee, Royal Brisbane & Women's Hospital, Metronorth Health Services District.

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement Data sets are available with the corresponding author dwarakanathan_ranganathan@health.qld.gov.au.

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