1.1 Title Page

Full / Long Title

A Multi site, placebo controlled, double blind randomised clinical trial evaluating the effectiveness of sodium zirconium cyclosilicate versus placebo to enable safe optimisation of RASi therapy in patients with diabetic kidney disease.

Short title and/or Acronym

The ORTIZ Study: **O**ptimising **R**ASi **T**herapy **w**ith S**Z**C

Sponsor Barts Health NHS Trust

Representative of the Sponsor:
Dr Mays Jawad
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REC Number 21/WS/0082

Sponsor Reference (EDGE): 136721

2.0 Research Reference Numbers

IRAS Number:	1003542
EudraCT Number:	2020-002988-62
Sponsor ReDA Number:	012668
ISRCTN Number / Clinical trials.gov Number:	NCT04983979

3.0 Signature Pages

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: kieran mccafferty

Signature: kieran mccafferty
kieran mccafferty (Sep 6, 2022 17:49 GMT+1)

Date: Sep 6, 2022

Statistician's Agreement

The study as detailed within this research protocol plan will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments, and ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and for the statistical analysis and oversight of this study.

Statistician's name: Thomas Godec

Signature: Thomas Godec
Thomas Godec (Sep 6, 2022 17:14 GMT+1)

Date: Sep 6, 2022

4.0 Principal Investigator Agreement Page

Principal Investigator Agreement Page
The clinical study as detailed within this research protocol **(Version 1.1, dated 05 Jul 2022)**, or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research , the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator Name:

Principal Investigator Site:

Signature and Date:

4.0 Key Trial Contacts

Chief Investigator	Kieran McCafferty Kieran.mccafferty4@nhs.net phone:07980620627
Trial Co-ordinator/Manager	Charlie Mizon Barts Cardiovascular Clinical Trials Unit (Barts CVCTU) William Harvey Heart Centre Barts and The London School of Medicine Queen Mary University of London Charterhouse Square London EC1M 6BQ a.bellin@qmul.ac.uk cvctu@qmul.ac.uk
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Funder and IMP manufacturer	AstraZeneca 1 Francis Crick Ave, Trumpington, Cambridge CB2 0AA Tamsin Morris Tamsin.Luff@astrazeneca.com>
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Statistician	Thomas Godec Barts Cardiovascular Clinical Trials Unit (Barts CVCTU) William Harvey Heart Centre Barts and The London School of Medicine Queen Mary University of London Charterhouse Square London EC1M 6BQ t.godec@qmul.ac.uk
Trial pharmacist	Rahi Shah Senior Clinical Trials Pharmacist Royal London Hospital Barts Health NHS trust Rahi.shah@nhs.net|rlhpharmacyct.bartshealth@nhs.net 02035946680
eCRF	CASTOR EDC 35 Ludgate Hill London EC4M7JN +44(0)2033184726 support@castoredc.com
Randomisation	Sealed Envelope 501 Clerkenwell Workshops 27-31 Clerkenwell Close London EC1R 0AT +44 (0)2034885064 Contact@selaedenvelope.com
IMP secondary packaging, labelling and distribution to sites	RenaClinical Ltd Unit 11, Gatwick Metro centre Horley RH6 9GA +44(0)1293368080 enquiry@renaclinical.com
Committees (TSC/ DMC)	For membership and contract details please see TSC/DMC charter

5.0 Trial Summary

Full title	A Multi site, placebo controlled, double blind randomised clinical trial evaluating the effectiveness of SZC versus placebo to enable safe optimisation of RAS therapy in patients with diabetic kidney disease.
Short title and/or Acronym	The ORTIZ Study **O**ptimising **R**ASi **T**herapy wi**t**h S**Z**C
Trial Design Methodology	Multi site, placebo controlled, double blind randomised clinical trial.
Phase of the Trial	II
Study Duration	18 months, including 14 months recruitment period
Study setting	Multi NHS site UK only
Investigational Medicinal Product(s)	sodium zirconium cyclosilicate
Medical condition or disease under investigation	Diabetic Kidney Disease
Planned Sample Size	116
(Maximum) Treatment duration	12 weeks
Follow up duration	2 weeks
End of Trial definition	The last visit of the last subject

6.0 Protocol Contributors

Key Protocol Contributors	Full contact details including phone, email and fax numbers
Kieran McCafferty	Consultant Nephrologist The Royal London Hospital Barts Health NHS Trust Kieran.mccafferty4@nhs.net phone: 07980620627
Thomas Godec	Senior Statistician Cardiovascular Clinical Trials Unit Queen Mary University of London Charterhouse Square Campus 02078825673 t.godec@qmul.ac.uk
Anna Bellin	Clinical Trials Manager Cardiovascular Clinical Trials Unit Queen Mary University of London Charterhouse Square Campus 02078825673 a.bellin@qmul.ac.uk
Robert Hughes	GCP and Governance Manager Joint Research Management Office Barts Health NHS Trust and Queen Mary University of London 02078827352 research.governance@qmul.ac.uk

7.0 List of Contents

8.0 List of Abbreviations / Glossary of Terms

ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
ADR	Adverse Drug Reaction
AE	Adverse event
ARB	Angiotensin receptor blocker
AZ	AstraZeneca
BMI	Body mass index
BNP	Brain-type natriuretic peptide
BNF	British National Formulary
BP	Blood Pressure
CI	Chief investigator
CKD	Chronic kidney disease
ECG	Electro cardio gram
CRF	Case report form
eCRF	Electronic case report form
eGFR	estimated Glomerular Filtration Rate
HDL	High-density lipoprotein
HRA	Health Research authority
IRAS	Integrated Research Approval System
GI	Gastrointestinal
K	Potassium
KDOQI	Kidney Disease Outcomes Quality Initiative
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mineralocorticoid receptor antagonist
NICE	The National Institute for Health and Care Excellence
NIMP	Non investigational medicinal product
OD	Once daily
PI	Principal Investigator
SmPC	Summary of product characteristics
RAS	Renin angiotensin system
RASi	Renin angiotensin system inhibitor
REC	Research Ethics Committee
SAE	Serious adverse event
SAR	Serious adverse reaction
SPC	Summary of product characteristics
SUB-I	Sub investigator
SUSAR	Serious unexpected serious adverse reaction
uACR	Urinary albumin to creatinine ratio
SZC	Sodium zirconium cyclosilicate
WOCBP	Woman of child bearing potential

9.0 Introduction

9.1 Background

Inhibiting the renin angiotensin (RAS) system has been the cornerstone of therapy for patients with proteinuric CKD for almost 2 decades, to slow the decline in renal function, delay the presence of dialysis and reduce cardiovascular events and death (Parving et al, Brenner et al,). There is evidence in both the cardiac and renal literature that suggests that maximising the dose of RAS therapy leads to improved outcomes over smaller doses of RAS therapy (Khan et al., Rossing et al.)

Indeed, many of the studies on which we base our care use doses which are higher than what the majority of our patients are taking. Thus patients are being systemically undertreated by therapies which have been shown to have robust reno protection. With up to 80% of patients on RASi therapy are not on maximal RASi therapy (Epstein et al, 2015), putting them at risk of a more rapid progression and poorer outcomes and increased healthcare costs (Epstein et al, 2016).

An important reason for this is the presence or fear around hyperkalaemia.

With reports of significantly increased rate of hyperkalaemia seen following increases in prescribing of RASi therapy (Juurlink et al.). These concerns have lead NICE to recommend not starting patients on RASi therapy if their potassium is >5mmol/l, and KDOQI guidelines recommending consideration of stopping RASi therapy if serum potassium is >5.5mmol/l.

ACE inhibitors and angiotensin receptor blockers are thought to confer long term renal protection through reduction of proteinuria. The reduction in glomerular pressure is a major mechanism leading to a reduction in proteinuria, and hence renal protection, however as a consequence there will also an acute fall in eGFR. Therefore, when starting/up titrating ACEi/ARB it is expected that there will be an acute fall in eGFR, which is expected to be more than compensated for due to the subsequent long term renal protection. Indeed, current NICE guidelines (NICE 2014) do not suggest any alteration in management until the drop in eGFR is >25%.

There is a currently huge unmet need to optimise RASi therapy in those patients with hyperkalaemia.

There have been recent advances in novel therapeutics which can lower potassium in patients. One such agent is Sodium zirconium cyclosilicate (SZC).

SZC is a highly selective inorganic cation exchanger designed to entrap potassium in the intestine.

It has been shown to effective in lowering potassium in patients with heart failure, Diabetes, CKD and RASi therapy (Anker et al., Packham et al. and Ash et al., Kosiborod et al.). With around a 1mmol/l fall in the serum potassium on those treated with SZC, compared to placebo.

In the 5-large clinical trials it appears efficacious, well tolerated and safe.

We propose the following study: the ORTIZ trial will investigate the safety and tolerability of SZC compared to placebo to maximise RASi therapy in patients with moderate to advanced CKD.

9.2 Assessment and management of risk

• The known and potential risks and benefits to human subjects.

SZC has been shown to be safe and efficacious in several published clinical trials.
However, in this study we will aim to maximise RASi therapy (Irbesartan) using SZC versus placebo.
ADR from SZC: We foresee very little risk in the use of this agent. See SmPC for SZC
There is a risk of hypokalaemia in those patients on SZC, however this is rarely at a level with is symptomatic or would lead to a discontinuation of therapy.

ADR from the NIMP irbesartan: (see attached SmPC for Irbesartan)
There are some risks due to the up titration of the RAS therapy, which are well established in our current standards of care.
Hyperkalaemia, in those patients not on SZC. However, we will be monitoring those patients very closely during the study (checking their potassium levels following any dose changes within 2 weeks. With a pre-specified dose escalation/down escalation/stopping protocol to minimise any risk of hyperkalaemia. In addition, all patients will be given advice on a low potassium diet.

Hypotension: as we increase the RASi (Irbesartan) therapy, this can lead to hypotension. However, these agents will only be increased if the BP is >120/70, so as to minimise the risks, and that the vast majority of the patients will be hypertensive as their background antihypertensive therapy will have been withheld at the start of the study.

• How high is the risk is compared to normal standard practice?
Given the frequency of follow up and the conservative nature of the dosing protocol used, there is only a very small increased risk above our standard clinical procedures.

• Justification for the choice of route of administration, dosage, dosage regimen, and treatment period(s).
Irbesartan is a commonly used RASi: it is being used entirely within its product license and dose.
The dose of SZC is used within its licenced indication and dose.

• Preclinical+ clinical Data –
There have been 5 studies published using this agent, 4 of which in populations similar to our study population, of patients with CKD, heart failure, and on RASi therapy.

• How the risk will be minimised/managed.

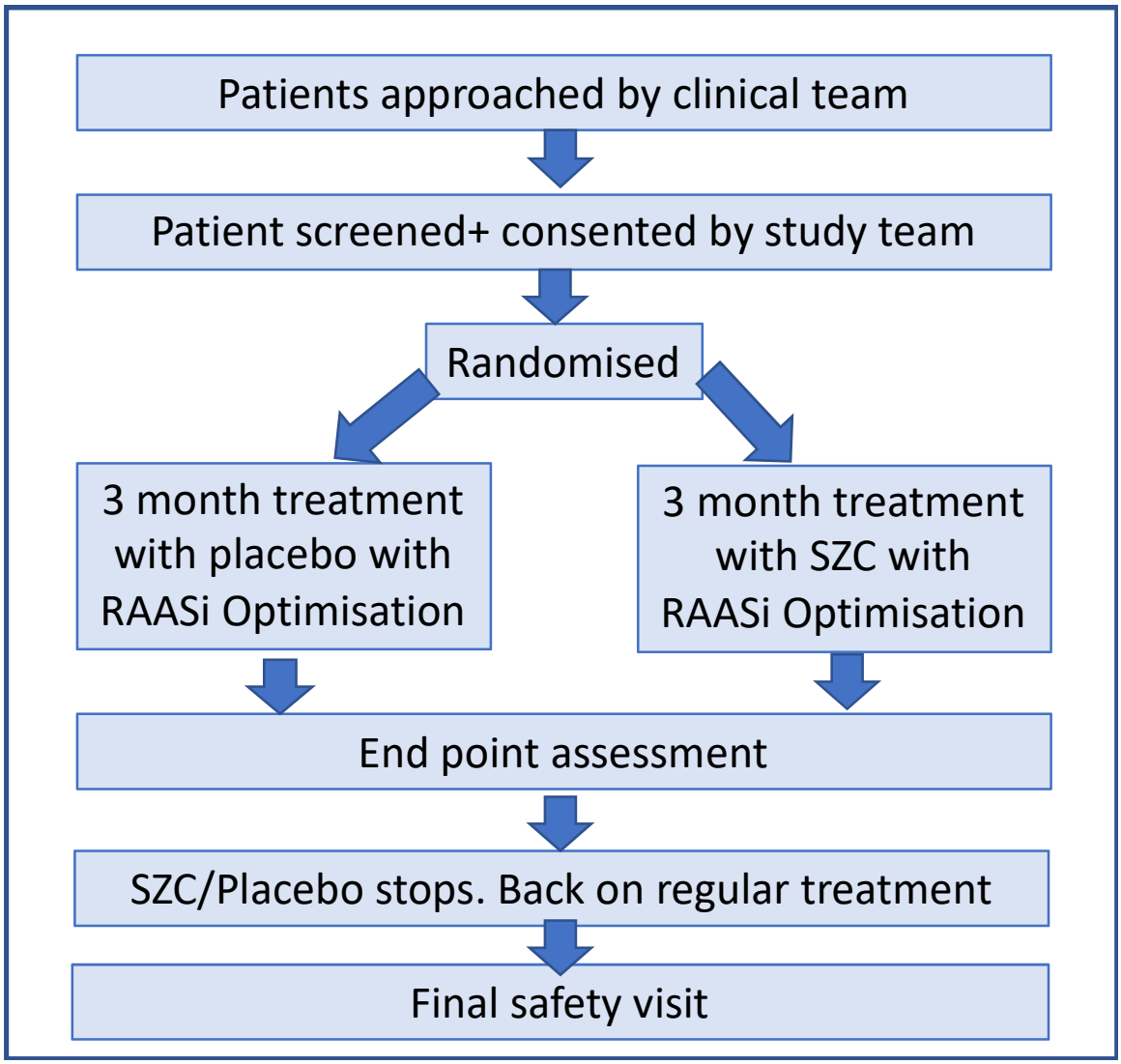
The study protocol of up/down titration is used to minimise any episodes of significant hyperkalaemia.

This trial is categorised as: Type A = No higher than the risk of standard medical care

9.3 Rationale for study design

Research Question: Can a 3-month treatment course of SZC enable safe optimisation of RASi therapy.
This is a double-blind placebo controlled study. The reason for the use of placebo as part of the double-blind study is to ensure a lack of bias/confounding.

10.0 Trial Flowchart



11.0 Trial Objectives and Design

11.1 Primary Objective/s

Our hypothesis is that 3 months' treatment with SZC versus placebo will enable RASi (Irbesartan) maximisation in a cohort of patients with diabetic kidney disease.

11.2 Secondary Objective/

The secondary objectives are to look at the effect of SZC on RASi maximisation on change in proteinuria, along with safety and tolerability outcomes

11.3 Endpoints

11.3.1 Primary Endpoint

- Proportion of patients on Maximum dose (300mg) Irbesartan therapy at the end of 12 weeks compared to placebo

11.3.2 Safety Endpoints

- Change in potassium from baseline at each time point
- Change in the BP at the end of the study from baseline
- Frequency of adverse events
- Proportion of patients who have a K of >6, or >6.5 at any time during the study
- Proportion of patients who have a K of <3.5 at any time during the study
- Proportion of patients whose GFR falls by >30% from the previous test
- Change in (eGFR) renal function at the end of study from baseline

11.4 Exploratory endpoints

- Change in pro BNP at the end of study from baseline
- Proportion of patients able to remain on 75/150/300mg dose of irbesartan at the end of the study
- Ratio of uACR between baseline and 3-month study visit in patients treated with placebo versus SZC
- Absolute uACR at end of study
- Change in Urea levels
- Change in Bicarbonate levels

11.5 Objectives and End Points Summary

Objective	How objective measured	outcome of measurement
Examine the ability of SZC to enable RASi (irbesartan) maximisation at 12 weeks	Dose of Irbesartan therapy at 12 weeks	Proportion of patients on Maximum dose Irbesartan therapy at the end of 12 weeks compared to placebo
Effect of SZC enabled RASi optimisation on potassium	lab potassium	Change in potassium from baseline at each time point
Effect of SZC enabled RASi optimisation on BP	clinic BP	change in BP between start and end of study
Examine the effect of SZC use on patient safety	SAE/AE	Frequency of adverse events
Effect of SZC enabled RASi optimisation on incidence of severe hyperkalaemia	lab potassium	Proportion of patients who have a K of >6, or >6.5 at any time during the study
Effect of SZC enabled RASi optimisation on incidence of hypokalaemia	lab potassium	Proportion of patients who have a K of <3.5 at any time during the study
Effect of SZC enabled RASi optimisation on incidence of AKI	eGFR	Proportion of patients whose GFR falls by >30% from the previous test
Effect of SZC enabled RASi optimisation on renal function	eGFR	Change in (eGFR) renal function at the end of treatment from baseline
Effect of SZC enabled RASi optimisation on markers of heart failure	lab BNP	change in pro BNP between start and end of treatment
Examine the ability of SZC to enable RASi (irbesartan) uptitration	Dose of Irbesartan therapy at each visit	Proportion of patients able to remain on 75/150/300mg dose of irbesartan at the end of treatment
Effect of SZC on enabled RASi optimisation on proteinuria	uACR	Ratio of uACR between baseline and 3-month study visit in patients treated with placebo versus SZC
Effect of SZC on enabled RASi optimisation on proteinuria	uACR	Absolute uACR at end of treatment

Effect of SZC on bicarbonate levels	Serum Bicarbonate	Change in serum bicarbonate levels between baseline and end of treatment
Effect of SZC on urea	Serum urea	Change in serum urea levels between baseline and end of treatment

11.6 Trial Design

This is a double-blind placebo controlled pilot study to determine if SZC enables safe dose maximisation of RASi therapy (Irbesartan) in patients with diabetic kidney disease.

Patients will be randomised in 1:1 ratio to SZC or placebo. This will be used in addition to Irbesartan, the RASi therapy of choice for this study.

• The number of study visits will be 8: screening visit, randomisation visit then at 2,4,6,8,12,14 weeks post randomisation.
• The treatment period will be 12 weeks; the patients will be in the study for 16 weeks.

11.7 Study Setting

This is multi centre study (5 sites), with no PIC sites.
The study will take place in an NHS setting:

- Barts Health NHS Trust, with PI Kieran McCafferty
- King's College Hospital NHS Foundation Trust, with PI Sapna Shah
- Imperial College Healthcare NHS Trust, with PI Andrew Frankel
- St George's University Hospitals NHS Foundation Trust, with PI Richard Hull
- Epsom and St Helier University Hospitals NHS Trust, with PI Pauline Swift

Patients will be recruited from a cohort of patients under the nephrology services in secondary care.

12.0 Eligibility Criteria

12.1 Inclusion Criteria

1) Subject must be able and willing to provide written informed consent
2) Adults ≥ 18years old
3) Type 2 Diabetes
4) CKD defined as eGFR 25-60ml/min
5) Albuminuria with uACR measured at >33.9.mg/mmol (300mg/g)
6) On a stable (>4 weeks) of sub-maximal RASi dose, defined as any ACE or ARB dose up to and including 50% of maximum dose as per BNF (see table below) with evidence of hyperkalaemia potassium level >5.0mmol/l OR not currently on RASi therapy due to documented issues of hyperkalaemia in the past necessitating RASi discontinuation

Drug name	Maximum dose
Trandrolapril	4mg
Captopril	100mg
Lisinopril	10 mg
Perindropril	8 mg
Quinapril	80 mg
Ramipril	10 mg
Fosinopril	40 mg
Imidapril	20 mg
Enapril	40 mg
Candesartan	32 mg
Azilsartan	80 mg
Eprosartan	600 mg
Irbesartan	300 mg
Losartan	100 mg
Omlesartan	40 mg
Valsartan	320 mg
Telmisartan	80 mg

12.2 Exclusion Criteria

1) Active malignancy
2) Patients who lack capacity to give informed consent
3) GI disturbance/chronic diarrhoea/stoma
4) Subjects with a life expectancy of less than 3 months.

5) Women who are pregnant, lactating, planning to become pregnant.
6) Women of childbearing potential who are unwilling to use effective methods of contraception* during the study.
7) Presence of any condition which, in the opinion of the investigator, places the subject at undue risk or potentially jeopardizes the quality of the data to be generated including NYHA class III/IV.
8) History of acute eGFR fall with RASi therapy (>30% in eGFR on initiation of RASi therapy)
9) Known hypersensitivity or previous anaphylaxis to SZC or Irbesartan
10) Hypotension: BP <120/70mm/hg at screening despite no antihypertensive agent use
11) Uncontrolled Blood pressure: BP >170/110 at screening
12) Evidence of prolonged QT on ECG QTc(f)>550msec
13) History of QT prolongation associated with other medications that required discontinuation of that medication
14) Treatment with lithium, or dual blockade with ACEi and ARB or mineralocorticoid inhibitor
15) History of congenital long QT syndrome
16) Symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted
17) Current or recent (within 3 months) participation in a clinical trial involving an investigational medicinal product.
18) Current treatment with a potassium binder medication
19) Potassium value > 6mmol/l at Randomisation

* Effective contraception defined as oral contraceptive pill, Intra-Uterine Device, double barrier methods or abstinence as a clearly defined lifestyle choice for the whole duration of the study.

13.0 Trial Procedures

13.1 Recruitment

13.2 Participant identification

Participants will be identified by their regular clinical team. Eligibility decision will be made by the CI/PI.

13.3 Informed Consent Procedures

Informed consent will be obtained prior to the participant undergoing procedures that are specific to the trial and are outside standard routine care at the participating site (including the collection of identifiable participant data or entering data into the study case report form).

13.3.1 Responsibility for obtaining consent

The Chief Investigator (CI)/ local PI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent occurs then details should be provided in the Site Delegation Log.

Consent can only be taken by the CI/PI or a medical practitioner trained in the study and delegated on the study log.

13.3.2 Consent Considerations

The right of a patient to refuse participation without giving reasons will be respected.

The participant must remain free to withdraw from the trial at any time without giving reasons and without this compromising his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent, for example if during the trial new Reference Safety Information becomes available, or following an amendment that affects the patient, or new information needs to be provided to a participant, it is the responsibility of the CI to ensure this is done in a timely manner.

13.3.3 Population

The patient population is adult patients under the care of the Nephrology departments in secondary care

13.3.4 Vulnerable participant's considerations

The CI or delegated local PIs take responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

13.3.5 Written/ reading / translation considerations

For patients who do not speak English, we will make every effort to offer independent advocates or standard clinical translation services (eg Language line) to enable informed consent to take place and for subsequent study visits.

13.3.6 Participants lacking capacity

We will not approach any patient who is felt not to have capacity to take part in the study.

13.3.7 Minors

Patients under 18 are not eligible to participate in the study.

13.3.8 Consenting process

Patients will be approached by a member of the clinical team and asked if they would like to know more about the study. If the patient is interested, the research team will contact the patient to discuss the trial. They will inform the potential participant or his/her legal representative about the nature and objectives of the trial and possible risks associated with their participation.

In addition, they will receive the PIS and have a minimum of 24 hours to read it and have all their queries satisfactorily answered.

13.3.9 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies

Patient samples will be stored and destroyed as per standard practice. Samples will not be not be used for future research.

13.4 Screening Procedures

All participants that undergo screening will be logged into a study specific screening log.

Following consent, and before randomisation takes place procedures will be performed see section 13.8.3 for details.

13.5 Treatment Allocation

13.5.1 Randomisation Method

The method of randomisation will be a simple 1:1 randomisation using a computer based randomisation sequence (sealed envelope).
Both the patient's details and study number will be documented in the Investigator site file.

13.5.2 Randomisation Procedure

An online Randomisation tool (sealed envelope) will be used and recorded as part of the eCRF/Study database. Please see the ORTIZ Randomisation and Unblinding procedure for full details.

13.5.3 Cohort allocation/sequential allocation

n/a

13.6 Blinding

This is a double-blind placebo study: both the patient and the study team will be blinded to the treatment intervention.

13.7 Unblinding

• The code breaks for the trial will be the responsibility of the CI.

• In the event a code is required to be broken if possible a formal request for unblinding must be made by the Investigator or treating health care professional or sponsor (following a SUSAR or SAE), however in the case of an emergency the PI or CI can unblind a participant via the unblinding software (sealed envelope).

• If the person requiring the unblinding is not the PI/CI or their team then that health care professional will notify the Investigator team that an unblinding is required for a trial subject and an assessment to unblind should be made in consultation with the clinical and research teams and CI.

• On receipt of the treatment allocation details the CI or treating health care professional will continue to deal with the participant's medical emergency as appropriate.

• The CI must document the breaking of the code and the reasons for doing so on the eCRF/data collection tool, in the site file and medical notes. The CI/PI will ensure it is also documented in the final study report and/or statistical report at the end of the study.

• The PI or delegate will notify the CI in writing as soon as possible following the code break detailing the necessity of the code break.

• The written information will be disseminated to the Trial Steering Committee/Drug Monitoring Committee for review.

•Upon receipt of a SUSAR notification, the JRMO GCP team will log in to Sealed Envelope to confirm the treatment allocation of the patient and to make an unblinded SUSAR report to the MHRA. The JRMO will not share the treatment allocation information with any blinded study team members.

13.8 Trial Schedule

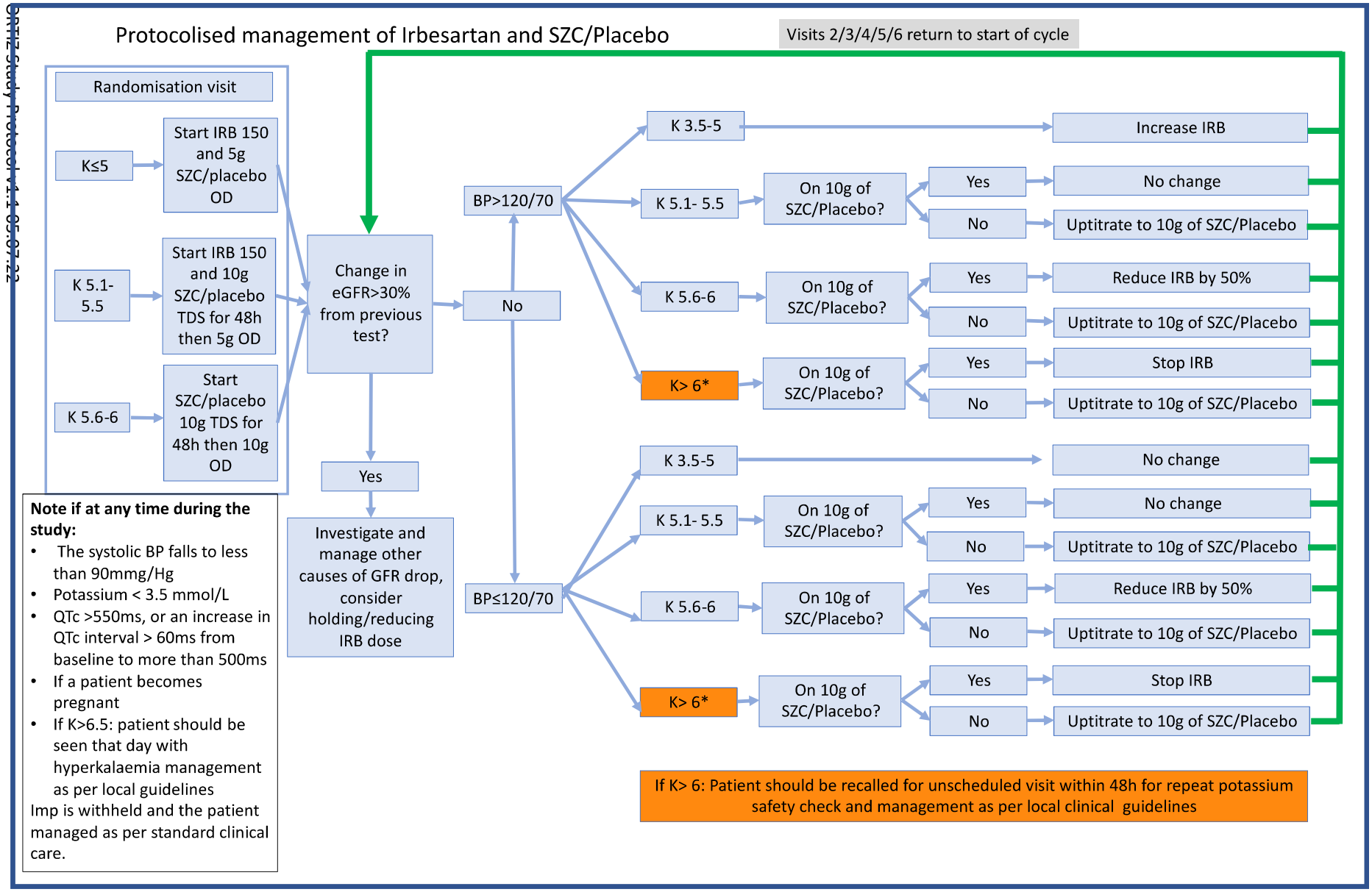
13.8.1 Schedule of Treatment for each visit

See study schedule table below

13.8.2 Schedule of Assessment (in Diagrammatic Format) and protocolised dosing management of IMP

Schedule of visits	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	follow up visit	Unscheduled	Early termination visit
Day	Day -14 to -7	Day 0	Day 7 (+/-2)	Day 14 (+/-4)	Day 28(+/-4)	Day 42 (+/-4)	Day 56(+/-4)	Day 84(+/-4)	Day 98 (+/-4)		
Informed Consent	X										
Eligibility criteria	X	X									
Demographic data	X										
Medical history	X										
Pregnancy test if WOCBP	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	if needed	X
Randomisation		X									
Stop background antihypertensives	X										
First IMP dose at site		X									
Drug accountability (IRB and SZC)			X	X	X	X	X	X		If needed	
IMP and NIMP drug dispense		X			X		X			If needed	
Physical examination	X	X	X	X	X	X	X	X	X	If needed	X
Vital signs	X	X	X	X	X	X	X	X	X	If needed	X
FBC		X						X		If needed	
U+E (+bicarbonate)	X	X	X	X	X	X	X	X	X	If needed	X
Pro NT BNP		X						X			
Optional POC potassium		X	X	X	X	X	X	X			
ECG	X	X	X	X	X	X	X	X	X	If needed	X
Urine collection (uACR)		X						X		If needed	
AE assessment		X	X	X	X	X	X	X	X	X	X
Uptitration of RASi			X	X	X	X	X			If needed	

RASi dose back to baseline								**X**			**X**


Protocolised management of Irbesartan and SZC/Placebo
Visits 2/3/4/5/6 return to start of cycle
Randomisation visit
K≤5
Start IRB 150 and 5g SZC/placebo OD
K 5.1-5.5
Start IRB 150 and 10g SZC/placebo TDS for 48h then 5g OD
K 5.6-6
Start SZC/placebo 10g TDS for 48h then 10g OD
Change in eGFR>30% from previous test?
Yes
Investigate and manage other causes of GFR drop, consider holding/reducing IRB dose
No
BP>120/70
K 3.5-5
Increase IRB
K 5.1- 5.5
On 10g of SZC/Placebo?
Yes
No change
No
Uptitrate to 10g of SZC/Placebo
K 5.6-6
On 10g of SZC/Placebo?
Yes
Reduce IRB by 50%
No
Uptitrate to 10g of SZC/Placebo
K> 6*
On 10g of SZC/Placebo?
Yes
Stop IRB
No
Uptitrate to 10g of SZC/Placebo
BP≤120/70
K 3.5-5
No change
K 5.1- 5.5
On 10g of SZC/Placebo?
Yes
No change
No
Uptitrate to 10g of SZC/Placebo
K 5.6-6
On 10g of SZC/Placebo?
Yes
Reduce IRB by 50%
No
Uptitrate to 10g of SZC/Placebo
K> 6*
On 10g of SZC/Placebo?
Yes
Stop IRB
No
Uptitrate to 10g of SZC/Placebo
Note if at any time during the study:
• The systolic BP falls to less than 90mmg/Hg
• Potassium < 3.5 mmol/L
• QTc >550ms, or an increase in QTc interval > 60ms from baseline to more than 500ms
• If a patient becomes pregnant
• If K>6.5: patient should be seen that day with hyperkalaemia management as per local guidelines
Imp is withheld and the patient managed as per standard clinical care.
If K> 6: Patient should be recalled for unscheduled visit within 48h for repeat potassium safety check and management as per local clinical guidelines

13.8.3 Trial assessments

Screening visit

a. Informed consent
b. Inclusion/Exclusion criteria
c. Demographic data
d. Concomitant Medication
e. Physical examination
f. Medical history
g. ECG with QTc (f) measured
h. Vital signs (weight/height/BP/pulse)
i. Laboratory investigations: U+E
j. Pregnancy test for women of childbearing potential
k. Stop all antihypertensive medications (unless judged by PI as fulfilling other purpose eg: beta blockers may continue in patients with angina/arrhythmia or as judged by PI as a risk to health to stop all antihypertensives.)

Rescreening: If patient does not meet the inclusion/exclusion criteria patients, but PI feels there is a likelihood of subsequently meeting criteria then the patient may be rescreened (up to a maximum of 3 times)

Within 7-14 days of screening visit

Randomisation visit 1

a. Concomitant Medication
b. ECG with QTc (f) measured
c. Confirmation of meeting Inclusion and no Exclusion criteria
d. Physical examination
e. Vital signs (weight/BP/Pulse)
f. Urine ACR
g. Lab bloods: U+E (including bicarbonate) , FBC, NT pro BNP
h. Point of care potassium (optional)_
i. Adverse event assessment (AE and SAE)
j. Randomisation
k. Study drug dispense and irbesartan dose chosen as per K value**
l. Patient shown how to take IMP and given first dose in clinic.

Visit 2,3,4,5,6: see protocolised

a. Concomitant Medication:
b. IMP accountability*
c. Physical examination
d. Vital signs (weight/BP/Pulse)
e. ECG with QTc(f) measured
f. Lab bloods: U+E (including bicarbonate)
g. Point of care potassium (optional)
h. Adverse event assessment (AE and SAE)
i. Up titration assessment using BP/K**/GFR : see protocol figure 13.8.2
j. Dispense IMP: visit 4 +6 only. At visits 2,3 and 5 unused IMP and nIMP are returned to the patient after accountability.

Visit 7

a. Concomitant Medication review
b. IMP and RASI accountability*
c. Physical examination
d. Vital signs (weight/BP/Pulse)
e. ECG with QTc (f) measured
f. Lab bloods: FBC, U+E (including bicarbonate), Pro NT BNP
g. Point of care potassium (optional)
h. uACR
i. Adverse event assessment (AE and SAE)
j. IMP stopped
k. Irbesartan stopped and patient returned to their original dose of ACE/ARB

13.8.4 Follow up Procedures

Visit 8

a. Concomitant Medication review
b. Vital signs (weight/BP/Pulse)
c. Lab bloods: U+E
d. Physical examination
e. ECG with QTc(f) measured
f. Adverse event assessment

BP/pulse to be recorded after resting seated for minimum of 5 minutes: performed in triplicate with the average rate, systolic and diastolic values taken from the second and third readings.
*IMP accountability includes SZC/placebo and the NIMP: Irbesartan. The patient will be asked to bring back the IMP and Irbesartan to each clinic visit for accountability. The IMP/NIMP will then be given back to the patient, except for visit 4 and 6 where new IMP will be dispensed.
** K value measured using local labs on the day of clinic (an optional point of care potassium can be used to determine the potassium for dispensing purposes if sites use this routinely. Note if there is a discrepancy between point of care potassium and local lab potassium then local lab potassium will be taken as the correct value for protocol decisions)

If K>6 at clinic visit, patient should have repeat K check as an unscheduled visit and management as per local guidelines.

13.9

IMP withholding criteria

The IMP will be withheld immediately and the patient will receive appropriate medical intervention, but continue in the study if:

- Potassium < 3.5 mmol/L, at any time during the study*
- Potassium is found to be >6.5 despite not being on ARB any time during the study.
- If an absolute QTc(f) >550ms, or an increase in QTc interval > 60ms from baseline to more than 500ms is reached . All patients meeting the QTc(f)>500ms criterion should immediately have potassium assessed, if not already done within 1 hour of performing the ECG.
- If it is felt to be in the participant's best interest to stop the study treatment
- if the investigator feels that individual adverse events or IMP related side effects compromise the patient's safety or quality of life for example if the investigator feels that hyperkalaemia is a safety risk, then the IMP/or NIMP may be stopped and the patient treated as per local standard of care.
- In addition the patient may be brought up for an unscheduled visit to recheck potassium if felt to be clinically needed as per local practice
- The investigator feels that individual adverse events or new information gained mean that it is not safe to continue the study
- If the patient becomes pregnant.
- If the patient is found to be non-adherent to the study medication (see section 15.19)

If at a subsequent visit(s), and after appropriate management and if the withholding criteria are no longer present the PI may elect to reintroduce the IMP.

*If a patient develops hypokalaemia (<3.5mmol/l) the IMP will be withheld and the patient will be manged as standard of care. The IMP can only be restarted if hypokalaemia has resolved and the serum potassium has risen to >5mmol/l. If hypokalaemia (serum K <3.5mmol/l) recurs on reintroducing IMP then IMP is permanently withdrawn.

** If a patient develops severe hyperkalaemia with a serum K of >6.5mmol/l despite not being on an ARB. The patient will be withdrawn from the IMP permanently and receive standard of care as per local policies/national guidelines (Alfonzo et al 2019), which may include but are not limited to: admission to hospital for cardiac monitoring, cardiac stabilisation with IV calcium, insulin/dextrose, nebulised salbutamol, bicarbonate treatment if acidotic, addition of loop or thiazide diuretics or potassium binders/resins cessation of NSAIDS, non selective beta blockers, mineralocorticoid receptor antagonists, trimethoprim, reinforcement of dietary restrictions or dialysis.

Patients will remain on the study and continue with the study visits, but will stop the IMP and may need to reduce their RASi back to their original dose.
Patients would be encouraged to continue with the study visits for safety, however should they not want to take part in any further study visits, they can withdraw from the study and continue to be followed up by their clinical care team as standard.

Routine clinical data collection will continue for patients who have withdrawn from the study unless they specifically opt out of using routine clinical data collection.

Should a patient withdraw from the study this will be documented on the CRF using a study termination form which including recording reasons for withdrawal and consent for any follow-up information being collected.

13.10 Early withdrawal

If a patient is withdrawn from the IMP early they will continue with their standard care at the unit.
It will be documented in the CRF and medical notes if the patient is happy to continue on with study visit schedule and assessments (without the IMP) or continue to have their clinical data collected or no further data collected.

13.11 End of trial (EOT)

It is the CI's responsibility to submit the EOT notification to REC and MHRA once obtaining sponsor approval. The EOT notification must be received by REC and MHRA within 90 days of the end of the trial.

If the study is ended prematurely, the Chief Investigator will notify the Sponsor, REC & MHRA including the reasons for the premature termination (within 15 days).

End of Trial definition: is after the last patient has completed their last visit.

14.0 Laboratories and samples

14.1 Central Laboratories

No central labs will be used.

14.2 Local Laboratories

Biochemistry and haematology samples will be sent to the local site Laboratory. Lab tests performed are: renal function (U+E), NT pro BNP, uACR FBC.

14.3 Sample Collection/Labelling/Logging

Samples will be collected by the research nurse or trained phlebotomist as per standard of care.
Samples will be labelled with patient identification and sent to the local labs as per routine care and the results logged on the eCRF.

• Volume of sample(s) to be collected:
The total volume of bloods which will be taken on top of routine care is:

2 tea-spoons (3-5ml) of blood per clinic visit (7x5ml samples of blood) in a lithium heparin tube provided locally.

• No tissue or blood will be stored as part of the study

14.4 Sample Receipt/Chain of Custody/Accountability

Samples will be sent to the lab by the research nurse, where they will be processed per the lab's standard SOPs under their UKAS accreditation. The research team will have responsibility for the custody of the samples until they are handed over the lab technicians at the sample collection point.

14.5 Sample Analysis Procedures

14.5.1 The arrangements for sample analysis

Samples will be taken to the local lab by the research nurse/team after being taken. All samples will be processed in accordance with local procedures.
No samples will be shipped to external labs/sites. No samples will be retained.

14.5.2 Sample Storage Procedures

n/a

14.6 Sample and Data Recording/Reporting

Data will be recorded on the source data worksheets and eCRF.
The eCRF will be completed by a member of the study team delegated by the PI at each of the participating sites.

14.7 End of study

No material will be kept in the department. All biological samples will have been sent to the lab and disposed of as per their routine SOP.

15.0 Trial Medication

15.1 Name and description of investigational medicinal product (IMP) and non-investigational medicinal product (NIMP)

IMP: 5g/10g sodium zirconium cyclosilicate (SZC) or placebo powder for oral suspension sachets.

SZC/placebo will be provided free of charge to hospital sites for use in patients being treated within the ORTIZ clinical trial.
SZC/placebo will be packaged in two types of IMP kits:

- **Induction kit**: carton containing 6 sachets of 10g SZC/placebo
- **Maintenance kit**: carton containing 30 sachets of 5g SZC/placebo

NIMP: Irbesartan 75mg/150mg/300mg tablets (see product SMPC for full details).
Irbesartan will be supplied from the local hospital stock as per standard of care.

Refer to the ORTIZ Pharmacy Manual for further information regarding the IMP and NIMP

15.2 Legal status of the drug

SZC is currently licensed in the UK for the treatment of hyperkalaemia in adult patients

15.3 Summary of Product Characteristics (SmPC) or IB

Refer to the current SMPC for the products SZC and Irbesartan for further information.

15.4 Drug storage and supply

The IMP/placebo will be shipped securely to the clinical trials pharmacy from the supplier, where it will be stored until needed. The research nurse will collect the IMP/placebo from the clinical trials pharmacy and give this to the study patients. All medicinal products left over after study completion will be destroyed.

15.5 Supplier

The final drug product (carton containing sachets of SZC/placebo) will be packaged, labelled and sent to site pharmacy by RenaClinical Ltd.

RenaClinical
Horley,
United Kingdom

15.6 Manufacturer

The sachets of SZC/placebo were manufactured by Sharp Packaging Solutions on behalf of AstraZeneca.

Sharp Packaging Solutions
7451 Keebler Way
Allentown, PA 18106, USA

AstraZeneca, Cambridge, UK

ThermoFisher is responsible for the distribution of the drug product on behalf of AstraZeneca, from Sharp Packaging Solutions to RenaClinical Ltd.

Depot in USA: Fisher Clinical Services, 700A Nestle Way Breinigsville, PA, 18031, USA
Depot in UK: Fisher Clinical Services, Langhurstwood Road, Horsham, West Sussex, RH12 4QD, UK

15.7 How the drug should be stored

SZC/placebo must be stored at room temperature, between 15 - 30^{o}C.

15.8 Details of accountability

SZC/placebo will be dispensed from pharmacy and given to the patient by a member of the research team on the delegation log.
The details of study medication received, dispensed, and returned should be recorded on the study accountability logs.
Accountability logs should be maintained by the clinical trial pharmacy.

15.9 Medication destruction/return and Recall

At visits 4, 6 and 7 any unused, used or partially used IMP and nIMP will be returned and counted. After the monitor has verified the accountability, the sponsor and CI will authorise destruction as per local policy.

15.10 Prescription of IMP / Placebo/NIMP

The IMP, (SZC/Placebo) will be prescribed by the PI or one of the sub-investigators using the study prescription template.
The NIMP, Irbesartan, will be prescribed by the PI or one of the sub-investigators as per standard of care, and it will be dispensed from local hospital stock.

15.11 Preparation and labelling of IMP

The active treatment is SZC 5g/10g. The placebo contains no active ingredient and is a visual match to the active.
The final drug product (cartons containing sachets of SZC/placebo) will be packaged, labelled and sent to site pharmacy by RenaClinical Ltd.

15.12 Preparation and Administration of IMP

For SZC/placebo, the contents of the sachet(s) should be stirred well in approximately 45ml water before ingestion.

Patients will be counselled on how to take the study medication during visit 1.

15.13 Dosage schedules

At visit 1 (randomisation visit) the patient will be dispensed IMP according to the potassium level.

- If serum potassium level is 5mmol/L or less the patient will receive SZC/placebo 5g OD.
- If the serum potassium level is 5.1-5.5 mmol/L the patient will receive SZC/placebo 10g TDS for 48h followed by SZC/placebo 5g OD.
- If the serum potassium level is 5.5-6 mmol/L the patient will receive SZC/placebo 10g TDS for 48h followed by SZC/placebo 10g OD.

SZC/placebo should be taken once a day with or without food.

Drug accountability will be assessed at visits 2-7 and finally at month 3 where patients will bring back their remaining unused supply. Non-adherence is defined as less than 70 % of medications taken.

15.14 Dispensing of IMP

There will be a dispensing guideline in place within pharmacy. Each member of staff who dispenses the IMP should sign the local/pharmacy dispensing log to document appropriate IMP tracking. Any members of the trial team should ensure that they have had study specific training and their involvement should be demonstrated by the study specific trial delegation log.

Refer to the ORTIZ Pharmacy Manual for the type and number of SZC/placebo kits to be dispensed at study visit.

15.15 Dosage modifications

The dose of SZC/placebo and irbesartan will be adjusted at each of the subsequent protocol visits (2, 3, 4, 5 and 6) following the baseline visit, depending on results from the safety assessments (eGFR change from previous test, blood pressure, and potassium level according to the protocolled SZC/placebo and irbesartan dosing schedule. These changes are described in figure in 13.8.2.

The max dose of SZC/placebo will be 10g (2 sachets) OD. The max dose of irbesartan will be 300mg OD.

15.16 Known drug reactions and interaction with other therapies

As SZC is not absorbed or metabolised by the body, and does not meaningfully bind other medicinal products, there are limited effects on other medicinal products.
SZC can transiently increase gastric pH by absorbing hydrogen ions and can lead to changes in solubility and absorption kinetics for co-administered medicinal products with pH-dependent bioavailability.
Therefore SZC should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability.
Examples of medicinal products that should be administered 2 hours before or after SZC to avoid possible raised gastric pH drug interaction are:

- **azole antifungals** (ketoconazole, itraconazole and posaconazole), **anti-HIV drugs** (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir and rilpivirine) and
- **tyrosine kinase inhibitors** (erlotinib, dasatinib and nilotinib)

15.17 Prior and Concomitant medication

Prohibited medications:
No other potassium binder medications are permitted (Patiromer/Calcium resonium)
During the study treatment period when patients are on irbesartan, they should not be commenced on any ACEi/ARB/MRA or direct renin inhibitors (eg aliskiren)

15.19 Assessment of adherence

IMP adherence will be assessed at each visit, when the research team will count the number of doses used and consider less than 70% adherence or >120% to be non-adherent. If the patient fails compliance on consecutive 2 visits they will be withdrawn from the study medication and returned to standard of care.
Overdose: if in the unlikely event the patient is found to have taken overdose of IMP (>150% of IMP taken), then IMP will be withheld and patient will be managed as per standard of care.

15.21 Arrangements for post-trial access to IMP and care

No arrangements have been made for post-trial access to IMP, however this drug is approved for treating hyperkalaemia in those patients with a potassium of >6. As such patients who have a potassium of >6 may receive this drug as per standard of care after the study.

17 Pharmacovigilance

17.1 General Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Event of Special interest (AESI)	*An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.*
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. SAEs will be collected from the time the patient signs the consent from until their last study visit. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

17.2 Site Investigators Assessment

The Chief Investigator is responsible for the care of the participant, or in his/her absence a delegated medical practitioner and is responsible for assessment of any event for:

- Seriousness
  Assessing whether the event is serious according to the definitions given in section 17.1.

- Causality
  Assessing the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

- Expectedness
  Assessing the expectedness of all SAEs according to the definition given. If the SAE is unexpected, then it is a SUSAR.

- Severity
  Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

    - **Mild**: Some discomfort noted but without disruption of daily life
    - **Moderate**: Discomfort enough to affect/reduce normal activity
    - **Severe**: Complete inability to perform daily activities and lead a normal life

17.3 Reference Safety information

Reference Safety Information (RSI) is the information used for assessing whether an adverse reaction is expected.

See attached SZC Summary of Product Characteristics | AstraZeneca UK Limited

For the nIMP Irbesartan we will use the SMPC for Irbesartan (Sanofi) as an example of the SMPC to be used when deciding expectedness, though multiple brand of irbesartan may be used.

17.4 Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

All AEs will be sent to AZ quarterly: AE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: +1 302 886 4114 or email if a secure is set up: AEMailboxClinicalTrialTCS@astrazeneca.com

This will be completed by the trial manager.

17.5 Notification of AEs of special interest

Potassium levels at any point >6.5mmol/l
Any potassium level <3.5mmol/l

17.6 Adverse events that do not require reporting

Specific biochemical and physiological parameters (potassium, BP, creatinine) will be expected to be altered as part of the predefined protocol and would not be expected to be reported as AEs: with the exception of those associated with an SAE or an AE of special interest (as above)

17.7 Notification and Reporting of Serious Adverse Events & SUSARs

All Serious Adverse Event (SAEs) will be recorded in the participants' notes, the CRF, the sponsor SAE form and reported to the sponsor (Barts Health NHS Trust Joint Research Management Office at research.safety@qmul.ac.uk) and to the cardiovascular clinical trials unit at cvctusafetyreporting@qmul.ac.uk within 24 hours of the CI or the PI or co-investigators becoming aware of the event. Nominated co-investigators (as listed in the delegation log) will sign the SAE forms in the absence of the PI at the participating sites.

Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur during the trial will be reported to the JRMO within 24 hours of the CI or co-investigator becoming aware of the event. SUSARs should be reported to the sponsor (Barts Health JMRO at research.safety@qmul.ac.uk) and to the cardiovascular clinical trials unit at cvctusafetyreporting@qmul.ac.uk within 24 hours. The sponsor will then report this to the MHRA.

SAEs that do not require expedited reporting to the local authorities need to be reported to AstraZeneca at least quarterly, preferably as they occur, either as individual case reports or as line-listings. This will be done by the central trial manager.

When reporting to AstraZeneca, a cover page should accompany the SAE form indicating the following:

-External Sponsored Research (ESR)

-The investigator's name and address

-The trial name/title and AstraZeneca ESR reference number

Investigative site must indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications.

Send SAE report and accompanying cover page

SAE to be reported to the AstraZeneca Safety mailbox (AEMailboxclinicaltrialTCS@astrazeneca.com) or fax to AstraZeneca's designated fax line: +1 302 886 4114

17.8 Sponsor Medical Assessment

The CI retains overall responsibility for oversight of IMP safety profile and medical assessment of SAEs and SUSARs. The CI must review all SAEs within 48 hours of receipt. This review should encompass seriousness, relatedness and expectedness. Day 0 for all SUSARs is when the SAE/SUSAR is received by the CI and /or coordinating team and /or sponsor whichever is first.

It is expected that the CI will achieve oversight of IMP safety profile through trial committees as per section 28.0.

17.9 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, approval from the Competent Authority prior to implementing these safety measures is not required. However, it is the responsibility of the CI to attempt, where possible, to discuss the proposed measures with the Sponsor and Medical Advisor at the MHRA (via telephone) prior to implementing them if possible.

The CI has an obligation to inform both the MHRA and Research Ethics Committee **in writing within 3 days**, in the form of a substantial amendment along with Astra Zeneca. The sponsor (JRMO) must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

17.10 Procedures for reporting blinded SUSARs

The CI as sponsor medical assessor will assess the event blinded, and will assess for active IMP and Placebo. For SUSARS the CI will remain blinded, however the Barts Health NHS Trust Joint Research Management Office will be unblinded in order to report unblinded SUSARs to the MHRA.

17.11 Pregnancy

If a patient becomes pregnant while on the IMP the study medication and the Irbesartan will be withdrawn but the patient will continue in the study. RASi therapy should be avoided in pregnancy as recommended by BNF. Should pregnancy occur, the patient's antihypertensive medication will be altered to those what are safe in pregnancy.

If a patient on the IMP gets pregnant the CI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. The initial report should be sent within 24 hours and follow up information submitted as and when it becomes available up to agreed follow up time after birth.
All pregnancies and outcomes of pregnancy should be reported to to the sponsor (Barts Health JMRO at research.safety@qmul.ac.uk) and to the cardiovascular clinical trials unit at cvctusafetyreporting@qmul.ac.uk AstraZeneca's designated fax line: +1 302 886 4114 or email: AEMailboxClinicalTrialTCS@astrazeneca.com if a secure line is set up

18.0 Annual reporting

Development Annual Safety Update (DSUR)
The DSUR will be written by the CI (using the Sponsor's template) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "notice of acceptance letter" from the MHRA. As delegated Sponsor Medical Assessor the CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial. REC will be sent a copy of the DSUR.

Annual Progress Report (APR)
The APR will be written by the CI (using HRA template) and submitted to the sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

19.0 Statistical and Data Analysis

19.0 Statistical and Data Analysis

19.1 Sample size calculation

From published data, reduction in serum potassium with SZC is between 0.7-1mmol/l. From this data we hypothesise that 60% of patients on the IMP will get to maximum dose of irbesartan (300mg), the drop outs being either change in eGFR or for hypotension, and 30% of patients will get to the top dose in the placebo arm. The sample size calculation using a 2-sided Chi-square test at the 2 sided 5% level of significance, with a 80% power to detect a difference, would indicate that the total sample size should be 98. With a 15% drop out rate, we would expect to randomize 116 patients.

19.2 Planned recruitment rate

Based on previous experience with trials in diabetic kidney disease It is expected that the recruitment will be complete within 14 months.

19.3 Statistical analysis plan (SAP)

Please refer to SAP for full details

Primary endpoint
Whether a patient is on Maximum dose Irbesartan therapy (300mg) at the end of 12 weeks treatment period

Null hypothesis

No difference in the likelihood that a patient is a success with respect to the primary endpoint between the SZC and the placebo groups

Analysis of the primary endpoint

The primary endpoint will be analysed using the ITT principle, i.e. all randomized patients will be included. The analysis itself will be performed by means of a 2-sided chi-squared test, with a p-value < 0.05 indicating that the null hypothesis of no difference can be rejected. Patients with missing primary endpoint will be excluded from the analysis. However, the impact of such an exclusion on the results will be evaluated by considering different hypothetical scenarios where e.g. all patients in the SZC group for which failure or success could not be determined are assumed to be “failures”, while all such patients in the placebo group are assumed to be “successes”.

Sub-group analyses for primary endpoint per e.g. S-K at screening might be performed in order to explore consistency of effect.

Safety endpoints

Change in potassium from baseline at each time point
Change in the BP at the end of the study from baseline
Adverse events
Whether a patient has a K of > 6 at any time during the study
Whether a patient has a K of > 6.5 at any time during the study
Whether a patient has a K of < 3.5 at any time during the study
Whether a patients' GFR falls by > 30% from the previous test
Change in (eGFR) renal function at the end of study from baseline

Analysis of the safety endpoints

The safety endpoints will be evaluated using all patients who received at least one dose of investigational product. For discrete endpoints, such as whether a patient has K > 6 at any point during the study, the number and percentage of such patients will be presented. In addition, for illustrative purposes, a 2-sided Chi-square test will be performed. For continuous endpoints, such as change from baseline of a safety lab, summary statistics such as mean, standard deviation, median, minimum and maximum, both for the absolute values and for changes from baseline, will be provided. In addition, an analysis of covariance will be conducted, with treatment and the baseline value included as covariates.

Adverse events will be tabulated by system organ class and preferred term, as well as by severity and causality as judged by the investigator. A more formal comparison between the adverse event rates in the respective treatment arms will also be performed by means of Poisson regression.

It should be noted that no multiplicity correction will be applied. Thus, the p-values obtained from the testing of the safety endpoints are to be regarded as possibly indicative rather than confirmatory and will be interpreted with caution.

Exploratory endpoints

1. Change in pro BNP at the end of study from baseline
2. Dose of irbesartan (75/150/300 mg) at the end of the study
3. Ratio of uACR between baseline and 3-month study visit
4. Change in absolute uACR at end of study from baseine

19.4 Summary of baseline data and flow of patients

Baseline data used:
Demographic data
Medical history
Vital signs

Baseline data will be presented overall and by treatment group. Continuous data will be reported as mean (SD) and median (IQR) and categorical data as number (%).

We plan to produce a consort flow diagram.

19.5 Primary outcome analysis

See Section 19.3 "**Analysis of the primary endpoint**" section for details

19.7 Subgroup analyses

No sub groups will be studied

19.8 Adjusted analysis

The primary analysis will be unadjusted.

19.6 Secondary outcome analysis

See section 19.3 for secondary outcome (safety/exploratory) end points.

19.9 Interim analysis and criteria for the premature termination of the trial

No interim analysis is planned.

19.10 Subject population

The study population will be those patients with diabetic kidney disease who satisfy the inclusion criteria and do not meet any of the exclusion criteria.

19.11 Procedure(s) to account for missing or spurious data

This is a short study; therefore, we do not expect dropout rates to be significant. In the consent form we will gain consent to access their GP records to allow us to follow the patients if they do drop out for outcome events.
We plan to minimise dropout rates as we are experience at delivering clinical trials, we have a good patient network and will not enrol patients who we feel are unlikely to complete the study.
If there is missing outcome data, sensitivity analysis will be undertaken to examine the impact..

20.0 Data Handling & Record Keeping

20.1 Confidentiality

The Principal Investigator has the responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorized parties. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act 2018, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) and all subsequent amendments as defined in the JRMO SOP 20 Archiving.

The Chief Investigator and the study team will adhere to these regulations to ensure that the participants' identities are protected at every stage of their participation in the study. To ensure this is done accordingly, at time of consent each participant will be allocated a unique screening number by either the CI or a member of the study team before undergoing any screening procedures.

Participant confidentiality will be maintained using study identification numbers to ensure compliance with the requirements of the Data Protection Act 2018.

All investigators and trial site staff will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

20.2 Data Custodian Details

• The Chief Investigator Kieran McCafferty, Royal London Hospital, E1 1BB is the 'Custodian' of the research data;
Identifiable information including name, address, phone number, hospital number and DOB will be collected at site. Only members of the study team who are on the delegation log will have access to this data along with the sponsor or delegates for audit purposes.

• The participants will be anonymised with regards to any future publications relating to this study.

• Personal information will be collected, kept secure, and maintained through:
The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.

Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.

20.3 Psuedononymisation

Data will be in the form of linked anonymised data. Unique study numbers will be used, which are linked to a treatment code. This will be contained in the ISF on the enrolment log.

20.4 Transferring/Transporting Data

All patient-identifiable information will be stored in a locked environment, or on password protected NHS computers or on a secure ECRF.
No data will be transferred out of this environment

20.5 Data collection tools and source document identification

The source document will be the electronic patients' record. Data from the paper source data worksheets will be uploaded to an eCRF.

20.6 Source Data

The source documents will comprise the site medical notes and health records (paper and electronic), including laboratory and pharmacy records.

20.7 Case Report Form

Data will be recorded directly to a database using electronic Case Report Forms. The eCRFs will be managed by a secure web application, accessible via HTTPS/SSL. Users will be issued with a username and password and will be required to login for web application access; their activity will be tracked using unique user identities and their access to data controlled by defined access roles. Patient Identifiable Data will be encrypted in the database and kept separately from the clinical data. Direct access to the database will be restricted to named users only.
A paper backup system will be established in case of technical failure or for local convenience. Where paper CRFs are used, they should be kept in the investigator file and they will be reviewed as part of source data verification during site monitoring. Patients will be identified only by initials, trial number.
The eCRFs will be completed by the Investigator or suitably trained research staff, as designated in the site delegation log, as accurately and completely as possible throughout the study.

20.8 CRFs as Source Documents

The source documents will be paper source document worksheets

20.9 Data handling and record keeping

Data will be recorded from study visits in the source data and transcribed to the eCRF. All documents (source data worksheets, signed consent forms etc. will be kept according to the sponsor's requirements. All research staff will be trained on the use the database and CRF.

20.10 Access to Data, Source Data and Documents

Direct access will be granted to authorised representatives from the Sponsor or delegate, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Only people who have a 'legitimate relationship' with the patient (i.e. are members of the health care team) are entitled to have access to medical records.

21.0 Archiving

During the course of research and for archiving period, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 25 years.
Destruction of essential documents will require authorisation from the Sponsor.

• Archiving will be authorised by the sponsor following submission of the end of study report.

22.0 Monitoring, Audit and Inspection

22.1 Monitoring

A Trial Monitoring Plan will be developed and signed by the Sponsor and Chief investigator based on the sponsor's trial risk assessment, this will include on site monitoring. Monitoring procedures are detailed in the Trial Monitoring Plan. A sponsor monitor will monitor the trial on a regular basis.

22.2 Auditing

The sponsor retains the right to audit the trial, trial site. In addition, any part of the trial may be inspected by the regulatory bodies and funders where applicable.

22.3 Notification of Serious Breaches to GCP and/or the protocol

The CI (as single site this is also CI) is responsible for reporting any serious breaches to the sponsor (JRMO) **within 24 hours of becoming aware of the breach.**

The sponsor will work with the CI to investigate any potential breach. The sponsor will notify the MHRA, and the CI will notify the REC, within 7 working days of becoming aware of the serious breach.

22.4 Compliance

The CI will ensure that the trial is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and any subsequent amendments of the clinical trial regulations, current UK Policy Framework for Health and Social Care Research, GCP guidelines, the World Medical Association Declaration of Helsinki (1996), the Sponsor's SOPs, and other regulatory requirements as amended.

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

22.5 Non-Compliance

• Planned deviations or waivers to the protocol and specifically the eligibility criteria are not allowed

• Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

All deviations will be documented in the patient records, deviation log and CRF.

The CI and the coordinating team should assess the non-compliances and agree on a timeframe in which they need to be dealt with. This assessment should include the need to escalate to the sponsor. Any event with the potential to affect participant safety or data integrity should be reported to the sponsor within 24 hours of the Coordinating team becoming aware.

Where applicable corrective and preventative actions (CAPA) should be taken. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the Sponsor will agree an appropriate action, which could include an on-site audit.

22.6 Regulatory Compliance

Participants will not be recruited into the trial until permission has been granted by the sponsor.

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

Before any site can enrol participants into the trial, the Principal Investigator or designee will apply for NHS permission from the site's Research & Development (R&D) department.

For any amendment that will potentially affect a site's NHS permission, the Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D).

This study does not involve ionising radiation

23.0 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

All members of committee will sign a competing interests form

24.0 Ethical and Regulatory Considerations

Before the start of the trial, approval will be sought from the Research Ethics Committee (REC) and MHRA for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Decision whether an amendment constitutes a minor or substantial amendment lies with the sponsor.

Substantial amendments that require review by the Sponsor and REC and MHRA (where relevant) will not be implemented until the REC and or MHRA grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the Sponsor, REC and MHRA will be retained in the Trial Master File at the lead site and Investigator Site File at each site.

The Chief Investigator will notify the REC, MHRA and Sponsor of the end of the study.

25.0 Peer review

This protocol has undergone extensive peer review by the funder AstraZeneca.

26.0 Public and Participant Involvement

We will engage with our patient group (The Renal patient forum) to invite them to consider nominating one or more patients to sit on the Trial Steering Committee.

27.0 Indemnity

NHS Indemnity will apply to the Sponsor and host sites as all are NHS Trusts.

27.1 Amendments

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the sponsor must submit a valid notice of amendment to the licencing authority (MHRA) and to the HRA and REC for consideration. The MHRA,REC and HRA will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA,REC and HRA.

If applicable, other specialist review bodies (e.g. CAG) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments will also be notified to NHS R&D departments of participating sites to assess whether the amendment affects the NHS capability and capacity for that site.

The CI along with the steering committee will be responsible for making the decision to amend the protocol. Amendments will be submitted by the CI to the MHRA, HRA and REC and will inform the Trial registries and local R&D departments. Any changes to study documents will be subject to version control and amendment history.

27.2 Access to the final trial dataset

The steering committee will have access to the final dataset along with the CI.

28.0 Trial Committees

The Trial steering committee/Data monitoring committee will be set up in accordance with the sponsor's standard operating procedure for Trial Committees: JMRO SOP 47.

29.0 Publication and Dissemination Policy

29.1 Publication

Publications will occur at the end of the study.

The sponsor retains the right to review all publications prior to submission or publication.

Responsibility for ensuring accuracy of any publication from this study is delegated to the Chief Investigator.

All publications should acknowledge the Sponsor. The correct designation for the sponsor is Barts Health NHS Trust
Publication authorship will be decided by the TSC

The full study report will be accessible via Eudra CT.

29.2 Dissemination policy

Data arising from the trial is owned by the sponsor.
The DKC will be acknowledged in any publications arising from the study.
Participants will be notified of the outcome of the trial in writing.
Their non-blinded treatment allocation will be made available to patients on request following publication.

The trial protocol and the full study report, will be made publicly available via EudraCT

30.0 References

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This protocol is based on JRMO CTIMP Protocol Template June 2015 version 4.0.

ORTIZ Protocol v1.1 - Clean Updated

Final Audit Report 2022-09-06

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