STATISTICAL ANALYSIS PLAN

1. TITLE PAGE

Full 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/Acronym	**ORTIZ**: **O**ptimising **R**AS**i** **T**herapy with S**Z**C
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Chief Investigator Barts Health NHS Trust	**Dr Kieran McCafferty** Phone: +44(0)20 7882 7260 Email: Kieran.mccafferty4@nhs.net
Designated Sites	4 sites all in an NHS setting (Barts Health NHS Trust and 3 other sites)
SAP author	Thomas Godec

2. SAP SIGNATURES

I give my approval for the statistical analysis plan (SAP) for the study: 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, version 1.1 dated July 2023.

Trial Statistician

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3. SAP REVISION HISTORY

Protocol Version	Updated SAP version No.	Section number changed	Description of and reason for change	Date changed
1.0				
1.1	1.1	2	Update of senior statistician	7th July 2023
		Throughout	Font change for ease of readability	7th July 2023
		8, 9, 10, 15	Removal of exploratory endpoints from analysis due to small obtained sample size	7th July 2023
		13, 14, 15, 16	Removal of reference to per protocol analysis and any hypothesis testing due to small obtained sample size	7th July 2023

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CONTENTS

5. GLOSSARY OF TERMS AND ABBREVIATIONS

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	Electrocardiogram
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
ITT	Intention to treat
GI	Gastrointestinal
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
PP	Per protocol
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

6. INTRODUCTION

This SAP was written based on information from the ORTIZ study protocol version 1.0, dated 18 May 2021.

6.1. Preface

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 [1,2].

There is evidence in both the cardiac and renal literature that suggests that maximising the dose of RASi therapy leads to improved outcomes over smaller doses of RASi therapy [3,4]. Indeed, many of the studies on which we base our care, use doses which are higher than most patients are taking. Thus, pa*tients are being systemically undertreated by therapies which have been shown to have robust reno protection. Up to 80% of patients on RASi therapy are not on maximal dose [5], putting them at risk of a more rapid disease progression, poorer outcomes, and increased healthcare costs [6].

One of the main reasons for this undertreatment of RASi therapy is the fear of hyperkalaemia, with reports of significantly increased rates of hyperkalaemia seen following increases in prescribing of RASi therapy [7]. These concerns have led 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, consequently 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 compensated for by 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 be effective in lowering potassium in patients with heart failure, diabetes, CKD and RASi therapy [8–10]. With around a 1mmol/L fall in the serum potassium on those treated with SZC, compared to placebo. In 5-large clinical trials it appears efficacious, well tolerated and safe.

The purpose the ORTIZ trial is to investigate the safety and tolerability of SZC as compared to placebo to maximise RASi therapy in patients with moderate to advanced CKD.

6.2. Purpose of the trial

The purpose the ORTIZ trial is to investigate the safety and tolerability of SZC as compared to placebo to maximise RASi therapy in patients with CKD. More specifically, the main research question being addressed is whether a 3-month course of treatment with SZC can enable safe optimisation of RASi therapy in patients with moderate to advanced CKD.

7. TRIAL DESIGN

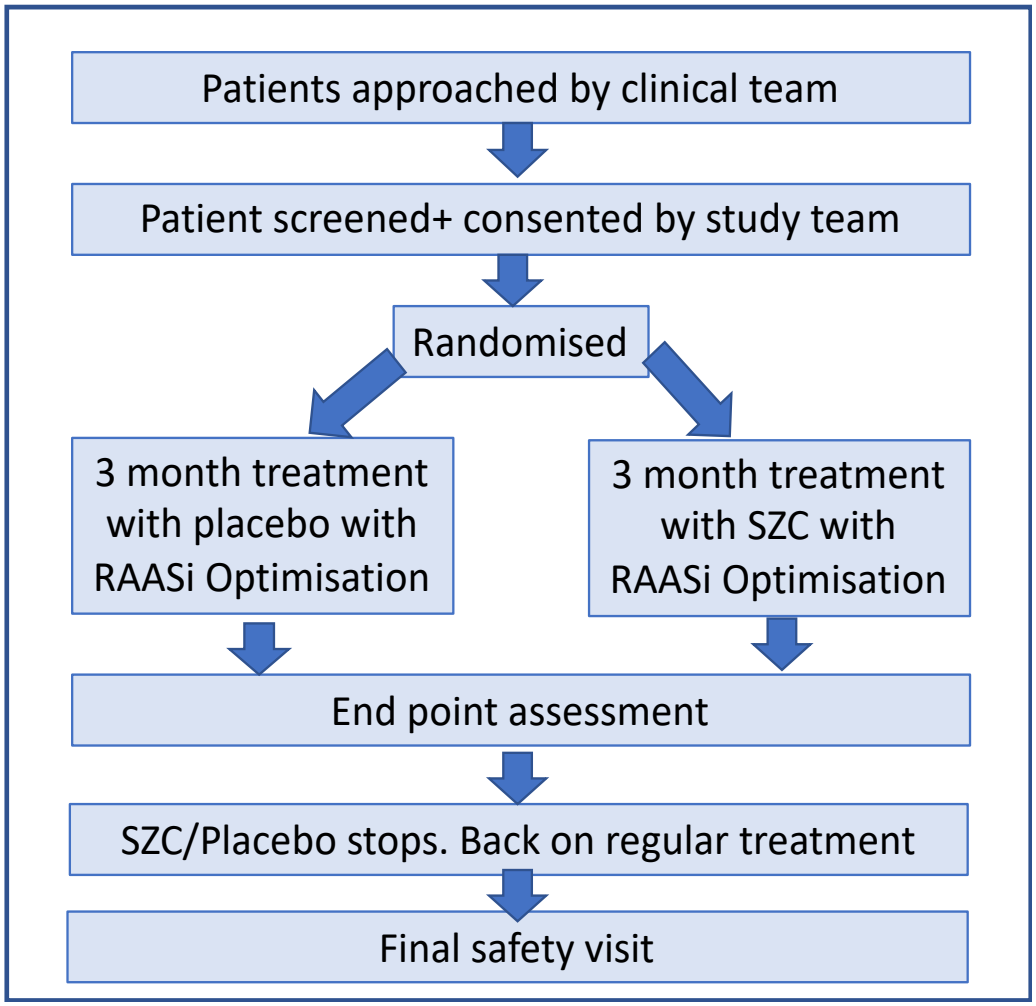
7.1. Design

The ORTIZ trial is a phase II, double-blind, placebo-controlled trial, designed to evaluate the safety and efficacy of treatment with SZC to enable RASi therapy optimisation in patients with CKD.

7.2. Trial flowchart

Figure 1 presents a trial flowchart for the ORTIZ trial.

Figure 1: ORTIZ trial flowchart



7.3. Randomisation process

Eligible participants will be randomly allocated to either active treatment with SZC or placebo in an equal ratio using predefined randomisation. The randomisation list will be generated using randomly permuted blocks of randomly varying lengths of 2, 4, and 6. Randomisation will not be stratified by any factors. The randomisation list will be created by Sealed Envelope (www.sealedenvelope.com), and the implementation of allocation revealment will be conducted using the Sealed Envelope online system.

8. SUMMARY TABLE OF OBJECTIVES, ENDPOINTS, AND OUTCOME MEASURES

8.1. Primary objective

	Primary Objective	**Primary Endpoint**	**Outcome measure**
1.1	**To assess the efficacy of treatment with SZC to enable RASi (irbesartan) maximisation as compared to placebo, in patients with CKD.**	Reaching maximum dose of irbesartan (300 mg) at the end of the trial (12 weeks).	The difference in proportion of patients reaching maximum irbesartan dose (300 mg) at the end of the trial (12 weeks) between SZC and placebo groups.

8.2. Safety objectives

	Safety Objectives	**Secondary Endpoints**	**Outcome measures**
2.1	**To compare the change in potassium levels over the trial between SZC and placebo groups.**	Change in potassium from baseline to the time-point of each trial visit (1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 12 weeks).	Mean difference in change in potassium from baseline to each trial visit between SZC and placebo groups.
2.2	**To compare the change in BP over the trial between SZC and placebo groups.**	Change in office BP (Systolic and diastolic) from baseline to the end of the trial (12 weeks).	Mean difference in change in BP from baseline to the end of the trial (12 weeks) between SZC and placebo groups.

2.3	**To compare the proportion experiencing an adverse event during the trial between SZC and placebo groups.**	Experiencing adverse events during the trial (to 12 weeks).	The difference in proportion of patients experiencing a adverse events between baseline and the end of the study (12 weeks) between SZC and placebo groups.
2.4	**To compare the proportion experiencing high levels of potassium at any point during the trial between SZC and placebo groups.**	Experiencing potassium levels higher than 6 mmol/L, and higher than 6.5 mmol/L at any point during the trial (to 12 weeks).	Difference in proportion of patients experiencing potassium levels higher than 6 mmol/L, and higher than 6.5 mmol/L at any point during the trial (to 12 weeks) between SZC and placebo groups.
2.5	**To compare the proportion experiencing low levels of potassium at any point during the trial between SZC and placebo groups.**	Experiencing potassium levels lower than 3.5 mmol/L at any point during the trial (to 12 weeks).	Difference in proportion of patients experiencing potassium levels lower than 3.5 mmol/L at any point during the trial (to 12 weeks) between SZC and placebo groups.
2.6	**To compare the proportion experiencing sudden large decline is eGFR during the trial between SZC and placebo groups.**	Experiencing a reduction in eGFR more than 30% from the previous visit test.	Difference in proportion of patients experiencing reduction in eGFR more than 30% from the previous visit test between SZC and placebo groups.
2.7	**To compare the change in eGFR over the trial between SZC and placebo groups.**	Change in eGFR from baseline to the end of the trial (12 weeks).	Mean difference in change in eGFR from baseline to the end of the trial (12 weeks) between SZC and placebo groups.

9. STUDY OBJECTIVES

9.1. Primary objective

The primary objective of the ORTIZ study is to assess the efficacy of treatment with SZC to enable RASi (irbesartan) maximisation as compared to placebo, in patients with CKD.

9.2. Safety objectives

Secondary objectives are to:

- compare the change in potassium levels over the trial between SZC and placebo groups
- compare the change in BP over the trial between SZC and placebo groups
- compare the proportion experiencing an adverse event during the trial between SZC and placebo groups
- compare the proportion experiencing high levels of potassium at any point during the trial between SZC and placebo groups
- compare the proportion experiencing low levels of potassium at any point during the trial between SZC and placebo groups
- compare the proportion experiencing sudden large decline is eGFR during the trial between SZC and placebo groups
- compare the change in eGFR over the trial between SZC and placebo groups.

10. STUDY ENDPOINTS

10.1. Primary endpoint

The primary endpoint is the achievement of reaching maximum dose of irbesartan at the end of the trial (12 weeks).

10.2. Safety endpoints

Safety endpoints are:

- change in potassium from baseline to the time-point of each trial visit (1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 12 weeks)
- change in office BP (systolic and diastolic) from baseline to the end of the trial (12 weeks)
- experiencing an adverse event during the trial (to 12 weeks)
- experiencing potassium levels higher than 6 mmol/L, and higher than 6.5 mmol/L at any point during the trial (to 12 weeks)
- experiencing potassium levels lower than 3.5 mmol/L at any point during the trial (to 12 weeks)
- experiencing a reduction in eGFR more than 30% from the previous visit test
- change in eGFR from baseline to the end of the trial (12 weeks).

11. ASSESSMENT OF OBJECTIVES

Upon successful screening and meeting all eligibility criteria for inclusion into the trial, as specified in the protocol, consenting patients will be randomised to either receive SZC therapy or placebo. Patients will receive trial treatment in accordance with the protocolised management of irbesartan and SZC/placebo, as described in Figure 2.

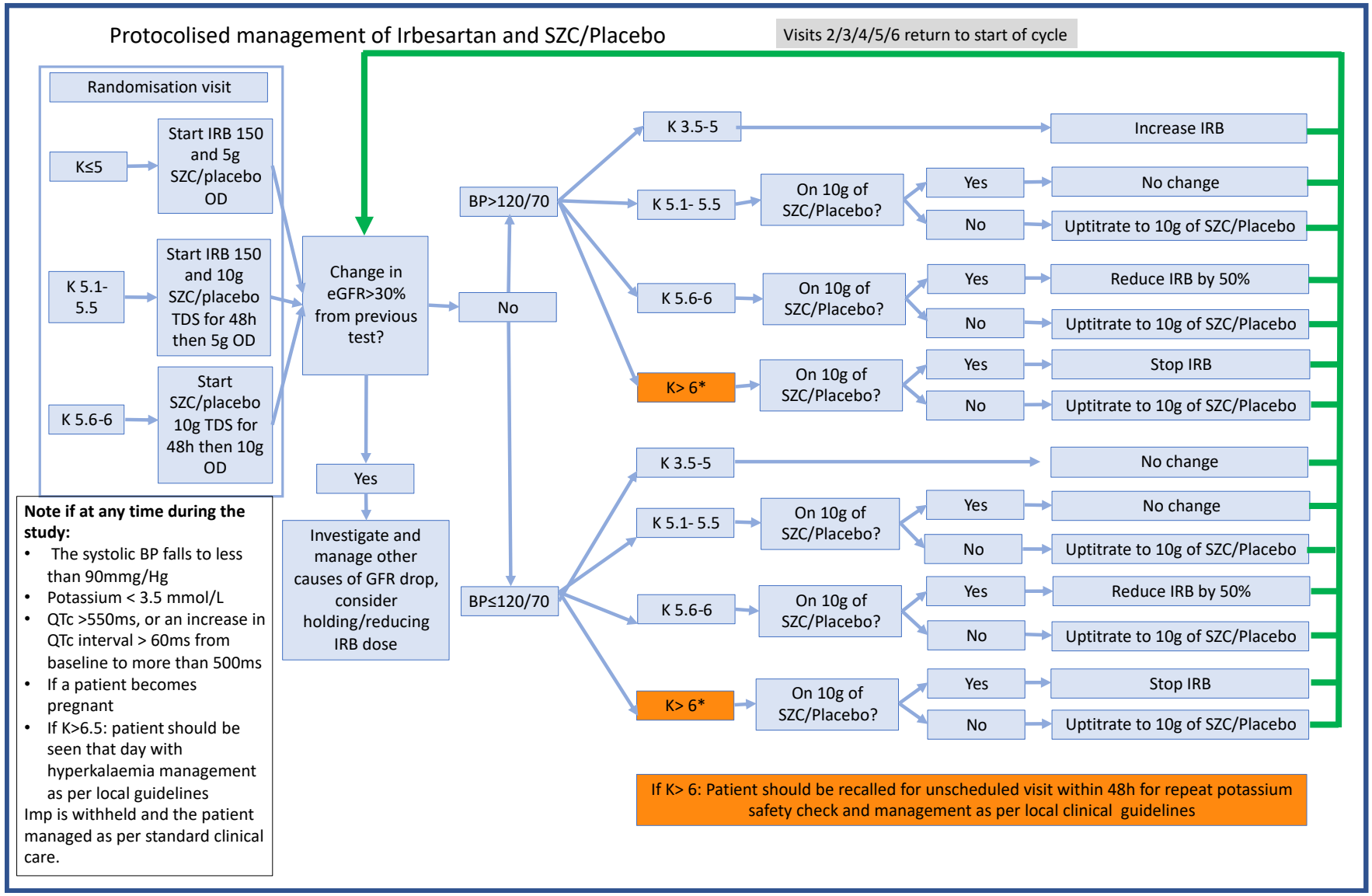
After screening and baseline, patients will be assessed at 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks and 12 weeks (end of the trial), as well as a further follow-up assessment at 14 weeks post baseline. The assessment schedule is shown in the Table 1.

Table 1: Schedule of assessment

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/Month	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	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**

Figure 2: Protocolised management of irbesartan and SZC/placebo



12. POWER CALCULATION

From published data, reduction in serum potassium with SZC is between 0.7-1mmol/l. From this data we hypothesise that 30% of patients on placebo will get to maximum dose of irbesartan (300 mg) and double the number of patients (60%) on irbesartan will get to maximum dose of irbesartan by the end of the study (12 weeks). Under these assumptions, the sample size calculation using a 2-sided Chi-square test at the 5% level of significance, with 80% power to detect the assumed difference, led to a total sample size of 98 patients (49 in each trial group).

We envisage reasons for possible patient drop-out from the trial to be either a result of a decline in eGFR or hypotension. Assuming a 15% drop-out rate, we inflate the sample size to 116 patients (58 in each trial group).

12.1. Obtained sample size

Due to early study closure the calculated sample size has not been reached. Data analysis will focus on making the best use of the obtained sample.

13. GENERAL ANALYSIS DEFINITIONS

13.1. Analysis populations

13.1.1. Primary and exploratory analyses

All analyses will be conducted on an intention-to-treat (ITT) population, based on the group to which they were randomised, regardless of their compliance or which treatment they received. Those subjects who are removed from the trial early due to having been found to not meet entry criteria for the trial will not be included in analyses.

The main approach to the analysis of trial endpoints will include all subjects that have data on the endpoint being analysed, i.e., complete case analysis for each endpoint.

13.1.2. Safety analyses

All safety endpoints will be evaluated on subjects who receive at least 1 dose of investigational product (SZC or placebo).

13.2. Missing data

All endpoints will be analyzed on a complete case basis, on all subjects with available data for the endpoint being analysed. The level of missing data (number and percentage) will be presented for each endpoint by the trial group.

13.3. Level of significance

Hypothesis testing will not be carried out due to the small obtained sample size. .

13.4. Covariate adjustment

Covariate adjustment will not be utilised due to the small obtained sample size.

13.5. Assumptions for analysis

Continuous endpoints will be assessed for normality visually using histograms. This assessment will inform the data presentation/analysis.

The data will be assessed for unrealistic values. If any continuous endpoints are considered to be unrealistic, they will be replaced with a missing value. If an endpoint is extreme but still considered possible, then it will be kept in the analysis.

13.6. Multiple comparisons

13.7. Hypothesis testing will not be performed meaning that no correction for multiple testing are necessary. Subgroup analysis

No subgroup analyses will be performed due to the small obtained sample size.
Interim analysis

No formal interim analyses are planned.

14. DEMOGRAPHICS AND BASELINE CHARACTERISITCS

Participants enrolled to the study will be described with respect to demographic data, medical history, and baseline vital signs. These descriptions will be presented separately by trial group and overall.

For continuous data, the number of subjects with data, the mean and SD (if normally distributed), median and interquartile range (if not normally distributed) will be presented. For categorical data, the number and percentage in each category will be presented.

The number of participants screened, the number excluded from participation (with reasons), the number randomised into each group, the number attending each scheduled visit, the number attending the final visit (at week 12), the number lost to follow-up, and the number assessed for the primary outcome will be shown in a trial flow diagram. The number and reasons for early withdrawal from both cohorts will be presented.

15. ANALYSIS OF OUTCOMES

15.1. Methods for analysis of the primary endpoint

The primary endpoint of the reaching the maximum dose of irbesartan (300 mg) at the end of the study (12 weeks) will be compared between trial groups. The number (and percentage) achieving the outcome will be presented in each trial group.

The number of subjects with no available data for the primary endpoint will be given.

15.2. Methods for analysis of safety endpoints

15.2.1. Change in potassium levels over the trial

The change in potassium level from baseline will be calculated for each scheduled trial visit (1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 12 weeks).

15.2.2. Change in blood pressure levels over the trial

The change in office BP from baseline to the end of the trial (12 weeks) will be calculated as the difference between baseline and end of trial BP. This analysis will be repeated for systolic and diastolic BP.

Mean office BP at baseline and at the end of the trial will be calculated as the mean of the 2nd and 3rd office readings for each occasion. If only 2 readings were recorded, the mean of those 2 will be used. If only 1 reading was recorded, then that lone recording will be used. Mean BP at baseline and the end of the study will be calculated separately for SBP and DBP.

15.2.3. The mean change in BP will be presented by treatment group. Experiencing an adverse event during the trial

15.2.3.1. Adverse events (AEs)

AEs will be summarised using counts and percentages, separately by treatment group and overall. The number of subjects having at least one AE will be presented. The number of subjects with AEs of mild/moderate/severe intensity will be presented. The number of subjects with an AE at least possibly related to trial treatment (SZC/Placebo) will be presented.

Adverse events will be tabulated by system organ class and preferred term, as well as by severity and causality as judged by the investigator.

15.2.3.2. Fatal and non-fatal serious adverse events (SAEs)

Deaths and non-fatal SAEs will be listed separately along with details of treatment for both treatment groups, and whether the event is unexpected and whether it is thought to be related to treatment.

15.2.4. Experiencing high or low levels of potassium during the trial

The number and proportion of subjects experiencing high levels of potassium (defined as 6 mmol/L or high) at any point during the trial, between baseline and the end of the trial (12 weeks) will be presented. In addition, the number and proportion of subjects experiencing low levels of potassium defined as levels lower than 3.5 mmol/L at any point during the trial.

15.2.5. Experiencing sudden large decline in eGFR during the trial

The number and proportion of subjects experiencing a decline in eGFR of more than 30% between any trial visit and the next (from baseline to the end of the trial at 12 weeks) will be presented.

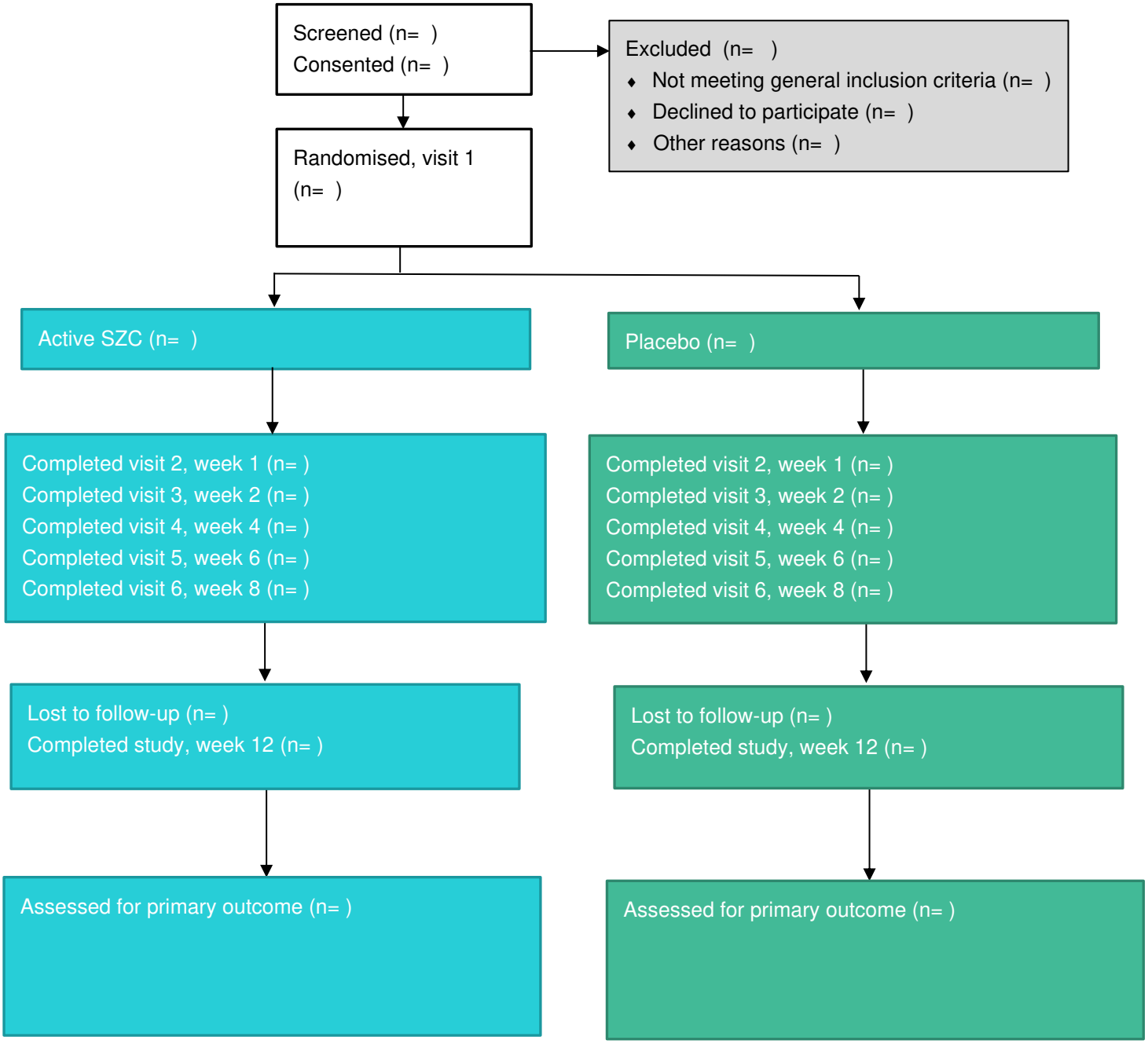
15.2.6. Change in eGFR over the trial

The change in eGFR from baseline to the end of the trial (12 weeks) will be calculated as the difference between baseline and end of trial BP. The mean change in eGFR will be presented by treatment group.

16. PRESENTATION OF ANALYSIS

Results will be presented as follows.

Figure 1: Study flow diagram



- **Table 1: Demographics and baseline characteristics, by study cohort**

Table 2: Primary outcome – reaching maximum dose of irbesartan (300mg) at end of trial

Analysis population	Number (%)		Odds ratio (95% CI)
	SZC Group	Placebo Group	
Primary outcome	N (%)	N (%)	
	N (%)	N (%)	

Table 5: Safety endpoints (safety population) – continuous

Safety endpoint		Mean (SD)		Mean difference (95% CI)
		SZC Group	Placebo Group	
Change in potassium, mmol/L		**(N=)**	**(N=)**	
Change in blood pressure, mmHg	Systolic	**(N=)**	**(N=)**	
	Diastolic			
Change in eGFR, ml/min/1.73 m^2		**(N=)**	**(N=)**	

Table 6: Safety endpoints (safety population) – binary

Exploratory endpoint	**SZC Group** (N=)	**Placebo Group** (N=)	**Odds ratio (95% CI)**
Potassium higher than 6.5 mmol/L at any point during the trial			
Potassium higher than 6.0 mmol/L at any point during the trial			
Potassium lower than 3.0 mmol/L at any point during the trial			
Reduction in eGFR more than 30% from one trial visit to the next			

- **Table 10: Safety analysis (AEs, safety population)**
- **Table 11: Safety analysis (fatal and all SAEs, safety population)**
- **Table 12: SAE listing**

17. REFERENCES

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ORTIZ SAP V1.1 July 2023

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